

hypotension (n=3). Search terms for adverse events included: “hypoten”, “low blood pres”, “lighthead”, and “synco”. Approximately half of the patients were taking duloxetine 60 mg daily.

7.1.3.3.5 Elevation of Blood Pressure

At therapeutic doses, duloxetine therapy is associated with a mean increase of up to 2.1 mmHg in systolic blood pressure and up to 2.3 mmHg in diastolic blood pressure. See safety 7.1.8, Vital Signs, for more information on fibromyalgia study findings.

7.1.3.3.6 Activation of Mania/Hypomania

As stated in the duloxetine label, a major depressive episode may be the initial presentation of bipolar disorder. In placebo-controlled studies of patients with major depressive disorder, activation of mania or hypomania was reported in 0.1% (2/2327) of duloxetine-treated patient and 0.1% (1/1460) of placebo-treated patients. No activation of mania or hypomania was reported in DPNP or GAD placebo-controlled trials. No episodes of acute mania or hypomania were reported in the fibromyalgia studies.

7.1.3.3.7 Mydriasis

Duloxetine is associated with an increased risk of mydriasis and the label states that the product should be used cautiously in patients with controlled narrow-angle glaucoma. In the clinical trials of duloxetine for fibromyalgia, there were several reports of visual changes and blurred vision (n=57). In the placebo-controlled studies, there were 3 cases of mydriasis in the duloxetine arm and none in the placebo arm. One of these episodes led to discontinuation from the trial. There was 1 additional case of mydriasis in the long-term study HMEH.

7.1.3.3.8 Withdrawal Symptoms

The product label states that “discontinuation symptoms have been systematically evaluated in patients taking duloxetine.” Upon abrupt discontinuation, the following symptoms have been reported in placebo-controlled trials: dizziness, nausea, paresthesia, vomiting, irritability, nightmares, insomnia, diarrhea, anxiety, hyperhidrosis, and vertigo. Other SSRIs and SNRIs have spontaneously reported withdrawal symptoms which include dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures.

In the fibromyalgia studies HMEF, HMCA, and HMCJ, which employed a 2-week, double-blind taper phase, more patients in the duloxetine group (33.5%) than in the placebo group (12%) reported at least 1 taper-emergent adverse event. The most common taper-emergent adverse events, reported by > 2 patients who entered the drug-tapering phases described above were dizziness, nausea, insomnia, myalgia, fatigue, headache, and abnormal dreams (for details see Table 7.16 below).

Table 7.16
Adverse Events Reported In Fibromyalgia Studies By Patients Who Entered Drug-Tapering Phase In Studies HMEF, HMCA, and HMCJ (Reported by ≥ 3 Patients)

MedDRA Preferred Term	PLACEBO (N=92) n (%)		DULOXETINE (N=203) n (%)	
Patients with ≥ 1 Discontinuation-Emergent Adverse Event	11 (12.0)		68 (33.5)	
Dizziness	1	(1.1)	18	(8.9)
Nausea	1	(1.1)	12	(5.9)
Insomnia	1	(1.1)	8	(3.9)
Diarrhoea	0	(0)	7	(3.4)
Myalgia	1	(1.1)	6	(3.0)
Fatigue	2	(2.2)	4	(2.0)
Headache	0	(0)	6	(3.0)
Abnormal dreams	0	(0)	4	(2.0)
Depression	0	(0)	4	(2.0)
Anxiety	0	(0)	3	(1.5)

Applicant's Table, Page 131, Summary of Clinical Safety

These data demonstrate that withdrawal symptoms may occur even after gradual taper. The label will be modified to reflect this finding.

7.1.3.3.9 Seizures

Although duloxetine has not been systematically evaluated in patients with a seizure disorder, and such patients have been excluded from clinical studies, a total of 3 patients out of 8504 (0.04%) treated with duloxetine in placebo-controlled studies have developed seizures while on therapy compared to 1 patient out of 6123 (0.02%) treated with placebo. In fibromyalgia studies, there were no reported seizures.

7.1.3.3.10 Hyponatremia

Cases of severe hyponatremia (sodium > 110 mmol/L) have been reported in patients taking duloxetine which were reversible when it was discontinued. In the fibromyalgia studies there were no reported cases of severe hyponatremia.

7.1.3.3.11 Abnormal Bleeding

SNRIs are believed to have effects on platelet function and labeling revisions now warn about interactions with warfarin. In the fibromyalgia studies, there was one patient assigned to 20 mg QD who experienced the SAE of heavy uterine bleeding and required a hysterectomy. Another patient, assigned to 120 mg QD, experienced a subdural hemorrhage after being struck by a motorcycle. Duloxetine causality can not be definitively established in either one of these cases.

7.1.3.3.12 Urinary Retention

Although there were no SAEs related to urinary retention, there were 5 (0.4%) reported TEAEs of urinary retention and 12 (1%) cases of urinary hesitation (see Table 7.18 below for Common AEs).

7.1.4 Other Search Strategies

Not applicable.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

All spontaneously reported, elicited, and observed adverse events were recorded on the adverse event reporting forms. Adverse events were elicited by open-ended questioning of the patient, clinical observation by the study investigator, and source document review. During active treatment, patients reported to weekly study visits and pertinent events were recorded.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were captured as verbatim comments in case report forms and then coded by the investigators as actual terms using the Medical Dictionary for Regulatory Activities (MedDRA) terms by blinded study personnel. MedDRA versions 4.0, 6.1, and 9.1 were used. The incidence of TEAEs was summarized as follows: lower level term, preferred terms, high level term, higher level group term and by SOC by decreasing frequency, and my maximum severity. The Applicant's coding was found to be consistent and reasonably accurate.

7.1.5.3 Incidence of common adverse events

The applicant defined treatment-emergent adverse events (TEAEs) as events that first occurred or worsened in severity (relative to baseline) at any time during the clinical study. As mentioned previously, analyses sets included 4 placebo-controlled studies (HMBO, HMCA, HMCJ, and HMEF) with up to 6 months of treatment and 1 long-term uncontrolled study (HMEH) of 60 weeks duration. An additional 10 patients were treated with open-label, compassionate use duloxetine (Study HMCN). Doses in these studies ranged from 20 – 120 mg daily, with most patients receiving 120 mg/day (n=221 received 120 mg QD; n=220 received 60 mg BID; n=369 received 60 mg QD, n=37 received 30 mg QD, and n=29 received 20 mg QD).

Eli Lilly analyzed adverse event data in multiple ways. Their primary focus was on the adverse event reporting which occurred in $\geq 5\%$ (at the preferred term level) of patients in placebo-controlled studies. This analysis revealed that there were more duloxetine-treated patients (778; 89%) than placebo-treated patients (425; 79%) who reported at least 1 TEAE. The placebo-controlled studies were all similar in design, dose, choice of control, and duration (3 months with or without an additional 3 months). There were a total of 1411 patients enrolled in the placebo-controlled trials (placebo = 535 & duloxetine = 876).

In the fibromyalgia duloxetine-treated patient database of controlled and uncontrolled studies, there were 1115 patients (n=1236; 90%) who reported at least 1 TEAE. This analysis set includes data from the long-term (1 year) uncontrolled study HMEH.

7.1.5.4 Common adverse event tables

In fibromyalgia placebo-controlled studies, Eli Lilly states that the following TEAEs had an incidence of $\geq 5\%$ and were more common in the duloxetine group than the placebo group: nausea, headache, dry mouth, insomnia, fatigue, constipation, diarrhea, dizziness, somnolence, hyperhidrosis, and decreased appetite (for more details see Table 7.17 below). These AEs appear consistent with common adverse event findings described in the duloxetine product label for other indications. A table of TEAEs occurring in $\geq 1\%$ of fibromyalgia patients can be found in the Appendix.

Table 7.17
Treatment-Emergent Adverse Events by Decreasing Frequency Reported in $\geq 5\%$ Fibromyalgia Patients By MedDRA Preferred Term

Event	Fibromyalgia Placebo-Controlled	
	PBO N=535 n(%)	DLX N=876 n(%)
ANY EVENT	425(79)	777(89)
Nausea	61(11)	257(29)
Headache	64(12)	175(20)
Dry mouth	29(5)	159(18)
Insomnia	49(9)	127(15)
Fatigue	38(7)	118(14)
Constipation	19(4)	127(15)
Diarrhoea	42(8)	102(12)
Dizziness	36(7)	96(11)
Somnolence	15(3)	84(10)
Hyperhidrosis	6(1)	60(7)
Decreased appetite	3(1)	57(7)

PBO = placebo, DLX = duloxetine
 Modified from Applicant's Table, Page 39, Clinical Safety Summary

The Applicant's original primary assessment of common adverse events was based on events occurring by maximum dose tolerated. Via teleconference, we asked the Applicant to submit tables of adverse events by assigned doses at 3 and 6 months. For my review of common adverse events, I concentrated on treatment-emergent adverse events in placebo-controlled fibromyalgia studies at 3-months by assigned dose by system organ class and high-level group term. Table 7.20 below includes events that occurred more commonly in the duloxetine arm and at a rate greater than 5%.

Common adverse events in this table are consistent with the AEs described by the applicant. As expected, AE rates are similar for duloxetine 60 mg BID and 120 mg QD, except for insomnia (Sleep Disorders and Disturbances, 29% vs. 20%) which occurs in more patients receiving twice daily dosing. Fatigue (General Disorders and Administration Site Conditions) is also higher in the 60 mg BID arm (29% vs. 18%), possibly as a result of an increased rate of sleep disturbances.

The most common adverse events listed above (nausea, headache, insomnia, fatigue, constipation, diarrhea, dizziness, somnolence, hyperhidrosis, and decreased appetite) appeared more frequently at the highest doses (120 mg/day). Duloxetine 20 mg QD and duloxetine 60 mg

QD had a similar adverse event profile except for dry mouth, which occurred in 9% of patients at 20 mg QD and 17% at 60 mg QD.

For a complete listing of common adverse events by system organ class and high level group term by assigned dose at three months, see Appendix 10.4, Table 7.20.

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Table 7.18 Treatment-Emergent Adverse Events by Assigned Dose By System Organ Class and by High Level Group Term All Randomized Patients in Fibromyalgia Placebo-Controlled Studies at 3 Months (HMBO, HMCA, HMCJ & HMEF)					
EVENT (Patients with ≥ 1 TEAE)	Placebo (N=535)n(%)	DLX 20 QD (N=79)n(%)	DLX 60 QD (N=430)n(%)	DLX 60 BID (N=220)n(%)	DLX 120 QD (N=147)n(%)
All Body Systems Combined	394(73.64%)	65(82.28%)	367(85.35%)	191(86.82%)	130(88.44%)
Cardiac Disorders	12(2.24%)	2(2.53%)	11(2.56%)	5(2.27%)	6(4.08%)
Cardiac arrhythmias	4(0.75%)	0(0.00%)	3(0.70%)	0(0.00%)	1(0.68%)
Eye Disorders	16(2.99%)	5(6.33%)	18(4.19%)	10(4.55%)	11(7.48%)
Vision disorders	3(0.56%)	2(2.53%)	8(1.86%)	3(1.36%)	4(2.72%)
Eye disorders NEC	5(0.93%)	1(1.27%)	4(0.93%)	2(0.91%)	2(1.36%)
Gastrointestinal Disorders	147(27.48%)	34(43.04%)	227(52.79%)	115(52.27%)	78(53.06%)
Gastrointestinal signs and symptoms	87(16.26%)	24(30.38%)	148(34.42%)	70(31.82%)	51(34.69%)
Gastrointestinal motility and defecation conditions	61(11.40%)	12(15.19%)	96(22.33%)	34(15.45%)	36(24.49%)
Salivary gland conditions	26(4.86%)	7(8.86%)	72(16.74%)	43(19.55%)	27(18.37%)
General Disorders & Administration Site Conditions	101(18.88%)	17(21.52%)	98(22.79%)	72(32.73%)	33(22.45%)
General system disorders NEC	90(16.82%)	15(18.99%)	82(19.07%)	63(28.64%)	27(18.37%)
Immune System Disorders	12(2.24%)	1(1.27%)	6(1.40%)	8(3.64%)	4(2.72%)
Allergic conditions	12(2.24%)	1(1.27%)	6(1.40%)	8(3.64%)	4(2.72%)
Infections & Infestations	142(26.54%)	21(26.58%)	96(22.33%)	41(18.64%)	38(25.85%)
Infections – pathogen class unspecified	110(20.56%)	15(18.99%)	75(17.44%)	34(15.45%)	34(23.13%)
Viral infectious disorders	25(4.67%)	6(7.59%)	21(4.88%)	9(4.09%)	5(3.40%)
Bacterial infectious disorders	8(1.50%)	2(2.53%)	7(1.63%)	0(0.00%)	2(1.36%)
Investigations	15(2.80%)	1(1.27%)	24(5.58%)	13(5.91%)	16(10.88%)
Hepatobiliary investigations	3(0.56%)	0(0.00%)	6(1.40%)	1(0.45%)	2(1.36%)
Metabolism & Nutrition Disorders	28(5.23%)	9(11.39%)	50(11.63%)	30(13.64%)	22(14.97%)
Appetite and general nutritional disorders	20(3.74%)	7(8.86%)	44(10.23%)	27(12.27%)	19(12.93%)
Glucose metabolism disorders (incl diabetes mellitus)	1(0.19%)	1(1.27%)	2(0.47%)	0(0.00%)	2(1.36%)
Musculoskeletal & Connective Tissue Disorders	122(22.80%)	17(21.52%)	88(20.47%)	39(17.73%)	20(13.61%)
Musculoskeletal and connective tissue disorders NEC	62(11.59%)	9(11.39%)	36(8.37%)	23(10.45%)	6(4.08%)
Muscle disorders	29(5.42%)	6(7.59%)	32(7.44%)	17(7.73%)	13(8.84%)
Joint disorders	31(5.79%)	4(5.06%)	26(6.05%)	6(2.73%)	3(2.04%)
Nervous System Disorders	123(22.99%)	26(32.91%)	173(40.23%)	96(43.64%)	69(46.94%)
Neurological disorders NEC	62(11.59%)	15(18.99%)	89(20.70%)	57(25.91%)	45(30.61%)
Headaches	64(11.96%)	12(15.19%)	88(20.47%)	50(22.73%)	29(19.73%)
Movement disorders (incl Parkinsonism)	5(0.93%)	2(2.53%)	21(4.88%)	8(3.64%)	17(11.56%)
Mental impairment disorders	9(1.68%)	2(2.53%)	8(1.86%)	4(1.82%)	4(2.72%)
Sleep disturbances (incl subtypes)	4(0.75%)	1(1.27%)	6(1.40%)	3(1.36%)	0(0.00%)
Psychiatric Disorders	119(22.24%)	12(15.19%)	100(23.26%)	86(39.09%)	47(31.97%)
Sleep disorders and disturbances	55(10.28%)	6(7.59%)	58(13.49%)	64(29.09%)	29(19.73%)
Anxiety disorders and symptoms	29(5.42%)	2(2.53%)	23(5.35%)	20(9.09%)	9(6.12%)
Depressed mood disorders and disturbances	32(5.98%)	1(1.27%)	11(2.56%)	8(3.64%)	5(3.40%)
Sexual dysfunctions, disturbances & gender identity disorders	3(0.56%)	4(5.06%)	12(2.79%)	7(3.18%)	12(8.16%)
Changes in physical activity	3(0.56%)	3(3.80%)	10(2.33%)	3(1.36%)	7(4.76%)
Mood disorders and disturbances NEC	11(2.06%)	1(1.27%)	7(1.63%)	2(0.91%)	2(1.36%)
Suicidal and self-injurious behaviors NEC	2(0.37%)	0(0.00%)	0(0.00%)	0(0.00%)	1(0.68%)
Renal & Urinary Disorders	16(2.99%)	4(5.06%)	21(4.88%)	5(2.27%)	11(7.48%)
Urinary tract signs and symptoms	13(2.43%)	3(3.80%)	20(4.65%)	5(2.27%)	9(6.12%)
Respiratory, Thoracic & Mediastinal Disorders	40(7.48%)	11(13.92%)	37(8.60%)	21(9.55%)	18(12.24%)
Respiratory disorders NEC	29(5.42%)	8(10.13%)	28(6.51%)	11(5.00%)	16(10.88%)
Upper respiratory tract disorders (excl infections)	11(2.06%)	5(6.33%)	10(2.33%)	9(4.09%)	4(2.72%)
Skin and Subcutaneous Tissue Disorders	47(8.79%)	13(16.46%)	62(14.42%)	24(10.91%)	27(18.37%)
Skin appendage conditions	18(3.36%)	6(7.59%)	39(9.07%)	14(6.36%)	18(12.24%)
Epidermal and dermal conditions	25(4.67%)	6(7.59%)	22(5.12%)	8(3.64%)	9(6.12%)
Vascular Disorders	19(3.55%)	2(2.53%)	24(5.58%)	12(5.45%)	8(5.44%)
Vascular disorders NEC	12(2.24%)	2(2.53%)	17(3.95%)	9(4.09%)	6(4.08%)

N = Number of randomized patients, n = Number of patients with TEAE, for HMCJ & HMEF visit 8 is last visit of comparator period
 Applicant's Table, Regulatory Response 4-March-2008 – Adverse Events by Dose, Pages 94- 104.

7.1.5.5 Identifying common and drug-related adverse events

The following adverse events occurred in at least 5% of duloxetine-treated fibromyalgia patients at a frequency 10% higher than for placebo patients: nausea, dry mouth, and constipation. The cut-off of a 10% difference was chosen arbitrarily due to the large size of the adverse event database. To analyze these adverse events in more detail, I searched the fibromyalgia placebo-controlled TEAE database for several text strings listed within the Adverse Event term column. For nausea and vomiting, I used “nausea”, “vomit”, and “retch”. For constipation, I used “constip” and “hard stool”. Lastly for dry mouth, I simply used the term “dry mouth”. My search results were similar to the applicant’s results which were listed in the table above.

7.1.5.6 Additional analyses and explorations

7.1.5.6.1 Nausea and Vomiting

A total of 257 out of 876 (29%) patients treated with duloxetine in placebo-controlled trials reported experiencing nausea and vomiting, compared to 61 out of 535 (11%) treated with placebo. Most (72%) adverse events were reported within the first 7 days of product administration and there was no obvious dose-response effect. Also, there were no noticeable differences in adverse event reporting based on race and gender.

7.1.5.6.2 Constipation

A total of 127 out of 876 (15%) patients treated with duloxetine in placebo-controlled trials reported the adverse event of constipation, compared to 19 out of 535 (4%) treated with placebo. The majority of these adverse events (62%) occurred after the first week of therapy which would be expected if the adverse event was drug-related, since constipation likely requires several days to develop. Again, there were no noticeable differences in adverse event reported based on race and gender and no dose-response effect was detected.

7.1.5.6.3 Dry Mouth

A total 159 out of 876 (18%) patients treated with duloxetine in placebo-controlled trials reported to have experienced the adverse event of “dry mouth”, compared to 29 out of 535 (5%) treated with placebo. A majority of these events (61%) were reported during the first week of therapy. This adverse event appears to be dose-related, as only 5% of the placebo patients experienced dry mouth compared to 9% in the 20 mg QD arm and close to 20% of all patients in the 60 mg QD, 60 mg BID and 120 mg QD groups. No differences were noted in reporting based on race and gender.

7.1.6 Less Common Adverse Events

Since duloxetine has been on the market since 2004 and is reasonably well characterized, many of the less common adverse events are described in the approved product label (for details see Section 7.1.3.3, Other Significant Adverse Events).

7.1.6.1 Insomnia

Insomnia was reported by 13% (n=67) of patients receiving placebo and by 23% (n=51) of patients in the duloxetine 120 mg QD group and 32% (n=71) of patients in the duloxetine 60 mg BID group. The higher incidence observed in the arm that was dosed twice daily possibly indicates that duloxetine is more likely to cause sleep disturbances when dosed in the evening. This suggests that patients who experience sleep disturbances with duloxetine may benefit from taking the product in the morning and not in the evening.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

During phase 2 and 3 studies, standard clinical laboratories including hematology, chemistry, and urinalysis were obtained at baseline and again at multiple time intervals throughout the studies. Using — reference ranges, Eli Lilly assessed laboratory analytes for changes from baseline to endpoint, changes from baseline to maximum, treatment-emergent abnormally high or low values at any time and at endpoint, and treatment-emergent potentially clinically significant (PCS) values at any time.

Treatment-emergent abnormal laboratory values were defined as a change from normal at baseline to abnormal at any post-baseline assessment (or at endpoint). Patients who were considered abnormal at baseline were not included in the analysis of treatment-emergent abnormal laboratory values for the analyte being evaluated. For treatment-emergent PCS values, a patient was counted if the endpoint value was abnormal or if there were 2 consecutive abnormal values in the post-baseline period.

Duloxetine is known to cause elevations of liver function tests, primarily ALT and AST. In addition to standard transaminases, GGT, ALKPH, and TBILI were checked regularly. Additional tests of liver synthetic function, such as coagulation studies, were not performed routinely. For more information on results of liver function tests, see Section 7.1.3.3.2 Hepatotoxicity.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The Applicant's review of laboratory results primarily focused on data from fibromyalgia placebo-controlled trials (HMBO, HMCA, HMCJ, and HMEF). Pooled data from all fibromyalgia patient duloxetine exposures was used to assess potentially clinically significant data.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

The tables below show the mean changes in chemistry (Table 7.19) and hematology (Table 7.20) analytes observed from baseline to endpoint for duloxetine and placebo groups. As described previously in Section 7.1.3.3.2, Hepatotoxicity, elevations in ALKPH, AST, and ALT were noted. Incidentally, and likely not of any clinical significance, there were slight reductions observed for total bilirubin, chloride, and uric acid. As noted in the product label for duloxetine, creatine phosphokinase (CPK) values were also found to be elevated in the fibromyalgia studies.

The approved product label for duloxetine states that in placebo-controlled trials patients have been noted to have small increases from baseline to endpoint in mean CPK values. Table 7.19 below, demonstrates that in fibromyalgia studies, CPK values in the placebo arms increased from a baseline value of 84 to an endpoint value of 86 (SD = 56), whereas duloxetine arms increased from a baseline value of 90 to an endpoint value of 116 (SD = 596). I reviewed all CPK values and found that in the fibromyalgia placebo-controlled studies, there were a total of 77 placebo-treated (n=504, 15%) and 157 duloxetine-treated (n=819, 19%) patients who developed an elevated CPK.

For the duloxetine arm, CPK elevations did not appear to be dose-dependent. Also, many patients with elevated CPK values entered the trial with elevated baseline CPK values and many of these patients were not re-tested.

For hematology analytes, no clinically relevant trends were detected. Slight elevations in both eosinophils and platelets were noted.

Table 7.19
Laboratory Values – Chemistry Analytes Change from Baseline to Endpoint
All Randomized Patients in Fibromyalgia Placebo-Controlled Trials

Lab Test	Unit	Therapy	N	Baseline		Change to Endpoint	
				Mean	SD	Mean	SD
ALKALINE PHOSPHATASE	U/L	Placebo	505	74.95	23.22	-0.97	10.04
		Duloxetine	819	76.20	23.55	2.79	12.97
ALT/SGPT	U/L	Placebo	504	20.73	9.89	-0.36	8.10
		Duloxetine	818	21.53	10.36	2.94	31.36
AST/SGOT	U/L	Placebo	503	20.75	6.13	0.18	5.79
		Duloxetine	810	21.17	6.77	2.32	18.65
BICARBONATE, HCO ₃	mmol/L	Placebo	503	23.99	2.41	-0.52	2.71
		Duloxetine	819	23.91	2.58	-0.35	2.81
BILIRUBIN, TOTAL	umol/L	Placebo	504	7.29	3.90	-0.08	2.85
		Duloxetine	820	7.60	3.79	-0.52	2.84
CALCIUM	mmol/L	Placebo	505	2.45	0.10	-0.01	0.10
		Duloxetine	820	2.46	0.10	-0.02	0.10
CHLORIDE	mmol/L	Placebo	505	104.64	2.55	0.15	2.46
		Duloxetine	818	104.79	2.88	-0.48	2.88
CHOLESTEROL	mmol/L	Placebo	505	5.50	1.08	-0.18	0.70
		Duloxetine	820	5.52	1.03	-0.01	0.72
CREATINE PHOSPHOKINASE	U/L	Placebo	504	84.00	48.32	2.29	55.94
		Duloxetine	819	90.09	68.68	26.16	595.78
CREATININE	umol/L	Placebo	505	95.90	12.74	0.16	8.99
		Duloxetine	820	96.44	13.08	0.28	9.18
GGT (GGPT/SGGT/YGGT)	U/L	Placebo	505	24.01	28.52	-0.94	17.00
		Duloxetine	818	26.02	21.94	-0.00	19.69
INORGANIC PHOSPHORUS	mmol/L	Placebo	505	1.15	0.17	0.00	0.18
		Duloxetine	820	1.18	0.17	-0.02	0.19
POTASSIUM	mmol/L	Placebo	505	4.30	0.40	-0.01	0.41
		Duloxetine	817	4.30	0.41	0.01	0.42
SODIUM	mmol/L	Placebo	504	141.38	2.39	-0.16	2.81
		Duloxetine	817	141.46	2.69	-0.37	3.21
TOTAL PROTEIN	g/L	Placebo	505	72.64	4.09	-1.17	3.68
		Duloxetine	820	72.79	4.18	-1.23	3.81
UREA NITROGEN	mmol/L	Placebo	505	5.19	1.44	-0.02	1.23
		Duloxetine	820	5.21	1.47	-0.07	1.25
URIC ACID	umol/L	Placebo	505	290.01	74.45	-0.65	41.26
		Duloxetine	820	294.62	78.92	-10.40	45.94

N = Number of patients with a baseline and at least one non-missing post-baseline measurement.
 SD = standard deviation

Modified from Applicant's Table, Page 79-80, Clinical Safety Summary

Table 7.20
Laboratory Values – Hematology Analytes Change from Baseline to Endpoint
All Randomized Patients in Fibromyalgia Placebo-Controlled Trials

Lab Test	Unit	Therapy	N	Baseline		Change to Endpoint	
				Mean	SD	Mean	SD
BANDS	G/L	Placebo	313	0.00	0.01	0.00	0.01
		Duloxetine	487	0.00	0.01	-0.00	0.01
BASOPHILS	G/L	Placebo	363	0.05	0.03	0.00	0.03
		Duloxetine	565	0.05	0.02	0.00	0.03
EOSINOPHILS	G/L	Placebo	363	0.14	0.11	-0.00	0.08
		Duloxetine	565	0.14	0.11	0.02	0.10
ERYTHROCYTE COUNT	T/L	Placebo	363	4.72	0.39	-0.06	0.24
		Duloxetine	565	4.74	0.38	-0.06	0.25
HEMATOCRIT	Actual Count	Placebo	361	0.42	0.04	-0.01	0.03
		Duloxetine	564	0.42	0.03	-0.00	0.03
HEMOGLOBIN	mm/L	Placebo	363	8.49	0.72	-0.17	0.45
		Duloxetine	565	8.48	0.68	-0.13	0.48
LEUKOCYTE COUNT	G/L	Placebo	363	6.74	1.79	-0.03	1.39
		Duloxetine	565	6.64	1.69	0.04	1.40
LYMPHOCYTES	G/L	Placebo	363	2.06	0.64	-0.02	0.44
		Duloxetine	565	2.06	0.61	-0.02	0.42
LYMPHOCYTES, ATYPICAL	G/L	Placebo	225	0.00	0.01	-0.00	0.01
		Duloxetine	387	0.00	0.00	0.00	0.01
MEAN CELL HEMOGLOBIN (MCH)	fmol	Placebo	363	1.81	0.13	-0.01	0.06
		Duloxetine	563	1.79	0.11	-0.00	0.06
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)	mm/L	Placebo	361	20.40	0.95	-0.12	0.86
		Duloxetine	564	20.29	0.85	-0.11	0.85
MEAN CELL VOLUME (MCV)	fL	Placebo	361	88.66	5.49	-0.06	3.39
		Duloxetine	564	88.56	4.76	0.24	3.21
MONOCYTES	G/L	Placebo	363	0.34	0.12	0.02	0.11
		Duloxetine	565	0.34	0.12	0.03	0.11
NEUTROPHILS, SEGMENTED	G/L	Placebo	363	4.14	1.38	-0.03	1.20
		Duloxetine	565	4.05	1.34	0.01	1.21
PLATELET COUNT	G/L	Placebo	359	283.80	64.67	-5.15	42.12
		Duloxetine	561	280.68	60.94	5.58	42.19

N = Number of patients with a baseline and at least one non-missing post-baseline measurement.

SD = standard deviation

Modified from Applicant's Table, Pages 94 - 95, Clinical Safety Summary

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Changes in chemistry analytes detected when analyzing shifts from normal to abnormal were similar to the changes seen from baseline to endpoint. Again, increases liver function tests were observed (e.g., AST, ALT, and ALKPH). However, also found to be slightly elevated were bicarbonate, CPK, Cholesterol, and GGT. These changes were small and of unknown clinical significance. For additional information, see Appendix 10.4, Table 7.5.

Hematology analytes followed a similar pattern to the one seen in changes from baseline to endpoint, as eosinophils and platelets were again found to be slightly elevated. Additionally, MCH was mildly elevated. For more information, see Appendix 10.4, Table 7.6.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Continuing the trend described above, an evaluation of chemistry outliers, finds that more subjects treated with duloxetine developed elevated liver function tests, including ALKPH, AST, and ALT. In addition, there were more duloxetine-treated patients who developed elevated CPK. See Appendix 10.4, Table 7.7 for more information on individual laboratory values.

For hematology analytes, there were no obvious trends to describe outliers and dropouts. For more information see Appendix 10.4, Table 7.8.

7.1.7.4 Additional analyses and explorations

For more information on hepatic toxicity, see Section 7.1.3.3.2, Hepatotoxicity.

7.1.7.5 Special assessments

Not applicable.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

The applicant's primary analysis of vital signs and weight focused on change from baseline to endpoint and for potentially clinically significant changes at any time and at endpoint. Sustained elevation of blood pressure was defined as a diastolic blood pressure ≥ 90 mmHg and increase from baseline ≥ 10 mmHg for 3 consecutive visits or a systolic blood pressure ≥ 140 mmHg and increase from baseline ≥ 10 mmHg for 3 consecutive visits.

Blood pressure and heart rate were measured during screening and again at weekly visits for the entirety of the trials. Weight was measured at screening and again at each weekly visit.

Duloxetine has known effects on blood pressure that are described on the label. "In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases

of up to 2.1 mmHg in systolic blood pressure and up to 2.3 mmHg in diastolic blood pressure.” Additionally, at higher doses there are also small increases in heart rate.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

All fibromyalgia placebo-controlled studies were used for the analysis of vital signs.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

As mentioned above, duloxetine has known effects on heart rate and blood pressure. The results of these effects are of unknown clinical significance and are likely due to duloxetine’s norepinephrine reuptake inhibition. A mean change in pulse of 1.22 beat per minute was seen for duloxetine-treated patients at end of therapy. Diastolic blood pressure was noted to have a mean rise of 0.91 mmHg and systolic blood pressure 1.04 mmHg. The small rise in heart rate and blood pressure is likely due to lower doses administered to patients in fibromyalgia studies compared to studies for other indications, possibly suggesting a dose-response effect of undetermined significance. For more information see Table 7.21 below.

Weight was noted to decrease an average of 0.43 kg at endpoint in the placebo-controlled trials.

Table 7.21 Vital Signs and Weight Change from Baseline to Endpoint – All Randomized Patients in Fibromyalgia Placebo-Controlled Trials						
Vital	Therapy	N	Baseline		Change to Endpoint	
			Mean	SD	Mean	SD
Pulse	Placebo	527	73.32	9.89	-0.42	9.45
	Duloxetine	855	73.68	9.74	1.22	10.55
Sitting Diastolic BP	Placebo	527	122.48	14.93	-1.58	13.23
	Duloxetine	855	122.31	15.34	0.91	14.69
Sitting Systolic BP	Placebo	527	76.68	9.15	-1.17	8.85
	Duloxetine	855	76.44	8.93	1.04	9.21
Weight(Kg)	Placebo	499	77.94	18.24	0.28	2.39
	Duloxetine	823	79.93	19.45	-0.43	4.15

Note: N = Number of patients with a baseline and at least one non-missing post-baseline measurement.
 Applicant’s Table, Page 111, Clinical Safety Summary

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Outlier values for heart rate were defined as pulse ≤ 50 and decrease from baseline ≥ 15 beats per minute. For systolic blood pressure, low outliers were ≤ 90 mmHg and decrease from baseline ≥ 20 mmHg and high outliers were ≥ 180 mmHg and increase from baseline ≥ 20. For diastolic blood pressure, low outliers were ≤ 50 mmHg and decrease from baseline ≥ 15 mmHg and high outliers were ≥ 105 mmHg and increase from baseline ≥ 15. Weight low outliers were decrease from baseline ≥ 10% and high outliers were increase from baseline ≥ 10%.

Although there were more duloxetine-treated patients with outlier values for pulse, diastolic blood pressure, and systolic blood pressure the number of patients was small. There were more patients with outlier value of low for weight in the duloxetine-treated group, but again the total number of patients was low. For more information see Appendix 10.4, Table 7.9.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Again, the trend towards outliers for vital signs favors elevations in pulse and blood pressure. The total number of marked outliers for vital sign abnormalities was low.

7.1.8.4 Additional analyses and explorations

Not applicable.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

The duloxetine label states that “no clinically significant differences were observed for QTc, QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients.” Additionally, “a positive-controlled study in healthy volunteers using duloxetine up to 200 mg BID, no prolongation of the corrected QT interval was observed.” In the fibromyalgia studies submitted, there were no new findings with respect to ECG data.

In study HMBO, ECGs were performed at baseline and again week 12. In study HMCA, ECGs were only performed during screening. In study HMEF, ECGs were performed at baseline and again at weeks 13 and 27. In study HMCJ, ECGs were performed at baseline and again at weeks 15 and 28. No ECG data was collected for study HMEH.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

No ECG data was collected for study HMEH, the long-term safety study, and thus the applicant’s analysis of ECGs focuses on the fibromyalgia placebo-controlled studies. As discussed above, duloxetine is associated with a small increase in pulse rate; therefore associated changes in ECG are expected (decrease in PR and QRS).

The applicant assessed ECG data for changes from baseline to endpoint in PR, QRS, QT, and corrected QT. ECG data was also analyzed for incidence of treatment-emergent potentially clinically significant values, incidence of treatment-emergent abnormal values, and incidence of changes in QTcF, which was defined as increase < 30 msec, increase \geq 30 msec but < 60 msec, increase \geq 60 msec at any time, and incidence of QTcF \geq 500 msec at any time.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

As mentioned previously, there was a mean increase in heart rate at endpoint for duloxetine-treated patients with concomitant decreases in PR and QRS (see Table 7.22 below). However, there was no difference in change of QTc between treatment groups at endpoint.

Table 7.22 Electrocardiogram Intervals and Heart Rate Change from Baseline to Endpoint All Randomized Patients in Fibromyalgia Placebo-Controlled Trials						
ECG Parameters	Therapy	N	Baseline		Change to Endpoint	
			Mean	SD	Mean	SD
HR	Placebo	354	67.73	9.91	-0.01	8.29
	Duloxetine	545	68.16	9.26	3.50	9.12
PR	Placebo	354	156.60	21.74	1.03	12.18
	Duloxetine	545	155.27	21.13	-3.30	12.82
QRS	Placebo	354	94.34	11.02	0.40	7.83
	Duloxetine	545	95.76	11.24	-0.33	8.03
QT	Placebo	354	399.22	28.19	1.69	22.35
	Duloxetine	545	398.13	27.14	-5.27	23.18
QTcB	Placebo	354	421.29	20.36	1.92	16.29
	Duloxetine	545	421.81	20.37	4.83	17.41
QTcF	Placebo	354	413.59	18.52	1.87	14.64
	Duloxetine	545	413.63	19.04	1.26	15.13

N = Number of patients with a baseline and at least one non-missing post-baseline measurement.
 Modified from Applicant's Table, Page 119, Clinical Safety Summary

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

There were no obvious differences between treatment groups in incidence of abnormal values. For more information, see Appendix 10.4, Table 7.11.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

There were no obvious differences between treatment groups with respect to incidence of marked outliers and dropouts. For more information, see Appendix 10.4, Table 7.12.

7.1.9.4 Additional analyses and explorations

Not applicable.

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

No new carcinogenicity studies were performed during the fibromyalgia development program. Previous studies mentioned in the duloxetine label found that in female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose) there was an increase incidence of hepatocellular adenomas and carcinomas. No effects were seen at 50 mg/kg/day (4 times the maximum recommended human dose and 2 times the human dose of 120 mg/day). Also, in vitro studies did not find duloxetine to be mutagenic, clastogenic, or genotoxic.

7.1.12 Special Safety Studies

No additional duloxetine safety studies were performed during the fibromyalgia development program.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Duloxetine is not a controlled substance and the product label states that animal studies have not indicated that there is any abuse potential. However, withdrawal symptoms are common after abrupt discontinuation and adverse event data from the fibromyalgia studies indicates that withdrawal symptoms may occur even with tapered discontinuation. For more information on withdrawal, see section, 7.1.3.3.8, Withdrawal Symptoms.

7.1.14 Human Reproduction and Pregnancy Data

Pregnancy Category C has been assigned to duloxetine. When administered to rats and rabbits during organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the maximum recommended human dose). However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg (2 times the maximum recommended human dose).

7.1.15 Assessment of Effect on Growth

Safety and efficacy in pediatrics has not been established. However, duloxetine is generally associated with weight loss and the label states that adults treated with duloxetine for up to 10-weeks experienced a mean weight loss of approximately 0.5 kg.

7.1.16 Overdose Experience

There is limited clinical experience with duloxetine overdose in humans. The product label states that in clinical trials, there were cases of acute ingestions up to 3 grams, alone or in combination with other drugs, none of which were fatal. However, in post-marketing experience, there have been reports of fatal outcomes with acute ingestion of doses lower than 3 grams. Signs and symptoms of overdose, at doses as low as 1000 mg, include serotonin syndrome, somnolence, vomiting, and seizures. However, most of these events involve polypharmacy.

7.1.17 Postmarketing Experience

Duloxetine for [redacted] of fibromyalgia has not been approved in any other country. However, duloxetine has been approved and marketed in the United States since August 3, 2004 and post-marketing experience from use in other indications is also available.

At the time of NDA filing, all fibromyalgia studies were complete. Periodic Safety Update Reports for duloxetine are completed every 6 months as of 3/8/2004. As of 9/28/2007, a total of 6 PSURs have been completed, representing six 6-month periods. For a listing of major regulatory actions taken for safety reasons since the original approval of Cymbalta (August 2004) through 5/2/2007, see Appendix 10.4, Table 7.19.

Exposure

To provide the best estimate of patient exposure, the combines several sources of data including, but not limited to: Intercontinental Marketing Services (IMS) Health prescription audit data, IMS National Disease and Therapeutic Index (NDTI) data, and internal bulk sales data. Worldwide, there are a total of [redacted] exposures, which constitute [redacted] patient-years of exposure.

Adverse Events

Based on spontaneous reporting, the most common events reported from 8/3/2004 – 5/2/2007 were nausea (3265), dizziness (1749), insomnia (1411), headache (1405), fatigue (1238), feeling abnormal (1113), hyperhidrosis (1095), somnolence (1086), diarrhea (1005), drug ineffective (958), vomiting (955), anxiety (872), tremor (847), constipation (674), dry mouth (615), weight increased (540), and blood pressure increased (531).

The most common system organ classes (SOC) affected were psychiatric disorders (9180), nervous system disorders (8951), gastrointestinal disorders (8767), general disorders and administration site conditions (7409), investigations (3346), and skin and subcutaneous tissue disorders (3061).

Drug Interactions

Through the most current PSUR cut-off date, 8/2/2008, there have been 163 drug interactions reported for duloxetine. The most common reported drug interactions have been warfarin (7.4%), venlafaxine (3.7%), and mirtazapine (3.7%). Study FIJ-MC-HMFP, a study of the effect of duloxetine on the pharmacodynamics of warfarin, is ongoing.

Overdosage

The approved product label relates the most recent data on overdosage, for more information, see Section 7.1.16, Overdose Experience.

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Special Topics

Hepatotoxicity: There have been a total of 622 reports of hepatic-related adverse events (reporting rate: 0.007%) and 325 of these were related to isolated enzyme elevations (52.3%). Although no fatalities have been definitively attributed to duloxetine, there have been 8 cases of severe hepatic injury that were probably attributed to duloxetine. Of the 91 clinically significant cases, 23 met the definition of Hy's rule. For details, see Table 7.23 below. Also see section 7.1.3.3.2 for a description of Dr. Marc Stone's analysis of postmarketing hepatic events.

<i>Clinical Significance Category</i>	<i>Etiologic Classification</i>				<i>Total</i>
	<i>Unlikely</i>	<i>Possible</i>	<i>Probable</i>	<i>Indeterminate</i>	
Fatality	11	2	0	2	15
Hepatic failure	6	8	0	2	16
Severe hepatic injury	12	31	8	9	60

Note: there were no unconfounded cases of hepatic failure and fatalities involving hepatic events associated with duloxetine.
 Applicant's Table, Page 39, Post-marketing Report.

Ongoing pharmacovigilance activities include:

- Study F1J-MC-B021, titled "Hepatic and Cardiovascular Events in Adults Taking Duloxetine Compared with Depressed Treated, Depressed Not Pharmacologically Treated, and Nondepressed Patients in a Large US managed Care Database".
- Targeted questionnaire for follow-up investigation of hepatic events and genotyping of patients
- Quarterly AERS analyses of hepatic adverse events
- Continued assessment of hepatic-related adverse event data and laboratory data at the time of completion of each clinical trial

Suicidality: There have been 877 reports of suicidality and based on patient exposures of approximately _____ patients worldwide as of 5/2/2007, the suicide behavior and ideation rate was 0.01%. The majority of these reports were in psychiatric conditions such as depression (77%) and anxiety (3%). For details, see Table 7.24 below.

<i>Diagnostic Category</i>	<i>Diagnosis Description</i>	<i>Total</i>
1	Completed suicide, fatal	143
2	Suicide attempt, nonfatal	240
3	Preparatory acts towards imminent suicidal behavior	11
4a	Suicidal ideation: active thoughts about killing self	468
4b	Suicidal ideation: passive thoughts about wanting to die	15
		<i>Total: 877</i>

Applicant's Table, Page 41, Post-marketing report.

Ongoing pharmacovigilance activities include:

- General Practice Research Database (GPRD) analysis of suicidality in SUI patients
- Targeted questionnaire for follow-up investigation of suicide-related events
- Active monitoring of suicidal ideation in non-psychiatric indications
- Periodic review of the clinical trial databases and spontaneous AE data for suicidality

Hyperglycemia: As of 2/2/2007, there have been a total of 223 reported events of glucose metabolism disorders (reporting rate 0.0033%). There were no reports of hyperglycemia in patients without a history of diabetes.

Stevens-Johnson Syndrome: There have been 10 cases of Stevens-Johnson Syndrome (reporting rate 0.00011%) and 4 cases of erythema multiforme (reporting rate 0.00005%). There have been no reported cases of Toxic Epidermal Necrolysis.

Renal Failure: There have been 90 cases of renal impairment/failure, at a reporting rate of 0.0013%. Of these, 39 cases had a positive dechallenge and there were no cases of positive rechallenge.

Cardiovascular Events: Hypertensive crisis has rarely been reported (<.01%). There have been 53 cases of myocardial infarction and 37 cases of ventricular fibrillation, none of which were “probably related” to duloxetine.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Section 7.1 describes the studies, summary reports, and databases that were used to evaluate the safety of duloxetine for ~~the~~ of fibromyalgia. During the End of Phase 2 Meeting on July 28, 2004, the Applicant was asked to expose at least 300 patients to the highest dose proposed for at least 6 months and 100 patients for 1 year. Both of these goals were achieved.

7.2.1.1 Study type and design/patient enumeration

See Section 4.1 Tables of Clinical Studies and Section 6.1.3 Study Design for more information on study types and designs.

7.2.1.2 Demographics

There were no significant differences between treatment groups with respect to baseline characteristics. Patients of both genders were enrolled in all studies except HMCA. Overall, the majority of patients were female (95%) and Caucasian (88%). Patients were between the ages of

18 and 83 years, with a mean age of 50.2 years. Fibromyalgia is understood to affect more women than men at a ratio of approximately 9 to 1. See Table 7.25 below for details.

In the long-term study HMEH, the population was similar with a majority of patients being female (96%) and Caucasian (61%). For more information, see Appendix 10.4, Table 7.13.

Therefore, men were somewhat under-represented in the clinical studies compared to their representation in the target population. The total male enrollment was too small to draw definitive conclusions about safety and efficacy in men.

In addition to demographics, patients in all fibromyalgia studies were similar with respect to disease severity, as they were required to meet 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 palpation examination with an approximate force of 4 kg/cm²) and also required to score ≥ 4 on the primary pain severity measures at both screening and baseline for each study.

Studies HMBO, HMCA, and HMCJ were conducted in the United States with Study HMCJ have some sites in Puerto Rico. Study HMEF was conducted in Germany, Spain, Sweden, United Kingdom, and the United States. Study HMEH was conducted in Argentina, Australia, Brazil, Canada, Mexico, Poland, and Taiwan.

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Table 7.25			
Patient Demographics and Baseline Characteristics			
All Randomized Patients in Fibromyalgia Placebo-Controlled Studies			
Variable	PLACEBO (N=535)	DULOXETINE (N=876)	TOTAL (N=1411)
ORIGIN: NO. (%)			
African	13 (2.4%)	20 (2.3%)	33 (2.3%)
Caucasian	463 (86.5%)	771 (88.0%)	1234 (87.5%)
East Asian	3 (0.6%)	3 (0.3%)	6 (0.4%)
Hispanic	51 (9.5%)	76 (8.7%)	127 (9.0%)
Native American	1 (0.2%)	2 (0.2%)	3 (0.2%)
Other	3 (0.6%)	2 (0.2%)	5 (0.4%)
West Asian	1 (0.2%)	2 (0.2%)	3 (0.2%)
AGE: YRS			
No. Patients	535	876	1411
Mean	49.61	50.62	50.24
Median	50.70	51.65	51.46
Standard Dev.	11.32	10.76	10.98
Minimum	18.75	19.13	18.75
Maximum	83.22	82.12	83.22
GENDER: NO. (%)			
Female	509 (95.1%)	829 (94.6%)	1338 (94.8%)
Male	26 (4.9%)	47 (5.4%)	73 (5.2%)
HEIGHT: CM			
No. Patients	534	871	1405
Mean	163.14	163.32	163.25
Median	162.56	162.56	162.56
Standard Dev.	7.49	7.78	7.67
Minimum	127.00	132.08	127.00
Maximum	187.96	198.12	198.12
WEIGHT: KG			
No. Patients	530	872	1402
Mean	78.15	79.71	79.12
Median	76.00	76.27	76.20
Standard Dev.	18.40	19.46	19.08
Minimum	46.76	43.13	43.13
Maximum	156.04	170.10	170.10
Applicant's Table, Page 22, Clinical Safety Summary			

7.2.1.3 Extent of exposure (dose/duration)

In duloxetine placebo-controlled trials for all indications, there were a total of 9445 patients exposed to duloxetine for a mean 63.35 days and 6770 patients exposed to placebo for a mean 66.74 days. Patients assigned to duloxetine reported fewer mean treatment of days on treatment compared to placebo-treated patients. This is likely due to early discontinuations due to adverse events. Overall, study medication exposure in the placebo-controlled studies represented 1638.23 patient-years of exposure to duloxetine and 1237.13 patient-years exposure to placebo.

In combined placebo-controlled and open-label studies, the fibromyalgia patients treated with duloxetine (n=1236), remained on the drug for a mean 168.94 days. Approximately 739 (60%) patients were treated with duloxetine for at least 3 months, 574 (46%) were treated for at least 6 months, and 219 (18%) were treated for one full year.

Placebo-controlled studies of duloxetine for fibromyalgia 876 patients were exposed to duloxetine for a mean of 110.15 days and 535 patients were exposed to placebo for a mean of 105.11 days. In the long-term study HMEH, a total of 350 patients were exposed to duloxetine for a mean 298.3 days and 285.1 patient-years of exposure.

Table 7.26	
Study Drug Exposure	
All Fibromyalgia Study Patients Treated with Duloxetine	
Variable	Duloxetine (N=1236)
Duration of Exposure (Days)	
No. Patients	1236
Mean	168.94
STD	138.84
Maximum	546.00
Median	139.50
Minimum	0.00
Patient years	571.69
Duration of Exposure n(%)	
No. Patients	1236
0	11 (0.9)
>0	1225 (99.1)
≥7	1146 (92.7)
≥14	1095 (88.6)
≥30	1026 (83.0)
≥60	950 (76.9)
≥90	739 (59.8)
≥120	648 (52.4)
≥183	574 (46.4)
≥365	219 (17.7)
N = Number of duloxetine fibromyalgia patients. Patient years calculated as total exposure days/365.25. Applicant's Table, Page 54, Summary of Clinical Safety Appendix	

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary clinical sources were used to evaluate the safety of duloxetine for of fibromyalgia.

7.2.2.1 Other studies

Not applicable.

7.2.2.2 Postmarketing experience

For more information on postmarketing data available, see Section 7.1.17 Postmarketing Experience.

7.2.2.3 Literature

To support the safety claims of duloxetine, the applicant relied on the large safety database that exists for other indications as well as the new safety data in the fibromyalgia studies. The most important safety finding discovered in the fibromyalgia population was the discovery of withdrawal symptoms despite drug tapering. For more information, see Section 7.1.3.3.8, Withdrawal Symptoms.

Slight elevations of liver function tests, a known side-effect of duloxetine, were once again seen in fibromyalgia patients. However, a small difference was noted in the frequency of transaminemia (ALT > 3 x ULN) in the fibromyalgia study population (1.37%) when compared to the overall duloxetine population (1.11%). For more information see Section 7.1.3.3.2, Hepatotoxicity. The applicant cites a review article by William M. Lee, M.D. from the New England Journal of Medicine (July, 2003), that states “for reasons that are unclear, women generally predominate among patients with drug-induced liver injury”.

7.2.3 Adequacy of Overall Clinical Experience

The new fibromyalgia studies submitted for this application add to an extensive safety database for duloxetine. Overall, there appear to be a sufficient number of patients treated for a reasonable amount of time. For details, see Sections 7.2.1.2, Demographics and 7.2.1.3, Extent of Exposure.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable.

7.2.5 Adequacy of Routine Clinical Testing

Clinical testing performed during the submitted fibromyalgia studies included vital signs, physical examination, general hematology, chemistry (including liver function tests), urinalysis, electrocardiograms, and questioning about adverse events (using open-ended questions and questionnaires). For detailed study schedules, see Appendix 10.4, Tables 7.14 – 7.18.

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7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No new interaction studies were conducted to support the application of duloxetine for of fibromyalgia. The applicant states that the pharmacokinetics of duloxetine in major depressive disorder, stress urinary incontinence, and diabetic peripheral neuropathic pain are similar to the similar to the pharmacokinetics seen in fibromyalgia. Drug interactions are well characterized and demonstrate that duloxetine is metabolized by cytochrome P450 1A2 (CYP1A2) and cytochrome P450 2D6 (CYP2D6) and that duloxetine is a moderate inhibitor of CYP2D6. The approved product label states that elimination half-life is approximately 12 hours (range 8 – 17 hours) and pharmacokinetics are dose proportional over the therapeutic range. Steady-state plasma concentrations are generally achieved after 3 days of dosing. Most (about 70%) duloxetine appears in the urine as metabolites and about 20% is excreted in feces. For more information, see Section 5, Clinical Pharmacology.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The primary safety concerns of duloxetine include suicidality, hepatotoxicity, and severe cutaneous reactions. For more information about these topics, see Section 7.1.3.3 Other Significant Adverse Events. Throughout the fibromyalgia studies, screening for these events was appropriate. No new studies were performed to analyze these topics of concern.

7.2.8 Assessment of Quality and Completeness of Data

The applicant's data was adequate to conduct the full safety review. Data sets were appropriately indexed, labeled, and tagged to allow a comprehensive review. Case report forms and patient narratives were easily accessible, generally legible, and complete.

7.2.9 Additional Submissions, Including Safety Update

The initial fibromyalgia sNDA submission included serious adverse events (SAEs) for all completed and ongoing duloxetine studies up to 5/12/2007, and deaths reported prior to 7/14/2007. A four-month safety update was submitted which included SAEs reported through 8/14/2007 and deaths reported prior to 10/15/2007. Data derived from now-completed extension phases of studies HMCJ and HMEF, from a now-completed study of LUTD, and from several ongoing studies (still blinded) were included in the safety update.

Updated duloxetine exposure table for FM is shown below:

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Table 7.27: Duloxetine Exposure

Variable	Duloxetine Original(1,2) (N=1236)	Duloxetine New(3,4) (N=492)	Duloxetine Total(2,5,6) (N=1411)
Duration of Exposure (Days)			
No. Patients	1236	492	1411
Mean	168.91	166.24	204.75
STD	138.86	83.17	159.65
Maximum	546.00	309.00	546.00
Median	139.50	196.00	173.00
Minimum	0.00	0.00	0.00
Patient years	571.60	219.37	790.98
Duration of Exposure n(%)			
No. Patients	1236	492	1411
0	11 (0.890)	1 (0.207)	11 (0.780)
>=0	1225 (99.110)	481 (99.793)	1400 (99.220)
>=7	1146 (92.718)	473 (98.133)	1314 (93.125)
>=14	1095 (88.592)	467 (96.898)	1261 (89.369)
>=30	1026 (83.010)	444 (92.116)	1179 (83.550)
>=60	950 (76.861)	420 (87.137)	1093 (77.463)
>=90	737 (59.628)	398 (82.573)	867 (61.446)
>=120	648 (52.427)	386 (80.083)	775 (54.926)
>=183	574 (46.440)	343 (71.162)	693 (49.114)
>=365	219 (17.718)	0 (0)	460 (32.601)

(1)=EMBO/HMCA/HMEN/HMCJ(Acute)/HMEF(Acute)/HMCM
 (2)=In the original submission, the baseline period for patients who received placebo in Study HMCA and then received duloxetine in Study HMCM was the pre-randomization visits. In this safety update, the baseline period extends through the first visit of Study HMCM, after which patients began receiving duloxetine. Results in this safety update may differ from those in the original submission due to data corrections.
 (3)= HMCJ(Extension)/HMEF(Extension)
 (4)= Includes patients who received placebo during the Acute Phase of Studies HMCJ and HMEF. The baseline period is all visits prior to the Extension Phase for all patients in these studies.
 (5)= EMBO/HMCA/HMEN/HMCJ(Acute & Extension)/HMEF(Acute & Extension)/HMCM
 (6)=Includes patients who received placebo during the Acute Phase of Studies HMCJ and HMEF, for which the baseline period is all visits prior to the Extension Phase. For patients who received duloxetine during the Acute Phase of these studies, the baseline period is all pre-randomization visits.
 N = Number of duloxetine fibromyalgia patients.
 Patient years calculated as total exposure days/365.25.
 Report: RMP_FLJO_SAFZ_Q307(FQEXP11)
 Program: RMP_FLJO_SAFZ_SASPGM_Q307(FQEXP11) Data: RMP_SAS_FLJM_NCSAFESW_Q307ADS

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No deaths in the FM population were reported in the safety update. There were 36 patients who reported one or more SAEs in the additional FM data. One additional case of suicidal ideation was reported. No additional cases involving hepatotoxicity or serious skin reactions were reported. One additional case of study drug discontinuation due to liver function test abnormality was reported, as well as 6 additional reports of “potentially clinically significant” ALT and AST values and 7 additional cases of potentially clinically significant GGT values.

Two cases of hyperglycemia were reported as SAEs, and Lilly notes that “The EU SPC for duloxetine lists hyperglycaemia as occurring “especially in diabetic patients”.”

The safety update also provided a list of verbatim reasons for study discontinuation in patients listed as discontinuing for physician, patient, or sponsor decision. Notable among these were several patients who discontinued due to adverse events or lack of efficacy but were mis-coded:

Table 7.28: Reasons for Discontinuation

HMBO	DLX	MD	“...discontinued at physician request. Elevated liver enzyme results were the reason for the request”
HMBO	DLX	Subject	narrative reports insomnia
HMCA	DLX	MD	“Pt could not tolerate side effects of study drug from 2 hours p 1 st dose. Investigator decision to withdraw pt from study”
HMCA	DLX	Subject	“Subject called and stated she stopped study medication after one day due to side effects”
HMCJ	DLX	Subject	“Pt fees depression is getting worse”
HMCJ	DLX	Subject	“Accumulation of all side effects”
HMEF	PLA	Subject	“concern increased creatinine”
HMEF	PLA	Subject	“feels drug is ineffective”
HMEH	DLX	Subject	“rash plus moving out of area”
HMEH	DLX	Subject	“no improvement”
HMEH	DLX	Subject	“adverse reactions”
HMEH	DLX	Subject	“felt TIA to be related to drug”

However, the most common verbatim explanation for subject decision to drop out of the study protocol was a wish to continue on Cymbalta rather than to taper off as required by the protocol.

The mis-classifications above would not materially affect the assessment of the safety or efficacy of the drug, as the events leading to discontinuation have already been identified as duloxetine-related.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Aside from withdrawal symptoms despite a tapered withdrawal, there were no new findings regarding the safety of duloxetine. The subjective withdrawal data gathered during the fibromyalgia studies is likely sufficient to support a labeling change related to withdrawal symptoms. The current label states:

For more information regarding proposed labeling, see Section 9.4, Labeling Review.

7.4 General Methodology

Methodology for analysis of efficacy is discussed in Section 6.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The rationale of pooling data for the safety analyses is discussed in Section 7.1.

7.4.1.2 Combining data

See Section 7.1.

7.4.2 Explorations for Predictive Factors

Except for neuropsychiatric adverse events (i.e. suicidality), adverse event rates were consistent among the different populations.

7.4.2.1 Explorations for dose dependency for adverse findings

These relationships, if present, are discussed individually for the observed adverse events.

7.4.2.2 Explorations for time dependency for adverse findings

See Section 7.1.5.6, Additional analyses and explorations.

7.4.2.3 Explorations for drug-demographic interactions

Most patients with fibromyalgia are white females. Although males were recruited into all fibromyalgia studies except for study HMCA, the total number of male patients is very small, therefore, safety explorations in this demographic are not practical with the current sample size. For more information, see Section 7.2.1.2 Demographics.

7.4.2.4 Explorations for drug-disease interactions

Duloxetine is used as first line therapy for major depressive disorder and approximately half of all patients with fibromyalgia suffer from major depressive disorder. Subtle drug-disease interactions may therefore be difficult to assess with the current fibromyalgia safety database.

7.4.2.5 Explorations for drug-drug interactions

A study of warfarin-duloxetine interactions is ongoing. For more information on drug-drug interactions, see Section 5, Clinical Pharmacology.

7.4.3 Causality Determination

For a discussion of important adverse events that are presumably related to duloxetine, see Section 7.1.3.3, Other significant adverse events.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The clinical trials focused on doses of 60 mg/day and 120 mg/day (given either as a single dose or in divided doses of 60 mg BID). Analysis of the efficacy results suggest that there is little advantage for the 120 mg/day dose over the 60 mg/day dose, and one study which specifically explored whether non-responders at 60 mg/day would respond if up-titrated to 120 mg/day did not demonstrate a benefit of this up-titration. Thus, because duloxetine has a number of concerning toxicities, some of which seem to have some dose-dependency, it seems prudent to recommend a dose of 60 mg/day for all patients, without up-titration.

Different titration regimens were explored in the efficacy studies, with titrations as short as 3 days to reach 60 mg BID and as long as two weeks. Titrations to the recommended dose, 60 mg QD, were either none at all (HMCA) or one week. The table below illustrates the improvement in the rate of dropout due to adverse events when a one-week titration is used. Therefore, the recommended dosing regimen would be 30 mg/day for one week, followed by titration to 60 mg/day.

	Length of titration	Placebo	DLX 60 QD
HMCA	None	14/120 (12%)	25/118 (21%)
HMCJ (first three months)^a	One week	17/144 (12%)	22/150 (15%)
HMEF (first 8 visits)^b	One week	14/168 (8%)	23/162 (14%)
HMEH (open-label phase)	One week		26/350 (7%)

^aAfter three months, patients on 20 mg were changed to 60 mg QD
^bAfter the first 8 visits, non-responders could be titrated upwards to 120 mg QD
(table constructed from sponsor's study reports)

Additionally, it must also be noted that the study which evaluated a 20 mg/day dose yielded very promising results. Although Lilly's own analysis does not support the efficacy of this dose, other analytic approaches employed by Dr. Buenconsejo suggest that this dose may well be useful in the treatment of FM. Lilly should be asked to conduct at least one additional study of a lower dose of duloxetine (20-30 mg) to explore whether the risk/benefit profile can be enhanced by using a lower dose of drug.

8.2 Drug-Drug Interactions

The Cymbalta labeling notes the potential for drug-drug interactions with inhibitors of CYP1A2, inhibitors of CYP2D6, MAO inhibitors, and other serotonergic drugs.

8.3 Special Populations

Dosing considerations based on race, gender, age, hepatic function, and renal function are already included in Cymbalta labeling. Information on the presence of duloxetine in breast milk is also included in labeling. Adverse effects on embryo/fetal and postnatal development have been identified in animal reproduction studies. Nevertheless, given the demographics of the FM population, use in pregnant women may be anticipated. Further evaluation of the safety of duloxetine in pregnant women (using, for example, a registry) would be beneficial.

8.4 Pediatrics

The Applicant has submitted a waiver requesting not to study duloxetine in children with fibromyalgia. However, fibromyalgia is diagnosed in children and adolescents and these populations present an unmet medical need. Therefore, the waiver request not to conduct studies in the pediatric age group should be denied.

8.5 Advisory Committee Meeting

No advisory meeting was held for this application.

8.6 Literature Review

Not conducted.

8.7 Postmarketing Risk Management Plan

No postmarketing risk management strategies beyond labeling seem necessary for this supplemental indication.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

My review of the data submitted by Lilly to support this application demonstrates that duloxetine hydrochloride is an effective treatment for fibromyalgia at doses of 60 mg QD and 120 mg QD. There is no evidence that doses higher than 60 mg/day improve efficacy and due to possible dose-related hepatotoxicity, at this time, I only recommend approval of the 60 mg/day dose for — of fibromyalgia.

9.2 Recommendation on Regulatory Action

I recommend approval of NDA 22-148, duloxetine for _____ of fibromyalgia.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No specific postmarketing risk management activities, or restricted distribution schemes are indicated at this time. Duloxetine is expected to have minimal abuse potential.

9.3.2 Required Phase 4 Commitments

Lilly should conduct an additional, adequately powered study to evaluate duloxetine at a dose of 20 mg QD or 30 mg QD.

9.4 Labeling Review

For more information, see Appendix 10.2 Line-by-Line Labeling Review.

9.5 Comments to Applicant

No additional comments for the Applicant at this time.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Protocol F1J-MC-HMCA

Title: Duloxetine Versus Placebo in the Treatment of Fibromyalgia Patients With or Without Major Depressive Disorder

10.1.1.1 Objective/Rationale

The primary objective was to assess the efficacy of duloxetine 60 mg twice daily (BID) compared with placebo on the reduction of pain severity as measured by the average pain item of the Brief Pain Inventory (BPI) during a 12-week, double-blind, acute therapy phase in women with American College of Rheumatology (ACR)-defined primary fibromyalgia, with or without major depression.

Secondary objectives included evaluating duloxetine 60 mg once daily (QD) compared with placebo on the reduction of pain severity as measured by the average pain item of the BPI; evaluating the efficacy of duloxetine 60 mg QD and 60 mg BID compared with placebo on a number of other pain measures, including patient-reported measures; assessing the relationship of depression and mood enhancement with pain reduction; and assessing the safety of duloxetine 60 mg QD and 60 mg BID compared with placebo.

10.1.1.2 Overall Design

The study was a multi-center, double-blind, placebo-controlled, randomized clinical trial designed to assess the efficacy and safety of duloxetine 60 mg once daily (QD) and 60 mg twice daily (BID) in comparison to placebo for the treatment of Fibromyalgia syndrome. The study included a 1-week screening phase, a 12-week acute therapy phase, and a 1-week discontinuation phase.

10.1.1.3 Population and Procedures

10.1.1.3.1 Inclusion/Exclusion Criteria

Planned enrollment was approximately 345 female subjects randomized 1:1:1 to each of three treatment arms:

- Placebo
- duloxetine 60 mg QD
- duloxetine 60 mg BID

To be eligible, subjects were required to meet the following criteria:

- Female outpatients > 18 years of age.
- Met criteria for primary fibromyalgia as defined by the ACR: widespread aching pain in all four 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/cm².
- Score of ≥ 4 on the average pain item of the Brief Pain Inventory (BPI) at Visit 2.

Subjects were to be excluded for:

- Any current primary *Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV)* Axis I diagnosis other than MDD, including a current diagnosis of dysthymia (as assessed by the Mini International Neuropsychiatric Interview (MINI) or diagnosed within the past year).
- Any current or previous DSM-IV Axis I diagnosis of psychosis, bipolar disorder, or schizoaffective disorder.
- Had any primary DSM-IV Axis I diagnosis of anxiety disorder *within the past year* (including panic disorder, agoraphobia without a history of panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, generalized anxiety disorder, and social phobia). **Note:** Patients with specific phobias may participate in the study.
- Any DSM-IV Axis II disorder which, in the judgment of the investigator, would interfere with compliance with the study protocol.
- Judged clinically to be at serious suicidal risk.
- History of substance abuse or dependence within the past year, excluding nicotine and caffeine.
- A positive urine drug screen for any substances of abuse or excluded medication. **Note:** If the patient had a positive drug screen at Visit 1 for an excluded prescribed or over-the-counter (OTC) medication that may not have had an adequate wash-out period, a retest was performed prior to Visit 2. If the retest was positive for the parent compound, the patient was excluded.
- Women who were pregnant or breast-feeding.
- Women with pain symptoms related to traumatic injury, structural rheumatic disease, or regional rheumatic disease (such as osteoarthritis, bursitis, tendonitis) that would interfere with interpretation of outcome measures.
- A confirmed current or previous diagnosis of rheumatoid arthritis, inflammatory arthritis, or infectious arthritis, or an autoimmune disease (for example, systemic lupus erythematosus).
- Any of the following laboratory values at Visit 1:
 - An abnormal C-Reactive Protein level (per Lilly reference ranges) that is indicative of autoimmune disease.
 - Antinuclear Antibody (ANA) with a dilution >1:160.
 - Rheumatoid factor > 15 IU/mL.
- Women who, in the opinion of the investigator, were treatment refractory or may have had response compromised by disability compensation issues.

- Serious or unstable cardiovascular, hepatic, renal, respiratory, or hematologic illness, symptomatic peripheral vascular disease, or other medical condition (including unstable hypertension and not clinically euthyroid) or psychological conditions that in the opinion of the investigator would have compromised participation or been likely to lead to hospitalization during the course of the study.
- At Visit 1, alanine aminotransferase (ALT) >1.5 times upper limit of normal (ULN), based on Lilly reference ranges.
- Were taking any excluded medications listed in the protocol attachment (Section 16.1; Protocol, Protocol Attachment HMCA.4) that could not be discontinued at Visit 1.
- Treatment with a monoamine oxidase inhibitor within 14 days prior to Visit 2.
- Treatment with fluoxetine within 30 days prior to Visit 2.
- Women with frequent or severe allergic reactions to multiple medications.
- Women with abnormal thyroid-stimulating hormone (TSH) concentrations.
- Were investigator site personnel directly affiliated with the study, or are immediate family of investigator site personnel directly affiliated with the study. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.
- Were employed by Lilly (that is, employees, temporary contract workers, or designees responsible for the conduct of the study).
- Immediate family of Lilly employees may participate in Lilly-sponsored clinical studies, but are not permitted to participate at a Lilly facility. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
- Received treatment within the last 30 days with a drug that had not received regulatory approval for any indication at the time of study entry (Visit 1).
- Had previously completed or withdrawn from this study or any other study investigating duloxetine or had previously been treated with duloxetine. (Note: Patients that had been previously screened for a duloxetine study other than this study and never received study drug were eligible for this study if they met all current entry criteria.)
- **Note:** Women previously diagnosed with hypothyroidism who had been treated on a stable dose of thyroid supplement for at least the past 3 months, had medically appropriate TSH concentrations (on replacement therapy the TSH value may be below the reference range), and were clinically euthyroid could participate in the study.

10.1.1.3.2 Procedures

The protocol described three study phases: a screening phase, an acute therapy phase, and a discontinuation phase.

A schematic diagram illustrates these phases:

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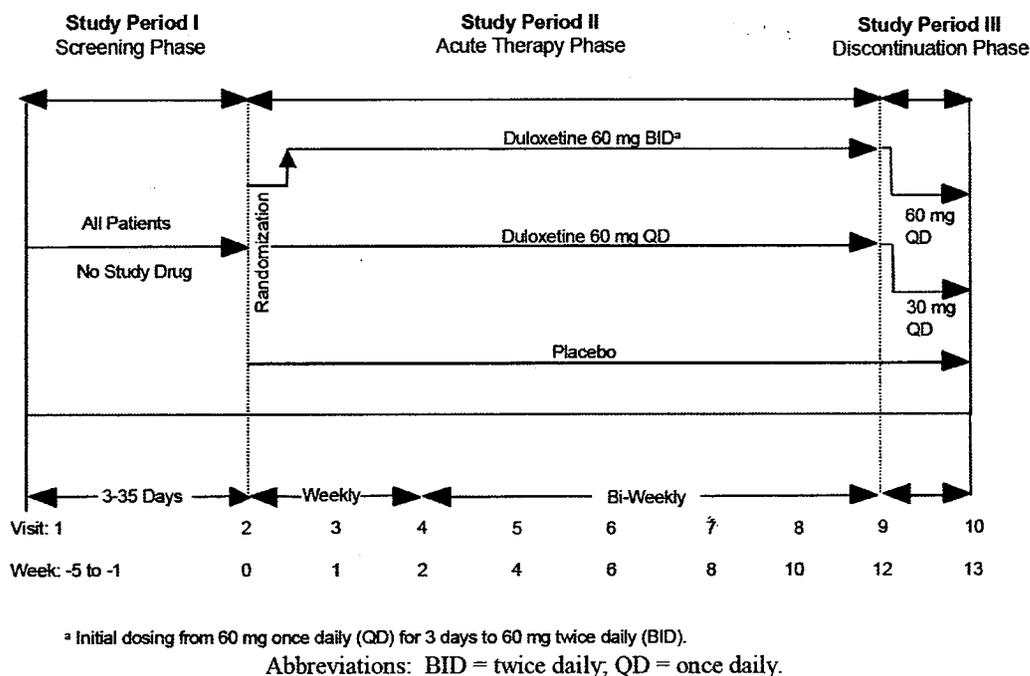


Figure HMCA.9.1. Illustration of study design for Study F1J-MC-HMCA.

Screening phase: Study Period I was a 1-week screening phase; during this period, no study drug was to be dispensed and patients were to be screened for study entry eligibility. Visit 1 entailed patient history, screening tests, electrocardiogram (ECG), assessment of ACR criteria, laboratory analyses (clinical chemistry, hematology, urinalysis, urine drug screen, and pregnancy test for all females). Visit 2 was to occur 3-9 days after Visit 1; at this visit, patients deemed eligible per Visit 1 screening results were to be enrolled.

Acute therapy phase: Eligible patients were to be randomized to double-blind treatment for 12 weeks in Study Period II (acute therapy phase). Patients randomly assigned to the placebo group or the 60 mg QD group were provided their assigned dose for 12 weeks. Patients assigned to the 60 mg BID group were provided with duloxetine 30 mg QD for the first 3 day, followed by duloxetine 60 mg BID for the remaining time of the 12 weeks.

Discontinuation phase: Study Period III was to be a 1-week double-blind discontinuation phase in which patient were to have their dosage reduced between Visit 9 and Visit 10. Patients randomized to duloxetine 60 mg QD were to be dosed with 30 mg QD for 4 days, patients randomized to duloxetine 60 mg BID were to be dosed with 60 mg QD for 4 days and both groups would then take placebo until Visit 10. Patient randomized to placebo were to continue on placebo but appear to be tapered during this time.

10.1.1.3.2.1 Dosing

As described above, eligible subjects were to be randomized to treatment with placebo, duloxetine 60 mg once daily (QD), or duloxetine 60 mg twice daily (BID) in the ratio of 1:1:1.

Randomization was to occur at Visit 2, with assignment to treatment groups determined by a computer-generated random sequence using an Interactive Voice Response System (IVRS). Patients were to be stratified for presence or absence of MDD, with each stratum (depressed and non-depressed) randomly assigned within sites to achieve a relative balance across treatments.

Study drug treatments included:

- 30-mg capsules of duloxetine enteric-coated pellets,
- Placebo capsules identical in appearance to duloxetine capsules.

Study drug was to be dispensed to patients at the study site, packaged in blister cards or in bottles containing additional capsules to allow for sufficient study medication in case of late study visits. Patients were instructed to take their first dose of study drug the morning after Visit 2. They were instructed to swallow the study drug whole and not to crush or break the capsules. Throughout the study patients were to take 2 capsules in the morning and 2 capsules in the evening.

The dosing regimen for each treatment arm is illustrated in the table below:

Treatment	Study Period	Dosage and Frequency ^a	Stage Duration	Packaging
Placebo	Acute Phase	2 placebo capsules BID	12 weeks	Blister cards
	Discontinuation Phase	2 placebo capsules BID	1 week	Blister cards
Duloxetine 60 mg QD	Acute Phase	2 duloxetine 30 mg capsules in AM and 2 placebo capsules in PM	12 weeks	Blister cards
	Discontinuation Phase	1 duloxetine 30 mg capsules and 1 placebo capsule in AM and 2 placebo capsules in PM x 4 days, then 2 placebo capsules BID x 3 days	1 week	Blister cards
Duloxetine 60 mg BID	Acute Phase	2 duloxetine 30 mg capsules in AM and 2 duloxetine 30 mg capsules in PM	12 weeks	Blister cards
	Discontinuation Phase	2 duloxetine 30 mg capsules in AM and 2 placebo capsules in PM x 4 days, then 2 placebo capsules bid x 3 days	1 week	Blister cards

a) Patients in all groups will take 2 capsules twice daily.

10.1.1.3.2.2 Schedule of Visits and Assessments

The overall study schematic is illustrated in the figure below.

Table HMCA.9.2. Study Schedule

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase							Study Period III Discontinuation Phase	
	1	2	3	4	5	6	7	8	9	10	ED <V10
Week	-5 to -1	0	1	2	4	6	8	10	12	13	
Clinical Assessments											
Informed consent	x										
Demographics	x										
Medical history	x										
Complete physical exam	x									x	x
Consumptive habits		x									
Historical illness and previous medications	x ^a										
ACR Criteria for Fibromyalgia	x										
Mini ^b (MDD diagnosis and others)	x										
Height		x									
Weight		x							x		x
ECG	x										
Patient summary										x	x
Blood pressure (sitting), heart rate	x	x	x	x	x	x	x	x	x	x	x
Preexisting conditions and adverse events	x ^a	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x ^a	x	x	x	x	x	x	x	x	x	x
Study Drug											
Dispense drug		x	x	x	x	x	x	x	x		
Return drug/accountability			x	x	x	x	x	x	x	x	x

(continued)

Table HMCA.9.2. Study Schedule (concluded)

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase							Study Period III Discontinuation Phase	
	1	2	3	4	5	6	7	8	9	10	ED <V10
Week	-5 to -1	0	1	2	4	6	8	10	12	13	
Efficacy Measurements											
FIQ		x	x	x	x	x	x	x	x		x
Tender point pain threshold ^b		x			x		x		x		x
CGI-Severity ^c		x			x		x		x		x
PGI-Improvement					x		x		x		x
Brief Pain Inventory		x	x	x	x	x	x	x	x		x
HAMD ₁₇ ^b		x			x		x		x		x
Health Outcomes Assessment											
SF-36		x							x		x
QLDS		x							x		x
SDS		x							x		x
Laboratory Assessments											
Hematology	x										
Clinical chemistry and electrolyte group	x	x			x		x		x		x
Urine drug screen	x										
Serum pregnancy test	x										
Urinalysis	x										
Thyroid function test	x										
Antinuclear antibody	x										
C-reactive protein	x								x		x
Rheumatoid factor	x										

x = Performed at this visit.

Abbreviations: ACR = American College of Rheumatology; CGI-Severity = Clinical Global Impressions of Severity; ECG = Electrocardiogram; ED = early discontinuation; FIQ = Fibromyalgia Impact Questionnaire; HAMD₁₇ = Hamilton Depression 17-item scale; MDD = major depressive disorder; MINI = Mini International Neuropsychiatric Interview; PGI-Improvement = Patient Global Impressions of Improvement; QLDS = Quality of Life Depression Scale; SDS = Sheehan Disability Scale; SF-36 = Medical Outcomes Study Short Form-36; V = visit.

- a Recorded on Source document at Visit 1 and entered on CRF at Visit 2.
- b Qualified study personnel, as defined in Lilly training materials, must perform these assessments.
- c A study physician must administer the CGI-Severity in the presence of the patient or after having been in the presence of the patient.

10.1.1.4 Evaluations/Endpoints

Primary Efficacy Measures

- The Brief Pain Inventory (BPI) (severity and interference scores) is a self-reported scale that measures the severity of pain and the interference of pain on function. The severity scores range from 0 (no pain) to 10 (pain as bad as you can imagine). There are four questions assessing the severity for worst pain, least pain, and average pain in the past 24 hours, and pain right now. The interference scores range from 0 (does not interfere) to 10 (completely interferes). There are seven questions assessing the interference of pain in the past 24 hours for general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life.
- The average pain score collected by the BPI is used as the primary efficacy measure, while the rest of the BPI scores are considered secondary.

Secondary Efficacy Measures

- The Fibromyalgia Impact Questionnaire (FIQ) is a self-administered questionnaire that measures fibromyalgia patient status, progress, and outcomes over the past week. This questionnaire was designed to measure the components of health status that are believed to be most affected by fibromyalgia. The FIQ is composed of a total of 20 items; the first 11 items measure physical functioning, and each item is rated on a 4-point Likert-type scale. Items 12 and 13 measure the number of days the patient felt well and the number of days the patient felt unable to work due to their fibromyalgia symptoms. Items 14 through 20 are numerical, 11-point Likert-type scales (marked in 10-mm increments) on which the patient rates work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression. Because some patients may not do some of the tasks listed, they are given the opportunity of deleting items from scoring. The total score ranges from 0 to 80 (see the protocol for the detailed algorithm for calculating the total score). A higher score indicates a more negative impact.
- The Tender Point Pain Threshold was assessed for all 18 tender points by a study physician or qualified study personnel, as defined in Lilly training materials. A dolorimeter (algometer) was used to exert the pressure at each point and to measure the threshold reading; when the patient first indicated pain, the threshold was recorded in kg/cm².
- The Clinical Global Impressions of Severity (CGI-Severity) scale evaluates the severity of illness at the time of assessment. The score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). The CGI-Severity must be administered by a study physician in the presence of the patient or after having been in the presence of the patient.
- The Patient Global Impressions of Improvement (PGI-Improvement) scale was completed by the patient and measures the degree of improvement at the time of assessment. The score ranges from 1 (very much better) to 7 (very much worse).

- Hamilton Depression Rating Scale (HAM-D17) is a widely used observational rating measure of depression severity. This must be completed by a Lilly-approved rater. The HAM-D17 will be used to assess the severity of depression and its improvement during the course of therapy. The HAM-D17 total score ranges from 0 (not at all depressed) to 52 (severely depressed).

Health Outcome Measures

- The Quality of Life in Depression Scale (QLDS), the Short Form 36 (SF-36), and the Sheehan Disability Scale were used to assess health outcomes.
- The QLDS was used to assess the patient's quality of life. This patient-rated scale, designed specifically for use with MDD patients, consists of 34 yes/no questions.
- The SF-36 was completed by the patient to measure how the patient perceived general health status. The SF-36 consists of 36 items that calculate eight health domains (subscales): bodily pain, general health, mental health, physical functioning, role-physical, role-emotional, social function, and vitality. Two summary scores are also derived from the 36 items to represent a physical and mental component summary.
- The patient-rated Sheehan Disability Scale was used to assess the patient's general level of disability. The scale measures a patient's evaluation of the degree to which his or her symptoms have disrupted work, social, and/or home life.

Safety Measures

- Adverse Events: During the study, adverse events were collected at every visit, regardless of relationship to study medication. These events were captured as actual terms and coded to Medical Dictionary for Regulatory Activities (MedDRA) terms by blinded Lilly clinical personnel.
- Discontinuations: If a patient's dosage was reduced or treatment was discontinued as a result of an adverse event, study site personnel clearly documented the circumstances and data leading to any such dosage reduction or discontinuation of treatment, using the CRF.
- Concomitant Medications: All concomitant medications taken during the study were recorded.
- Laboratory Data: During the study, standard laboratory tests, including chemistry, hematology, and urinalysis panels, were collected at regular intervals. A urine drug screen, thyroid function test, and pregnancy test (if applicable) were completed at screening.
- Vital Signs: During the study, vital signs, including sitting blood pressure (systolic and diastolic) and heart rate, weight, and height, were collected at regular intervals.
- Electrocardiograms (ECGs): An ECG was collected at screening only to determine eligibility of the patient for entry into the study.

10.1.1.5 Statistical Plan

Efficacy Analyses

The main interest of the study was to evaluate the efficacy of each duloxetine treatment group, especially 60 mg BID versus placebo in the treatment of pain due to fibromyalgia. Therefore, statistical inferences regarding efficacy focused on the pairwise comparisons between each duloxetine treatment group and placebo.

The primary efficacy measure was the BPI average pain score and the primary efficacy analysis was to test the null hypothesis that the differences on the baseline-to-endpoint change scores for the BPI average pain score between duloxetine 60 mg BID and placebo treatment groups is zero, after accounting for differences in baseline scores.

The null hypothesis was tested by a pairwise contrast from an ANCOVA model, with the terms of treatment, investigator, treatment-by-investigator interaction, and baseline scores. Treatment-by-investigator was tested at a significance level of 0.10. When the interaction was not statistically significant, treatment was evaluated using the model without the interaction term.

10.1.1.6 Results

10.1.1.6.1 Study Conduct/Outcome

10.1.1.6.1.1 Subject Characteristics

The Applicant screened 746 women and planned to enroll a total of 345 patients who met entry criteria. A total of 120 were assigned to placebo, 116 to duloxetine 60 mg BID and 118 to duloxetine 60 mg QD.

10.1.1.6.1.2 Enrollment by Center

Enrollment was distributed among centers as listed in the table below:

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Table HMCA.10.2. Patient Allocation by Investigator
 All Randomized Patients
 Acute Therapy Phase

The FREQ Procedure
 Table of INV by trtmt

INV(Clinical Investigator Number)
 trtmt(Therapy)

Frequency	Row Pct	PLACEDO	DLX60QD	DLX60BID	Total
101	8	7	7	7	22
	36.36	31.82	31.82	31.82	
102	3	3	2	2	8
	37.50	37.50	25.00		
103	8	9	7	7	24
	33.33	37.50	29.17		
104	11	10	9	9	30
	36.67	33.33	30.00		
105	5	5	6	6	16
	31.25	31.25	37.50		
106	8	9	8	8	25
	32.00	36.00	32.00		
107	7	6	7	7	20
	35.00	30.00	35.00		
Total		120	118	116	354

(Continued)

Program: EMP.F1JSEMCA.SASPGM(FQ1NVLLA) QCA700
 Data: EMP.SAS.F1JN.L.MCNCASW.FINAL

Table HMCA.10.2. Patient Allocation by Investigator
 All Randomized Patients
 Acute Therapy Phase (Continued)

The FREQ Procedure
 Table of INV by trtmt

INV(Clinical Investigator Number)
 trtmt(Therapy)

Frequency	Row Pct	PLACEDO	DLX60QD	DLX60BID	Total
108	2	2	1	1	5
	40.00	40.00	20.00		
109	7	7	6	6	20
	35.00	35.00	30.00		
110	4	5	4	4	13
	30.77	38.46	30.77		
111	7	7	8	8	22
	31.82	31.82	36.36		
112	2	2	3	3	7
	28.57	28.57	42.86		
113	11	11	11	11	33
	33.33	33.33	33.33		
114	1	0	1	1	2
	50.00	0.00	50.00		
Total		120	118	116	354

(Continued)

Program: EMP.F1JSEMCA.SASPGM(FQ1NVLLA) QCA700
 Data: EMP.SAS.F1JN.L.MCNCASW.FINAL

Table HMCA.10.2. Patient Allocation by Investigator
 All Randomized Patients
 Acute Therapy Phase (Concluded)

The FREQ Procedure
 Table of INV by trtmt

INV(Clinical Investigator Number)
 trtmt(Therapy)

Frequency	Row Pct	PLACEDO	DLX60QD	DLX60BID	Total
115	7	6	7	7	20
	35.00	30.00	35.00		
116	2	3	2	2	7
	28.57	42.86	28.57		
117	6	5	6	6	17
	35.29	29.41	35.29		
118	6	7	7	7	20
	30.00	35.00	35.00		
119	3	3	2	2	8
	37.50	37.50	25.00		
120	11	10	11	11	32
	34.38	31.25	34.38		
121	1	1	1	1	3
	33.33	33.33	33.33		
Total		120	118	116	354

Program: EMP.F1JSEMCA.SASPGM(FQ1NVLLA) QCA700
 Data: EMP.SAS.F1JN.L.MCNCASW.FINAL

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10.1.1.6.1.3 Subject Disposition

A total of 354 patients were randomized in a 1:1:1 ratio.

	Placebo N = 120	DLX 60 QD N = 118	DLX 60 BID 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%)

During the acute treatment phase, across all treatment groups, the most frequent reasons for withdrawal were adverse event (n=66), lack of efficacy (n=29), withdrawal of informed consent (n=18) lost to follow-up (n=10), patient decision (n=8), noncompliance (n=5), protocol violation (n=1), and physician decision (n=1).

During the discontinuation phase, one patient in the duloxetine 60 mg QD group discontinued due to an AE.

10.1.1.6.2 Demographics

The table below illustrates demographic and baseline characteristics of the 3 treatment groups. Overall, most patients were female Caucasians, with a median age of 50 years, a median weight of 77 kilograms, and a median height of 165 cm. Approximately 30% had a concomitant diagnosis of major depressive disorder and 10% had an anxiety disorder.

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**Table HMCA.11.1. Patient Demographics at Baseline
 All Randomly Assigned Patients
 Acute Therapy Phase**

Variable	PLACEBO (N=120)	DLX60QD (N=118)	DLX60BID (N=116)	Total (N=354)
ORIGIN: NO. (%)				
No. Patients	120	118	116	354
African Descent	3 (2.5)	2 (1.7)	2 (1.7)	7 (2.0)
Caucasian	107 (89.2)	106 (89.8)	104 (89.7)	317 (89.5)
East/Southeast A	0	0	1 (0.9)	1 (0.3)
Hispanic	10 (8.3)	10 (8.5)	9 (7.8)	29 (8.2)
AGE: YRS				
No. Patients	120	118	116	354
Mean	49.19	48.33	51.28	49.59
Median	49.87	49.41	52.39	50.78
Standard Dev.	11.83	10.54	9.97	10.86
Minimum	20.05	20.01	23.31	20.01
Maximum	79.59	76.67	75.34	79.59

**Table HMCA.11.1. Patient Demographics at Baseline
 All Randomly Assigned Patients
 Acute Therapy Phase (Continued)**

Variable	PLACEBO (N=120)	DLX60QD (N=118)	DLX60BID (N=116)	Total (N=354)
GENDER: NO. (%)				
No. Patients	120	118	116	354
Female	120 (100)	118 (100)	116 (100)	354 (100)
HEIGHT: CM (Visit: 2)				
No. Patients	120	118	116	354
Mean	163.32	161.98	162.67	162.66
Median	165.10	162.56	162.56	162.56
Standard Dev.	7.92	7.80	7.70	7.81
Minimum	127.00	134.62	132.08	127.00
Maximum	177.80	177.80	180.34	180.34

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**Table HMCA.11.1. Patient Demographics at Baseline
 All Randomly Assigned Patients
 Acute Therapy Phase (Continued)**

Variable	PLACEBO (N=120)	DLX60QD (N=118)	DLX60BID (N=116)	Total (N=354)
WEIGHT: KG (Visit: 2)				
No. Patients	120	117	116	353
Mean	78.28	74.79	76.40	76.50
Median	76.95	71.73	71.73	73.09
Standard Dev.	15.94	16.96	17.98	16.98
Minimum	51.30	43.13	43.13	43.13
Maximum	130.75	136.20	129.84	136.20
Unspecified	0	1	0	1
MAJOR DEPRESSIVE EPISODE (Y,N)				
No. Patients	120	118	116	354
N	88 (73.3)	89 (75.4)	84 (72.4)	261 (73.7)
Y	32 (26.7)	29 (24.6)	32 (27.6)	93 (26.3)

**Table HMCA.11.1. Patient Demographics at Baseline
 All Randomly Assigned Patients
 Acute Therapy Phase (Concluded)**

Variable	PLACEBO (N=120)	DLX60QD (N=118)	DLX60BID (N=116)	Total (N=354)
SECONDARY DIAGNOSIS OF ANXIETY (Y,N)				
No. Patients	120	118	116	354
N	29 (90.6)	27 (93.1)	28 (87.5)	84 (90.3)
Y	3 (9.4)	2 (6.9)	4 (12.5)	9 (9.7)
Unspecified	88	89	84	261

10.1.1.6.3 Dosing Information

The table below illustrates exposure duration and compliance with medication across treatment groups during the study. Groups were similar with respect to mean duration of exposure.

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**Table HMCA.12.1. Study Drug Exposure
 All Randomly Assigned Patients
 Acute Therapy Phase**

Variable	PLACEBO (N=120)	DLX60QD (N=118)	DLX60BID (N=116)	Total (N=354)
DURATION OF EXPOSURE (DAYS)				
No. Patients	120	118	116	354
Mean	65.00	66.73	64.07	65.27
Median	86.00	88.00	87.50	88.00
Standard Dev.	30.18	34.95	35.12	33.39
Minimum	0.00	1.00	1.00	0.00
Maximum	96.00	99.00	99.00	99.00

**Table HMCA.12.1. Study Drug Exposure
 All Randomly Assigned Patients
 Acute Therapy Phase (Concluded)**

Variable	PLACEBO (N=120)	DLX60QD (N=118)	DLX60BID (N=116)	Total (N=354)
DISTRIBUTION OF EXPOSURE (DAYS)				
No. Patients	120	118	116	354
0	1 (0.8)	0	0	1 (0.3)
>0 - <7	3 (2.5)	18 (15.3)	13 (11.2)	34 (9.6)
7 - <14	7 (5.8)	3 (2.5)	9 (7.8)	19 (5.4)
14 - <21	3 (2.5)	2 (1.7)	6 (5.2)	11 (3.1)
21 - <28	5 (4.2)	4 (3.4)	2 (1.7)	11 (3.1)
28 - <35	10 (8.3)	3 (2.5)	3 (2.6)	16 (4.5)
35 - <42	4 (3.3)	1 (0.8)	1 (0.9)	6 (1.7)
42 - <49	4 (3.3)	2 (1.7)	1 (0.9)	7 (2.0)
49 - <56	3 (2.5)	1 (0.8)	1 (0.9)	5 (1.4)
56 - <63	7 (5.8)	3 (2.5)	3 (2.6)	13 (3.7)
>=63	73 (60.8)	81 (68.6)	77 (66.4)	231 (65.3)

10.1.1.6.4 Protocol Violations

Protocol deviations were identified programmatically by searching the database for randomized subjects who had screening or baseline values falling outside of the ranges specified by inclusion or exclusion criteria (eg, values for age, weight, medical history, smoking history, laboratory parameters, etc). The database was also searched for subjects who used prohibited medications during the study and subjects who were withdrawn from the study due to protocol deviations. In addition, lists of protocol deviations were compiled by site monitors during routine center visits or during remote review of electronic data. All deviations identified by the methods described above were reviewed by Lilly for clinical significance. Those considered potentially significant are summarized in the table below.

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Summary of Significant Protocol Violations Patient Numbers by Investigative Site All Randomized Patients							
Site	ICD Not Administered Properly	Significant Drug Accountability	Failure to Follow Inclusion/Exclusion Criteria	Laboratory Issues	Failure to Follow Visit Schedule	Use of Exclusionary Medication/ Procedure	Total
101	1	2	1	0	10	3	17
102	6	0	0	0	5	0	11
103	0	0	0	0	17	2	19
104	0	7	1	0	20	6	34
105	0	3	0	0	8	2	13
106	1	0	1	0	13	2	17
107	1	0	0	0	9	1	11
108	0	0	0	0	7	0	7
109	2	2	0	0	24	1	29
110	0	3	1	0	5	2	11
111	3	1	2	0	10	4	20
112	0	1	0	1	5	0	7
113	0	7	1	2	27	3	40
114	0	0	0	0	0	0	0
115	0	0	0	0	7	1	8
116	2	0	0	0	7	0	9
117	0	0	0	0	8	3	11
118	6	0	0	0	2	2	10
119	3	3	0	0	4	1	11
120	0	6	1	2	35	13	57
121	0	0	0	0	0	1	1
Total	25	35	8	5	223	47	343

At nine sites, some patients failed to sign the updated ICD or data privacy statement, some patients signed an incorrect version of the informed consent document, or administrative problems occurred.

At 10 sites, some patients were less than 80% compliant with study drug dosing, some patients forgot to return unused study drug or blister packages, or administrative problems occurred.

Seven sites reported inclusion/exclusion criteria violations: all related to some patients taking excluded medications outside of the required window.

At three sites, patient visit laboratory measures were not taken in some cases.

Nineteen sites reported visit schedule violations: the majority were a result of visit window violations. At some sites, some patients completed some assessments incorrectly, some assessments were not completed at all, or some assessments were not completed by certified raters. One site was initially assigning patient numbers based on date of randomization, not date of consent.

At sixteen sites, some patients took excluded medications after randomization. The majority of these violations were one-time occurrences. However, use of prohibited medications might influence pain scores and might have influenced interpretation of study results. Prohibited concomitant medications were used by 12% of the placebo group, 10% of the 60 QD group and 16% of the 60 BID group. Because the most important conclusions were based on the responder rates calculated by Dr. Buenconsejo, she tabulated how many responders used prohibited concomitant medications during the study and calculated responder rates for patients who did not use concomitant medications. Prohibited medications were used by 17% of the placebo responders (30% improvement definition), and 20% of each of the duloxetine groups. However, the subgroup analysis below shows that a treatment effect is apparent even when these patients are excluded from analysis.

			≥ 30% Improvement in Pain	≥ 50% Improvement in Pain
	Treatment Group	N	n(%)	n(%)
Total	Placebo	120	24 (20%)	18 (15%)
	Duloxetine 60 mg QD	118	54 (46%)	42 (36%)
	Duloxetine 60 mg BID	116	45 (39%)	36 (31%)
Used Prohibited ConMed	Placebo	14 (12%)	4 (29%)	4 (29%)
	Duloxetine 60 mg QD	12 (10%)	10 (83%)	9 (75%)
	Duloxetine 60 mg BID	18 (16%)	9 (50%)	5 (28%)
Did not Use Prohibited ConMed	Placebo	106 (88%)	20 (19%)	14 (13%)
	Duloxetine 60 mg QD	106 (90%)	44 (42%)	33 (31%)
	Duloxetine 60 mg BID	98 (84%)	36 (37%)	31 (32%)

10.1.1.7 Efficacy Results

Applicant's Analysis

Brief Pain Inventory Average Pain Score

The primary objective of this study was to assess the efficacy of duloxetine 60 mg BID and duloxetine 60 mg QD compared with placebo on the reduction in pain severity as measured by the BPI average pain item at during the 3-month acute therapy phase. The Applicant states that both duloxetine doses were statistically superior to placebo. The table below shows the results of the BPI average pain score mean change from baseline to endpoint at the end of 3-months.

**Table HMCA.11.7. Brief Pain Inventory Average Pain Score
 Change From Baseline to Endpoint
 All Randomly Assigned Patients
 Acute Therapy Phase**

	Baseline					Endpoint					Change				
	N	Mean	SD	Median	Min Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
PLACEBO	118	6.47	1.47	6.0	4.0 10.0	5.22	2.36	5.0	0.0	9.0	-1.25	2.27	-1.0	-8.0	3.0
DLX60QD	116	6.38	1.41	6.0	4.0 10.0	3.97	2.45	4.0	0.0	10.0	-2.41	2.61	-2.0	-9.0	2.0
DLX60BID	114	6.36	1.60	6.0	2.0 10.0	3.94	2.29	4.0	0.0	10.0	-2.42	2.57	-2.0	-9.0	4.0

Interaction (Type II SS) Raw Data Therapy-by-Investigator F=0.87 df=28,302 p=0.652

Main Effects (Type II SS) Raw Data
 Therapy F=11.34 df=2,330 p<.001
 Investigator F=1.43 df=14,330 p=0.139

Least Squares Means for Change from Baseline
 PLACEBO -1.16 (SE=0.21)
 DLX60QD -2.39 (SE=0.22)
 DLX60BID -2.40 (SE=0.22)

Pairwise Comparison of LS Means
 DLX60QD - PLACEBO diff=-1.23 Two-sided 95% CI : (-1.02 , -0.64) t=-4.11 p<.001
 DLX60BID - PLACEBO diff=-1.24 Two-sided 95% CI : (-1.83 , -0.65) t=-4.12 p<.001
 DLX60BID - DLX60QD diff=-0.01 Two-sided 95% CI : (-0.60 , 0.58) t=-0.03 p=0.976

Type II Sums of Squares from ANOVA: Model: CHANGE OF BPAIN = POOLINV TRTMT BASELINE for main effect p-value.
 Model: CHANGE OF BPAIN = POOLINV TRTMT BASELINE TRTMT*POOLINV for the interaction p-value.
 Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.
 Program: RMP.FLJSHMCA.SASPGM(LOBPILIA) QCA700
 Data: RMP.SAS.FLJH.L.MCHMCASW.FINAL

Secondary Endpoints

Secondary outcome measures included the Fibromyalgia Impact Questionnaire (FIQ) total score. The Applicant states that duloxetine at doses of both 60 mg QD and 60 mg BID were statistically superior to placebo. The table below shows the results of the FIQ Total Score Change from baseline to endpoint at the end of 3-months.

**Table HMCA.11.10. Fibromyalgia Impact Questionnaire Total Score
 Change From Baseline to Endpoint
 All Randomly Assigned Patients
 Acute Therapy Phase**

	Baseline					Endpoint					Change				
	N	Mean	SD	Median	Min Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
PLACEBO	115	52.96	12.41	53.6	16.6 77.5	44.21	16.32	45.5	0.0	79.4	-8.75	15.50	-7.5	-66.7	30.9
DLX60QD	114	51.45	12.24	52.7	15.4 76.5	34.97	17.72	34.5	0.0	76.2	-16.48	17.72	-16.7	-58.3	28.0
DLX60BID	112	52.52	12.76	52.5	20.0 76.9	35.31	18.35	36.7	0.0	79.4	-17.21	18.43	-14.5	-69.1	37.3

Interaction (Type II SS) Raw Data Therapy-by-Investigator F=1.04 df=28,295 p=0.419

Main Effects (Type II SS) Raw Data
 Therapy F=10.34 df=2,323 p<.001
 Investigator F=1.32 df=14,323 p=0.191

Least Squares Means for Change from Baseline
 PLACEBO -8.35 (SE=1.53)
 DLX60QD -16.72 (SE=1.53)
 DLX60BID -16.81 (SE=1.54)

Pairwise Comparison of LS Means
 DLX60QD - PLACEBO diff=-8.38 Two-sided 95% CI : (-12.58 , -4.17) t=-3.92 p<.001
 DLX60BID - PLACEBO diff=-8.46 Two-sided 95% CI : (-12.68 , -4.25) t=-3.95 p<.001
 DLX60BID - DLX60QD diff=-0.09 Two-sided 95% CI : (-4.32 , 4.14) t=-0.04 p=0.968

Type II Sums of Squares from ANOVA: Model: CHANGE OF FIQTOTAL = POOLINV TRTMT BASELINE for main effect p-value.
 Model: CHANGE OF FIQTOTAL = POOLINV TRTMT BASELINE TRTMT*POOLINV for the interaction p-value.
 Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.
 Program: RMP.FLJSHMCA.SASPGM(LOPILIA) QCA700
 Data: RMP.SAS.FLJH.L.MCHMCASW.FINAL

Additional secondary efficacy measures included measures of pain severity, pain interference, and general illness/improvement, as assessed by the patient and clinician. The table below

summarizes the results of the secondary efficacy measures. Two statistical methodologies (repeated measures analysis and mean change analysis) were used for all randomly assigned patients.

**Table HMCA.11.12. Summary of Secondary Efficacy Measures
 Pain and General Illness/Improvement
 All Randomly Assigned Patients
 Acute Therapy Phase**

Variable	Treatment Group			p-Value		
	Placebo	Dulox 60 QD	Dulox 60 BID	Dulox 60 QD vs Placebo	Dulox 60 BID vs Placebo	Dulox 60 QD vs Dulox 60 BID
BPI Worst Pain Severity	n=118	n=115	n=114			
Mean Baseline (SD)	7.27 (1.98)	7.31 (1.63)	7.39 (1.87)			
LS Mean Change (SE) - ANCOVA	-1.35 (0.24)	-2.53 (0.25)	-2.37 (0.25)	p<.001	p=.003	p=.640
LS Mean Change (SE) - MMRM	-1.65 (0.30)	-2.98 (0.29)	-2.56 (0.30)	p=.001	p=.031	p=.307
BPI Least Pain Severity	n=118	n=116	n=114			
Mean Baseline (SD)	4.50 (2.10)	4.53 (2.06)	4.84 (2.20)			
LS Mean Change (SE) - ANCOVA	-0.58 (0.20)	-1.77 (0.20)	-1.76 (0.20)	p<.001	p<.001	p=.956
LS Mean Change (SE) - MMRM	-0.75 (0.23)	-2.08 (0.22)	-1.90 (0.23)	p<.001	p<.001	p=.583
BPI Severity: Pain Right Now	n=118	n=116	n=114			
Mean Baseline (SD)	6.23 (2.15)	6.12 (2.14)	6.31 (2.10)			
LS Mean Change (SE) - ANCOVA	-1.15 (0.23)	-2.40 (0.23)	-2.33 (0.23)	p<.001	p<.001	p=.826
LS Mean Change (SE) - MMRM	-1.35 (0.27)	-2.86 (0.26)	-2.54 (0.27)	p<.001	p=.002	p=.384
BPI Interference: General Activity	n=118	n=116	n=114			
Mean Baseline (SD)	5.94 (2.39)	6.09 (2.54)	5.72 (2.68)			
LS Mean Change (SE) - ANCOVA	-1.27 (0.24)	-2.53 (0.25)	-2.34 (0.25)	p<.001	p=.002	p=.590
LS Mean Change (SE) - MMRM	-1.54 (0.28)	-2.88 (0.27)	-2.65 (0.28)	p<.001	p=.005	p=.552

**Table HMCA.11.12. Summary of Secondary Efficacy Measures
 Pain and General Illness/Improvement
 All Randomly Assigned Patients
 Acute Therapy Phase (continued)**

Variable	Treatment Group			p-Value		
	Placebo	Dulox 60 QD	Dulox 60 BID	Dulox 60 QD vs Placebo	Dulox 60 BID vs Placebo	Dulox 60 QD vs Dulox 60 BID
BPI Interference: Mood	n=117	n=116	n=114			
Mean Baseline (SD)	5.89 (2.62)	5.45 (2.77)	5.86 (2.59)			
LS Mean Change (SE) - ANCOVA	-1.46 (0.24)	-2.94 (0.24)	-2.87 (0.24)	p<.001	p<.001	p=.855
LS Mean Change (SE) - MMRM	-1.73 (0.27)	-3.20 (0.26)	-3.24 (0.27)	p<.001	p<.001	p=.927
BPI Interference: Walking Ability	n=118	n=116	n=114			
Mean Baseline (SD)	5.42 (2.72)	5.33 (2.76)	5.63 (2.94)			
LS Mean Change (SE) - ANCOVA	-1.12 (0.23)	-2.01 (0.24)	-2.53 (0.24)	p=.007	p<.001	p=.116
LS Mean Change (SE) - MMRM	-1.56 (0.27)	-2.28 (0.26)	-2.66 (0.27)	p=.052	p=.004	p=.318
BPI Interference: Normal Work	n=118	n=116	n=114			
Mean Baseline (SD)	5.97 (2.40)	5.97 (2.44)	5.82 (2.55)			
LS Mean Change (SE) - ANCOVA	-1.20 (0.23)	-2.57 (0.23)	-2.47 (0.24)	p<.001	p<.001	p=.757
LS Mean Change (SE) - MMRM	-1.54 (0.27)	-2.91 (0.26)	-2.66 (0.27)	p<.001	p=.003	p=.508
BPI Interference: People	n=118	n=115	n=113			
Mean Baseline (SD)	5.04 (2.81)	4.34 (2.95)	5.03 (2.94)			
LS Mean Change (SE) - ANCOVA	-1.31 (0.21)	-2.49 (0.21)	-2.49 (0.21)	p<.001	p<.001	p=.999
LS Mean Change (SE) - MMRM	-1.41 (0.24)	-2.74 (0.23)	-2.69 (0.24)	p<.001	p<.001	p=.859

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**Table HMCA.11.12. Summary of Secondary Efficacy Measures
 Pain and General Illness/Improvement
 All Randomly Assigned Patients
 Acute Therapy Phase (continued)**

Variable	Treatment Group			p-Value		
	Placebo	Dulox 60 QD	Dulox 60 BID	Dulox 60 QD vs Placebo	Dulox 60 BID vs Placebo	Dulox 60 QD vs Dulox 60 BID
BPI Interference: Sleep	n=118	n=116	n=114			
Mean Baseline (SD)	7.21 (2.39)	7.26 (2.45)	7.49 (2.59)			
LS Mean Change (SE) - ANCOVA	-1.71 (0.28)	-2.67 (0.29)	-3.69 (0.29)	p=.016	p=.014	p=.963
LS Mean Change (SE) - MMRM	-1.99 (0.34)	-3.01 (0.33)	-2.95 (0.34)	p=.029	p=.044	p=.889
BPI Interference: Enjoyment of Life	n=118	n=116	n=114			
Mean Baseline (SD)	6.47 (2.59)	5.91 (2.89)	6.37 (2.79)			
LS Mean Change (SE) - ANCOVA	-1.68 (0.25)	-2.90 (0.26)	-2.89 (0.26)	p<.001	p<.001	p=.987
LS Mean Change (SE) - MMRM	-1.97 (0.29)	-3.20 (0.28)	-3.19 (0.29)	p=.002	p=.003	p=.974
BPI Interference: Average of Seven Questionnaires	n=118	n=116	n=114			
Mean Baseline (SD)	5.99 (2.06)	5.77 (2.13)	5.99 (2.33)			
LS Mean Change (SE) - ANCOVA	-1.43 (0.21)	-2.57 (0.22)	-2.58 (0.22)	p<.001	p<.001	p=.963
LS Mean Change (SE) - MMRM	-1.67 (0.24)	-2.87 (0.24)	-2.85 (0.24)	p<.001	p<.001	p=.952
Mean of 18 Tender Point Thresholds (kg/cm²)	n=109	n=111	n=110			
Mean Baseline (SD)	2.16 (0.87)	2.06 (0.74)	2.12 (0.75)			
LS Mean Change (SE) - ANCOVA	0.06 (0.08)	0.22 (0.08)	0.39 (0.08)	p=.159	p=.003	p=.113
LS Mean Change (SE) - MMRM	0.09 (0.09)	0.30 (0.09)	0.54 (0.09)	p=.113	p<.001	p=.061

**Table HMCA.11.12. Summary of Secondary Efficacy Measures
 Pain and General Illness/Improvement
 All Randomly Assigned Patients
 Acute Therapy Phase (concluded)**

Variable	Treatment Group			p-Value		
	Placebo	Dulox 60 QD	Dulox 60 BID	Dulox 60 QD vs Placebo	Dulox 60 BID vs Placebo	Dulox 60 QD vs Dulox 60 BID
# of TP with a Low Threshold	n=109	n=111	n=110			
Mean Baseline (SD)	16.97 (2.28)	17.00 (2.19)	17.05 (1.99)			
LS Mean Change (SE) - ANCOVA	-0.39 (0.26)	-0.42 (0.25)	-1.11 (0.25)	p=.934	p=.046	p=.054
LS Mean Change (SE) - MMRM	-0.46 (0.31)	-0.57 (0.30)	-1.52 (0.31)	p=.799	p=.016	p=.026
CGI-Severity	n=111	n=112	n=111			
Mean Baseline (SD)	4.20 (0.92)	4.04 (0.91)	4.15 (0.82)			
LS Mean Change (SE) - ANCOVA	-0.44 (0.10)	-0.84 (0.10)	-0.84 (0.10)	p=.005	p=.005	p=.993
LS Mean Change (SE) - MMRM	-0.53 (0.12)	-1.01 (0.11)	-1.04 (0.12)	p=.004	p=.003	p=.852
PGI-Improvement	n=111	n=114	n=111			
Mean (SD) - ANOVA	3.71 (1.50)	3.11 (1.77)	3.06 (1.73)	p=.005	p=.003	p=.864
LS Mean (SE) - MMRM	3.66 (0.17)	3.00 (0.16)	2.98 (0.16)	p=.005	p=.004	p=.924
HAMD₁₇	n=109	n=111	n=110			
Mean Baseline (SD)	11.28 (6.57)	11.33 (6.23)	11.55 (6.28)			
LS Mean Change (SE) - ANCOVA	-2.24 (0.45)	-3.79 (0.44)	-2.97 (0.45)	p=.014	p=.243	p=.191
LS Mean Change (SE) - MMRM	-3.04 (0.53)	-4.34 (0.50)	-3.71 (0.52)	p=.075	p=.366	p=.377

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; BID = twice daily; BPI = Brief Pain Inventory; CGI = Clinical Global Impressions; Dulox = duloxetine; HAMD₁₇ = 17-item Hamilton Depression Rating Scale; MMRM = mixed-models repeated measures; PGI = Patient Global Impressions; QD = once daily; SD = standard deviation; SE = standard error; TP = Tender Points.
 Note: n = the number of patients who had a baseline score and at least one nonmissing postbaseline score for that particular variable.

Reviewer's Analysis

Evaluation of Pain, Patient Global Improvement, FIQ Total Score and FIQ Pain Score

The primary efficacy analysis in Study HMCA was based on the mean change from baseline to endpoint in BPI average pain score. PGI Improvement was collected as part of several pre-specified secondary endpoints, but no pre-specified procedure was established to adjust for multiplicity.

Using BOCF and LOCF/BOCF approaches to missing data imputation, both duloxetine 60 mg QD and 60 mg BID were associated improvement in pain over placebo (see table below).

Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint at Endpoint: All Randomized Patients in the 3-Month Therapy Phase of Placebo-Controlled Study HMCA

Study	Treatment Group	BPI Average Pain Score (BOCF)			BPI Average Pain Score (LOCF/BOCF)	
		Baseline	LSMean Change	p-value	LSMean Change	p-value
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

†unadjusted p-value.
 Dr. Buenconsejo's Table.

As mentioned above, PGI-Improvement was a pre-specified secondary endpoint, but no adjustment was made for multiplicity. The table below shows the results for PGI-I.

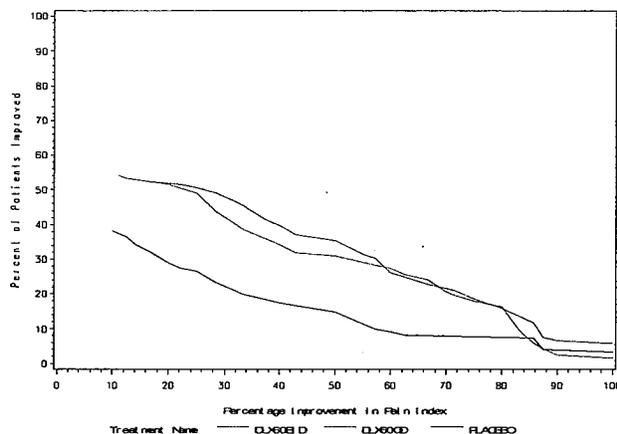
PGI-Improvement at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Study HMCA

Study	Treatment Group	N	PGI Improvement Score (LOCF)		PGI Improvement Score (WOCF)	
			LSMean Change	p-value	LSMean Change	p-value
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

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

Dr. Buenconsejo plotted a continuous responder curve for study HMCA. In this plot, the patients who drop out are considered non-responders. The x-axis shows the percent reduction in pain from baseline and the y-axis shows the percentage of patients achieving that level of pain reduction or greater. In the curve below, we see clear evidence of response for both duloxetine doses (60 mg QD and 60 mg BID) compared to placebo.

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The table below illustrates how duloxetine 60 mg QD and 60 mg BID are superior to placebo in terms of improvement of pain.

Responder Analysis of Brief Pain Inventory Average Pain Score at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Study HMCA						
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

Dr. Buenconsejo's Table.

Another secondary endpoint in HMCA was the Fibromyalgia Impact Questionnaire. Although multiplicity adjustments were not made, in the table below we see that there appears to be improvement.

Fibromyalgia Impact Questionnaire Total Score Change from Baseline to Endpoint*: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Study HMCA						
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	0.001	-14.2	0.002
	Duloxetine 60 mg BID	52.5	-12.9	0.003	-14.3	0.002

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

The table below shows yet another secondary endpoint of CGI-Severity. Again we see that both doses of duloxetine suggest an improvement in symptoms.

Change in CGI-Severity at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Study HMCA								
Study	Treatment Group	N	CGI Improvement Score (LOCF)		CGI Improvement Score (WOFC)		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	0.002	-0.8	0.007	-0.8	<0.001
	Duloxetine 60 mg BID	116	-0.8	0.002	-0.8	0.005	-0.7	0.003

* negative implies improvement
 Dr. Buenconsejo's Table.

Analysis by Subgroups

No men were enrolled in Study HMCA.

Endpoint mean BPI average pain score subdivided by race does not show treatment differences when subdivided by race.

Endpoint Mean Brief Pain Inventory Average Pain Score: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Study: HMCA							
Study	Treatment Group	N	White		Non-white		
			Baseline	Endpoint Mean	N	Baseline	Endpoint Mean
BOCF							
HMCA	Placebo	107	6.4	5.5	13	7.8	6.2
	Duloxetine 60 mg QD	106	6.3	4.2	12	7.0	5.8
	Duloxetine 60 mg BID	104	6.2	4.3	12	7.8	6.8
LOCF/BOCF							
HMCA	Placebo	107	6.4	5.3	13	7.8	6.2
	Duloxetine 60 mg QD	106	6.3	4.1	12	7.0	5.7
	Duloxetine 60 mg BID	104	6.2	4.0	12	7.8	6.3

Dr. Buenconsejo's Table.

Likewise, the table below indicates that endpoint mean BPI does not show treatment differences when subdivided by age.

Endpoint Mean Brief Pain Inventory Average Pain Score: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Study by Age: HMCA							
Study	Treatment Group	Age < 65			Age ≥ 65		
		N	Baseline	Endpoint Mean	N	Baseline	Endpoint Mean
BOCF							
HMCA	Placebo	109	6.6	5.7	11	5.5	3.6
	Duloxetine 60 mg QD	113	6.4	4.4	5	6.6	1.6
	Duloxetine 60 mg BID	105	6.3	4.4	11	6.6	5.7
LOCF/BOCF							
HMCA	Placebo	109	6.6	5.6	11	5.5	3.6
	Duloxetine 60 mg QD	113	6.4	4.3	5	6.6	1.6
	Duloxetine 60 mg BID	105	6.3	4.1	11	6.6	6.0

Dr. Buenconsejo's Table.

Endpoint mean BPI average pain score subdivided by presence or absence of major depressive disorder does not demonstrate major differences in treatment effect.

Endpoint Mean Brief Pain Inventory Average Pain Score: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Study HMCJ by Major Depressive Disorder Status							
Study	Treatment Group	No MDD			With MDD		
		N	Baseline	Endpoint Mean	N	Baseline	Endpoint Mean
BOCF							
HMCA	Placebo	88	6.3	5.2	32	7.2	6.4
	Duloxetine 60 mg QD	89	6.3	4.3	29	6.7	4.3
	Duloxetine 60 mg BID	84	6.2	4.5	32	6.8	4.6
LOCF/BOCF							
HMCA	Placebo	88	6.3	5.1	32	7.2	6.2
	Duloxetine 60 mg QD	89	6.3	4.3	29	6.7	4.1
	Duloxetine 60 mg BID	84	6.2	4.4	32	6.8	4.0

Dr. Buenconsejo's Table.

10.1.1.8 Conclusions Regarding Efficacy Data in Study

This study provides evidence that duloxetine at doses of 60 mg QD and 60 mg BID are effective for treatment of fibromyalgia. No treatment by subgroup differences were seen for gender, race, age, or presence or absence of major depressive disorder.

10.1.1.9 Safety Results

The table below shows the common adverse events observed in this study, as reported by Lilly in the final study report. Adverse events (MedDRA preferred terms) that occurred in more than 2% of subjects and at a frequency greater than placebo in the duloxetine treatment groups are summarized below. Among duloxetine-treated subjects, the most frequently reported adverse events were nausea, insomnia, headache, dry mouth, fatigue, and dizziness.

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Treatment-Emergent Adverse Events By Decreasing Frequency All Randomly Assigned Patients Acute Therapy Phase				
	PLACEBO N=120 n(%)	DLX60QD N=118 n(%)	DLX60BID N=116 n(%)	Total N=354 n(%)
Patients with >= 1 TESS	95(79.2)	109(92.4)	105(90.5)	309(87.3)
Nausea	16(13.3)	53(44.9)	45(38.8)	114(32.2)
Insomnia	19(15.8)	27(22.9)	29(25.0)	75(21.2)
Headache	18(15.0)	28(23.7)	24(20.7)	70(19.8)
Dry mouth	10(8.3)	25(21.2)	27(23.3)	62(17.5)
Fatigue	14(11.7)	17(14.4)	25(21.6)	56(15.8)
Dizziness	12(10.0)	16(13.6)	19(16.4)	47(13.3)
Constipation	3(2.5)	16(13.6)	20(17.2)	39(11.0)
Diarrhoea NOS	6(5.0)	17(14.4)	13(11.2)	36(10.2)
Somnolence	5(4.2)	6(5.1)	14(12.1)	25(7.1)
Appetite decreased NOS	1(0.8)	8(6.8)	14(12.1)	23(6.5)
Nasopharyngitis	2(1.7)	9(7.6)	7(6.0)	18(5.1)
Anxiety	6(5.0)	6(5.1)	5(4.3)	17(4.8)
Upper respiratory tract	9(7.5)	2(1.7)	5(4.3)	16(4.5)
Depression	6(5.0)	4(3.4)	5(4.3)	15(4.2)
Sweating increased	1(0.8)	6(5.1)	8(6.9)	15(4.2)
Unexpected therapeutic	3(2.5)	6(5.1)	6(5.2)	15(4.2)
Anorexia	0(0.0)	6(5.1)	8(6.9)	14(4.0)
Arthralgia	5(4.2)	4(3.4)	5(4.3)	14(4.0)
Dyspepsia	5(4.2)	4(3.4)	5(4.3)	14(4.0)
Muscle cramp	5(4.2)	3(2.5)	5(4.3)	13(3.7)
Sinusitis NOS	6(5.0)	4(3.4)	3(2.6)	13(3.7)
Vomiting NOS	3(2.5)	7(5.9)	3(2.6)	13(3.7)
Feeling jittery	0(0.0)	4(3.4)	8(6.9)	12(3.4)
Gastroenteritis viral N	5(4.2)	4(3.4)	3(2.6)	12(3.4)
Cough	4(3.3)	4(3.4)	2(1.7)	10(2.8)
Hot flushes NOS	2(1.7)	5(4.2)	3(2.6)	10(2.8)
Migraine NOS	4(3.3)	0(0.0)	6(5.2)	10(2.8)
Seasonal allergy	3(2.5)	2(1.7)	5(4.3)	10(2.8)
Back pain	3(2.5)	2(1.7)	4(3.4)	9(2.5)
Myalgia	2(1.7)	3(2.5)	4(3.4)	9(2.5)
Nervousness	0(0.0)	4(3.4)	5(4.3)	9(2.5)
Paraesthesia	3(2.5)	5(4.2)	1(0.9)	9(2.5)
Dysgeusia	2(1.7)	2(1.7)	4(3.4)	8(2.3)
Musculoskeletal stiffness	3(2.5)	2(1.7)	3(2.6)	8(2.3)
Nasal congestion	3(2.5)	3(2.5)	2(1.7)	8(2.3)
Night sweats	3(2.5)	5(4.2)	0(0.0)	8(2.3)
Pain NOS	3(2.5)	3(2.5)	2(1.7)	8(2.3)
Sinus headache	1(0.8)	4(3.4)	3(2.6)	8(2.3)

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10.1.2 Protocol F1J-MC-HMCJ

Title: Dose Response Study of Duloxetine Versus Placebo in the Treatment of Fibromyalgia Syndrome

10.1.2.1 Objective/Rationale

The primary objective of this study was to assess the efficacy of duloxetine 120 mg once daily (QD) compared with placebo on the treatment of pain in patients with American College of Rheumatology (ACR)-defined primary fibromyalgia syndrome (FMS), with or without major depressive disorder (MDD) in the 3-month acute therapy phase of the study. The primary objective was to be evaluated from two perspectives using the reduction of pain severity, as measured by the average pain item of the Brief Pain Inventory (BPI-Modified Short Form), and patient-reported improvement, as measured by the Patient's Global Impressions of Improvement (PGI-Improvement) questionnaire, as the co-primary efficacy measures.

Secondary objectives included (among others) assessment of efficacy of duloxetine 60 mg QD after three months of treatment, assessment of efficacy of duloxetine 20 mg QD after 3 months of treatment, and assessment of efficacy of the 60 mg QD and 120 mg QD regimens at the end of 6 months of treatment.

10.1.2.2 Overall Design

The study was a multi-center, double-blind, placebo-controlled, randomized clinical trial designed to assess the efficacy and safety of duloxetine 120 mg QD in comparison to placebo for the treatment of Fibromyalgia syndrome. The study included a 1-week screening phase, a 15-week acute therapy phase, a 13-week continuation phase, a 28-week extension phase, and a two-week taper phase.

10.1.2.3 Population and Procedures

10.1.2.3.1 Inclusion/Exclusion Criteria

Planned enrollment was approximately 490 subjects randomized 2:1:2:2 to each of four treatment arms:

- Placebo
- duloxetine 20 mg once daily (QD) (doses increases to 60 mg in the continuation therapy phase),
- duloxetine 60 mg QD
- duloxetine 120 mg QD

To be eligible, subjects were required to meet the following criteria:

- Male and female outpatients ≥ 18 years of age.

- Primary FMS as defined by the ACR: widespread aching pain in all four 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/cm².
- Score of ≥ 4 on the average pain item of the Brief Pain Inventory (BPI-Modified Short Form) at Visit 1 and Visit 2.

Subjects were to be excluded for:

- Any current primary Axis I diagnosis other than major depressive disorder (MDD), as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)
- Any current or previous DSM-IV Axis I diagnosis of psychosis, bipolar disorder, or schizoaffective disorder.
- Primary DSM-IV Axis I diagnosis of anxiety disorder within the past year (including panic disorder, agoraphobia without a history of panic disorder, obsessive compulsive disorder [OCD], post-traumatic stress disorder [PTSD], generalized anxiety disorder [GAD], and social phobia). Note: Patients with specific phobias were permitted to participate in the study.
- DSM-IV Axis II disorder, which, in the judgment of the investigator, would interfere with compliance with the study protocol.
- Suicidal risk as judged by the clinical investigator or as defined by a score of 2 or greater on question 9 of the Beck Depression Inventory-II (BDI-II).
- Past-year history of substance abuse or dependence, excluding nicotine and caffeine.
- Positive urine drug screen for any substance of abuse or excluded medication. Note: If the patient had a positive drug screen at Visit 1 for an excluded prescribed medication that may not have had an adequate wash-out period, a retest could be performed prior to Visit 2. If the retest was positive for the parent compound, the patient was to be excluded.
- Pregnancy/nursing
- Pain symptoms related to traumatic injury, structural rheumatic disease, or regional rheumatic disease (such as osteoarthritis, bursitis, tendonitis) that would interfere with interpretation of outcome measures.
- Regional pain syndrome, multiple surgeries or failed back syndrome.
- Confirmed current or previous diagnosis of rheumatoid arthritis, inflammatory arthritis, or infectious arthritis, or an autoimmune disease (for example, systemic lupus erythematosus).
- Any of the following laboratory values at Visit 1:
 - An abnormal C-Reactive Protein level (>12) that is indicative of autoimmune disease
 - Antinuclear antibody (ANA) with a dilution of $>1:320$
 - Rheumatoid factor of ≥ 15 IU/ml.
 - Alanine transaminase (ALT) >1.5 times the upper limit of normal (ULN), based on performing laboratory reference ranges.
 - Abnormal thyroid-stimulating hormone (TSH) concentrations. Note: Patients previously diagnosed with hypothyroidism who had been treated on a stable dose

of thyroid supplement for at least the past 3 months, with normal TSH concentrations and clinically euthyroid were permitted to participate in the study.

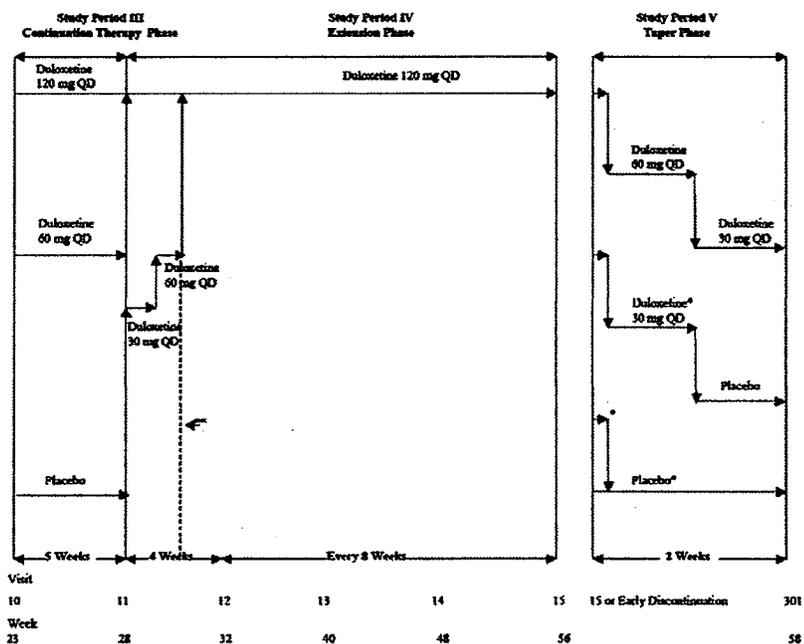
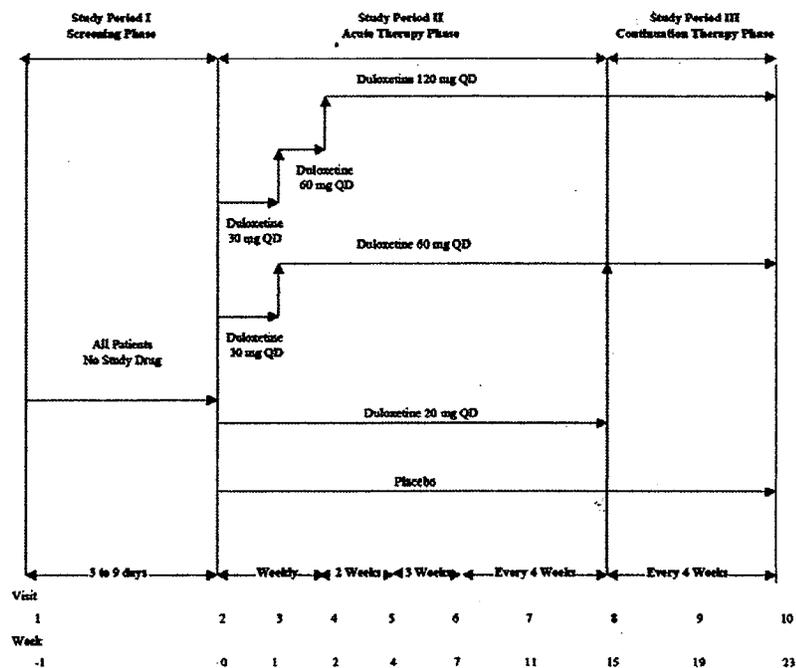
- Serious or unstable cardiovascular, hepatic, renal, respiratory, or hematologic illness, symptomatic peripheral vascular disease, or other medical condition (including unstable hypertension or not clinically euthyroid) or psychiatric conditions that, in the opinion of the investigator, would compromise participation or be likely to lead to hospitalization during the course of the study.
- Acute liver injury (such as hepatitis) or severe cirrhosis (Child- Pugh Class C).
- Uncontrolled seizures.
- Uncontrolled narrow-angle glaucoma.
- Any excluded medications that could not be discontinued at Visit 1.
- Recent (past 14 days) monoamine oxidase inhibitor (MAOI) or anticipated need to take within 5 days after discontinuing the study.
- Current or past treatment with duloxetine
- Previous participation in a duloxetine study
- Past 30 days investigational drug use
- Known hypersensitivity to duloxetine or any of the inactive ingredients history of frequent or severe allergic reactions to multiple medications.
- Patients could also be excluded if they were deemed by the investigator to be “treatment-refractory” or to have disability compensation issues that might compromise their responses.
- Employees of Lilly, Boehringer-Ingelheim, or investigator sites were also not eligible to participate.
- Disallowed concomitant medications included but were not limited to: monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), in addition to illicit drugs.

10.1.2.3.2 Procedures

The protocol described five study phases: a screening phase, an acute therapy phase, a continuation phase, an extension phase, and a taper phase.

A schematic diagram illustrates these phases:

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*To maintain the integrity of the blind, placebo-treated patients will remain on placebo, duloxetine 20 mg-treated patients will take placebo, and duloxetine 60 mg-treated patients will taper to 30 mg for one week followed by one week of placebo if they discontinue early.

**At Week 30 all patients will be on 120 mg.

Screening phase: Study Period I was a 1-week screening phase; during this period, no study drug was to be dispensed and patients were to be screened for study entry eligibility. Visit 1 entailed patient history, screening tests, electrocardiogram (ECG), assessment of ACR criteria, laboratory analyses (clinical chemistry, hematology, urinalysis, urine drug screen, and pregnancy test for all females). Visit 2 was to occur 3-9 days after Visit 1; at this visit, patients deemed eligible per Visit 1 screening results were to be enrolled.

Acute therapy phase: Eligible patients were to be randomized to double-blind treatment for 15 weeks in Study Period II (acute therapy phase). Patients randomly assigned to the placebo group or the 20 mg QD group were provided their assigned dose for 15 weeks. Patients assigned to the 60 mg QD group were provided with duloxetine 30 mg QD for the first week, followed by duloxetine 60 mg QD for 14 weeks. Patients randomly assigned to the 120 mg QD group were provided with 30 mg duloxetine QD for one week, 60 mg QD for the second week, and then duloxetine 120 mg QD for 13 weeks.

Continuation phase: Following the acute therapy phase, patients were to enter into the double-blind continuation phase (Study Period III), in which patients randomly assigned to the duloxetine 20 mg QD treatment group were blindly switched to duloxetine 60 mg QD. All other treatment groups were to continue the same therapy. All doses were to be taken for 13 weeks during this phase.

Extension phase: All patients who completed the continuation phase were eligible to enter the extension phase. Patients previously assigned to the placebo group were to be blindly titrated to duloxetine 120 mg QD over two weeks (duloxetine 30 mg QD for 1 week and duloxetine 60 mg for 1 week). Patients who ended the continuation phase taking duloxetine 60 mg QD or duloxetine 120 mg QD were to be treated with duloxetine 120 mg QD beginning at the first visit of the extension phase.

Taper phase: Patients who completed the extension phase of the study were to continue to the 2-week taper phase. Patients who discontinued the study at Visit 4 or beyond were also to undergo a 2-week taper phase. Patients receiving duloxetine 60 mg QD were to reduce their dose to 30 mg QD for 1 week and then take placebo QD for a second week. Patients receiving duloxetine 120 mg QD were to reduce their dose to 60 mg QD for 1 week and then take 30 mg QD for a second week. Patients receiving duloxetine 20 mg or placebo were to take placebo for the entire 2 weeks.

10.1.2.3.2.1 Dosing

As described above, eligible subjects were to be randomized to treatment with placebo, duloxetine 20 mg once daily (QD) (dose increases to 60 mg in the continuation therapy phase), duloxetine 60 mg QD, or duloxetine 120 mg QD in the ratio of 2:1:2:2.

Randomization was to occur at Visit 2, with assignment to treatment groups determined by a computer-generated random sequence using an Interactive Voice Response System (IVRS). Patients were to be stratified for presence or absence of MDD, with each stratum (depressed and non-depressed) randomly assigned within sites to achieve a relative balance across treatments.

Study drug treatments included:

- 20-mg capsules of duloxetine enteric-coated pellets,
- 30-mg capsules of duloxetine enteric-coated pellets,
- 60-mg capsules of duloxetine enteric-coated pellets,
- Placebo capsules identical in appearance to duloxetine capsules.

Study drug was to be dispensed to patients at the study site, packaged in blister cards or in bottles containing additional capsules to allow for sufficient study medication in case of late study visits. Patients were instructed to take their first dose of study drug the morning after Visit 2. They were instructed to swallow the study drug whole and not to crush or break the capsules. Dosing for the acute therapy phase, the continuation therapy phase, and the first 4 weeks of the extension phase required four capsules to be taken in the morning. The remaining 24 weeks of the extension phase, patients were to take two capsules. The tapering phase required four capsules (active and placebo) for blind taper.

The dosing regimen for each treatment arm is illustrated in the table below:

Treatment	Study Period	Dosage and Frequency	Dose Duration	Packaging
Placebo	Acute Phase	4 placebo capsules QD	15 weeks	Blister cards
	Continuation Phase	4 placebo capsules QD	13 weeks	Blister cards
	Extension Phase (Week 28)	1 duloxetine 30 mg capsule and 3 placebo capsules QD	1 week	Blister cards
	Extension Phase (Week 29)	2 duloxetine 30 mg capsules and 2 placebo capsules QD	1 week	Blister cards
	Extension Phase (Week 30 to Week 32)	4 duloxetine 30 mg capsules QD	2 weeks	Blister cards
	Extension Phase (Week 32 to Week 56)	2 duloxetine 60 mg capsules QD	24 weeks	Bottle
	Taper Phase ^a	4 placebo capsules QD	2 weeks	Blister cards
Duloxetine 20 mg	Acute Phase	1 duloxetine 20 mg capsule and 3 placebo capsules QD	15 weeks	Blister cards
	Continuation Phase	2 duloxetine 30 mg capsules and 2 placebo capsules QD	13 weeks	Blister cards
	Extension Phase (Week 28 to Week 32)	4 duloxetine 30mg capsules QD	4 weeks	Blister cards
	Extension Phase (Week 32 to Week 56)	2 duloxetine 60 mg capsules QD	24 weeks	Bottle
	Taper Phase ^b	4 placebo capsules QD	2 weeks	Blister cards
Duloxetine 60 mg	Acute Phase (Week 0 to Week 1)	1 duloxetine 30 mg capsule and 3 placebo capsules QD	1 week	Blister cards
	Acute Phase (Week 1 to Week 15)	2 duloxetine 30 mg capsules and 2 placebo capsules QD	14 weeks	Blister cards
	Continuation Phase	2 duloxetine 30 mg capsules and 2 placebo capsules QD	13 weeks	Blister cards
	Extension Phase (Week 28 to	4 duloxetine 30 mg capsules QD	4 weeks	Blister cards

	Week 32)			
	Extension Phase (Week 32 to Week 56)	2 duloxetine 60 mg capsules QD	24 weeks	Bottles
	Taper Phase ^c (Week 56 to Week 57)	1 duloxetine 30 mg capsule QD and 3 placebo capsule	1 week	Blister cards
	Taper Phase ^c (Week 57 to Week 58)	4 placebo capsules QD	1 week	Blister cards
Duloxetine 120 mg	Acute Phase (Week 0 to Week 1)	1 duloxetine 30 mg capsule and 3 placebo capsules QD	1 week	Blister cards
	Acute Phase (Week 1 to Week 2)	2 duloxetine 30 mg capsules and 2 placebo capsules QD	1 weeks	Blister cards
	Acute Phase (Week 2 to Week 15)	4 duloxetine 30 mg capsules QD	13 weeks	Blister cards
	Continuation Phase	4 duloxetine 30 mg capsules QD	13 weeks	Blister cards
	Extension Phase (Week 28 to Week 32)	4 duloxetine 30 mg capsules QD	4 weeks	Blister cards
	Extension Phase (Week 32 to Week 56)	2 duloxetine 60 mg capsules QD	24 weeks	Bottles
	Taper Phase (Week 56 to Week 57)	2 duloxetine 30 mg capsules and 2 placebo capsules QD	1 week	Blister cards
	Taper Phase (Week 57 to Week 58)	1 duloxetine 30 mg capsule and 3 placebo capsule QD	1 week	Blister cards
<p>a This dosage schedule was only to be used if patients discontinued early while on placebo. If patients on this arm did not discontinue early they were instead to follow the taper for duloxetine 120 mg, since they would have been on 120 mg during the extension phase. b This dosage schedule was only to be used if patients discontinued early while on duloxetine 20 mg. If patients on this arm did not discontinue early they were instead to follow the taper for duloxetine 120 mg, since they would have been on 120 mg during the extension phase. c This taper dosage schedule was only to be used if patients discontinued early while on duloxetine 60 mg. If patients on this arm did not discontinue early they were instead to follow the taper for duloxetine 120 mg, since they would have been on 120 mg during the extension phase.</p>				

10.1.2.3.2.2 Schedule of Visits and Assessments

The overall study schematic is illustrated in the figure below.

Appears This Way
 On Original

Study Schedule, Protocol F1J-MC-HMCJ

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase						Study Period III Continuation Phase			Study Period IV Extension Phase				Study Period V Taper Phase	ED 1 (Visits 3-11)	ED 2 (Visits 12-15)
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	301		
Visit																		
Week	-1	0	1	2	4	8	11	15	19	23	28	32	40	48	56	58		
Client Assessments																		
Informed Consent	x																	
Demographics	x																	
Medical History	x																	
Complete Physical Exam	x																	
Habits: Average Alcohol Consumption and Tobacco Consumption	x																	
Actual Alcohol Consumption		x						x		x					x		x	
Historical Illness and Previous Medications	x																	
ACR Criteria for FMS	x																	
MINI® (MDD diagnosis and others)	x																	

Height		x															
Weight		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG	x							x		x							
Patient Summary																x	x
Blood Pressure (Sitting), Pulse Rate	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

(continued)

Study Schedule, Protocol F1J-MC-HMCJ

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase						Study Period III Continuation Phase			Study Period IV Extension Phase				Study Period V Taper Phase	ED 1 (Visits 3-11)	ED 2 (Visits 12-15)
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	301		
Visit																		
Week	-1	0	1	2	4	8	11	15	19	23	28	32	40	48	56	58		
Preexisting Conditions and Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Study Drug																		
Dispense Drug		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Return Drug/Accountability			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Efficacy Measurements																		
Brief Pain Inventory	x	x	x	x	x	x	x	x	x	x	x		x		x		x	
PGI-Improvement			x	x	x	x	x	x	x	x	x		x		x		x	
PGI-Severity		x																
Tender Point Pain threshold ^a		x		x		x	x	x	x	x	x		x		x		x	
CGI-Severity ^b		x		x		x	x	x	x	x	x						x	
FIQ		x		x		x	x	x	x	x	x						x	
MFI		x		x		x	x	x	x	x	x						x	
BDI-II	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

HAMD ₁₇ ^a		x						x			x				x			x	x
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Study Schedule, Protocol F1J-MC-HMCJ

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase						Study Period III Continuation Phase			Study Period IV Extension Phase				Study Period V Taper Phase	ED 1 (Visits 3-11)	ED 2 (Visits 12-15)	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	30f			
Visit																			
Week	-1	0	1	2	4	8	11	15	19	23	28	32	40	48	56	58			
Health Outcomes Assessment																			
SDS		x								x			x		x			x	x
EQ-5D		x								x								x	
SF-36		x								x					x			x	x
Laboratory Assessments																			
Hematology	x									x					x			x	x
Clinical Chemistry	x				x		x	x	x	x					x			x	x
Fasting Lipid Profile	x									x					x			x	x
Urine Drug Screen	x																		
Pregnancy Test	x																		
Urinalysis	x																		
Thyroid Function Test	x																		
Antinuclear Antibody	x																		
C-Reactive Protein	x																		
Rheumatoid Factor	x																		

Abbreviations: ACR = American College of Rheumatology; BDI-II = Beck Depression Inventory –II; CGI-Severity = Clinical Global Impressions of Severity; Cont = continuation; ED = early discontinuation; ECG = electrocardiogram; EQ-5D = Euro-Qol Questionnaire – 5 Dimension; Ext = extension; FIQ = Fibromyalgia Impact Questionnaire; HAMD₁₇ = 17-item Hamilton Depression Rating Scale; MFI = Multidimensional Fatigue Inventory; MINI = Mini International Neuropsychiatric Interview; PGI-Improvement = Patient’s Global Impressions of Improvement; SF-36 = 36-item Short-Form Health Survey; SDS = Sheehan Disability Scale.

^a Qualified study personnel, as defined in Lilly training materials, must perform these assessments.

^b A study physician must administer the CGI-Severity in the presence of the patient or after having been in the presence of the patient.

^c If ED visit is being followed by the study drug tapering phase.

10.1.2.4 Evaluations/Endpoints

Primary Efficacy Measures

- The Brief Pain Inventory (BPI) – Modified Short Form (Severity and Interference scores) is a self-reported scale that measures the severity of pain and the interference of pain on function. The Severity scores range from 0 (no pain) to 10 (pain as bad as you can imagine). There are four questions assessing the severity for worst pain, least pain, average pain in the past 24 hours, and the pain right now. The Interference scores range from 0 (does not interfere) to 10 (completely interferes). There are seven questions assessing the interference of pain in the past 24 hours for general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life.
- The average pain score in the past 24-hours collected by the BPI will be used as a co-primary efficacy measure, while the rest of the BPI scores will be considered secondary.
- The Patient’s Global Impressions of Improvement (PGI-Improvement) scale will be completed by the patient and measures the degree of improvement at the time of

assessment after the randomization visit. The score ranges from 1 (very much better) to 7 (very much worse).

Secondary Efficacy Measures

- The Fibromyalgia Impact Questionnaire (FIQ) is a self-administered questionnaire that measures status of patients with fibromyalgia syndrome (FMS), progress, and outcomes over the past week. This questionnaire was designed to measure the components of health status that are believed to be most affected by FMS. The FIQ is composed of a total of 20 items; the first 11 items measure physical functioning, and each item is rated on a 4-point Likert-type scale. Items 12 and 13 measure the number of days the patient felt well and the number of days the patient felt unable to work due to their FMS symptoms. Items 14 through 20 are numerical, 11-point Likert-type scales (marked in 10-mm increments) on which the patient rates work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression. Because some patients may not do some of the tasks listed, they are given the opportunity of deleting items from scoring. The total score ranges from 0 to 80. A higher score indicates a more negative impact.
- The Clinical Global Impressions of Severity (CGI-Severity) scale evaluates the severity of illness at the time of assessment. The score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). The CGI-Severity must be administered by a study physician in the presence of the patient or after having been in the presence of the patient.
- The Tender Point Pain Threshold will be assessed for all 18 tender points by a study physician or qualified study personnel, as defined in Lilly training materials. A dolorimeter (algometer) will be used to exert the pressure at each point and to measure the threshold reading; when the patient first indicates pain, the threshold will be recorded in kg/cm².
- BPI Severity (worst pain, least pain, pain right now) and Interference scores is a self-reported scale that measures the severity of pain and the interference of pain on function. The Severity scores range from 0 (no pain) to 10 (pain as bad as you can imagine). There are four questions assessing the severity for worst pain, least pain, average pain in the past 24 hours, and the pain right now. The Interference scores range from 0 (does not interfere) to 10 (completely interferes). There are seven questions assessing the interference of pain in the past 24 hours for general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life.
- The Multidimensional Fatigue Inventory (MFI) is a 20-item, self-reporting instrument designed to collect data on the following 5 dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. Each dimension score is derived by summing the scores of the 4 individual items that pertain to each dimension. Item scores range from 1 to 5; thus, dimensional scores range from 4 to 20 with a higher score reflecting greater levels of fatigue.
- 17-item Hamilton Depression Rating Scale (HAMDI7) is a widely used observational rating measure of depression severity. This must be completed by a Lilly-approved rater. The HAMDI7 will be used to assess the severity of depression and its improvement

during the course of therapy. The HAMD17 total score ranges from 0 (not at all depressed) to 52 (severely depressed).

- Beck Depression Inventory-II (BDI-II) is a 21-item patient-completed questionnaire designed to assess characteristics of depression. Each item is rated on a 4-point scale (0 = not present; 3 = present in the extreme). This questionnaire will be used to rate the severity of depressive symptoms and any improvement during the course of the trial. The total score ranges from 0 to 63; the higher the score, the more severe the depressive symptoms.
- The Patient's Global Impressions of Severity (PGI-Severity) scale will be completed by the patient and measures the degree of severity at baseline.

Health Outcome/Quality of Life Measures

- The patient-rated Sheehan Disability Scale (SDS) will be used to assess the patient's general level of disability. The scale measures a patient's evaluation of the degree to which his or her symptoms have disrupted work, social, and/or home life.
- The patient-rated 36-item Short Form Health Survey (SF-36) consists of 36 questions covering eight 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 by summing the individual items and transforming the scores into a 0 to 100 scale, with higher scores indicating better health status or functioning. Two summary scores are constructed based on the eight SF-36 domains.
- The EuroQoL Questionnaire – 5 Dimension (EQ-5D) is a generic, multidimensional, health-related, quality-of-life instrument. The profile allows patients to rate their health state in five health domains: mobility, self-care, usual activities, pain/discomfort, and mood. A single score between 1 and 3 is generated for each domain. For each patient, the outcome rating on the five domains will be mapped to a single index through an algorithm. The index ranges between 0 and 1 with the higher score indicating a better health state perceived by the patient.

Safety Measures

- Adverse Events: During the study, adverse events were collected at every visit, regardless of relationship to study medication. These events were captured as actual terms and coded to Medical Dictionary for Regulatory Activities (MedDRA) terms by blinded Lilly clinical personnel.
- Discontinuations: If a patient's dosage was reduced or treatment was discontinued as a result of an adverse event, study site personnel clearly documented the circumstances and data leading to any such dosage reduction or discontinuation of treatment, using the CRF.
- Concomitant Medications: All concomitant medications taken during the study were recorded.
- Laboratory Data: During the study, standard laboratory tests, including chemistry, hematology, and urinalysis panels, were collected at regular intervals. A urine drug screen, thyroid function test, and pregnancy test (if applicable) were completed at screening.

- Vital Signs: During the study, vital signs, including sitting blood pressure (systolic and diastolic) and heart rate, weight, and height, were collected at regular intervals.
- Electrocardiograms (ECGs): An ECG was collected at screening only to determine eligibility of the patient for entry into the study.

10.1.2.5 Statistical Plan

Efficacy Analysis

The main objective was to evaluate the efficacy of 120 mg QD versus placebo in the treatment of patients with FM.

The co-primary efficacy measures were BPI average pain score and PGI-Improvement. The co-primary efficacy analyses were to test the null hypothesis that the treatment-group differences between duloxetine 120 mg QD and placebo on the baseline-to-endpoint change scores for the BPI average pain score or on the endpoint PGI-Improvement during the 3-month acute therapy phase was zero.

The null hypothesis was tested by a treatment group contrast from an ANCOVA model. For the analysis on changes on BPI average pain score, the baseline scores were used as a covariate; for the analysis on the endpoint of PGI, the score from the PGI-Severity at baseline were used as a covariate in the model. The treatment-by-investigator interaction was tested at the significance level of 0.10 with the addition of the term before drawing inferences from the previously detailed ANCOVA and ANOVA models. Treatment-group differences based on the difference in LSM means were tested at the significance level of 0.05 for each of the co-primary efficacy measures.

10.1.2.6 Results

10.1.2.6.1 Study Conduct/Outcome

10.1.2.6.1.1 Subject Characteristics

The Applicant planned to enroll 490 patients in this study. A total of 520 were randomized, 144 to treatment with placebo, 79 to duloxetine 20 mg QD, 150 to duloxetine 60 mg QD, and 147 to duloxetine 120 mg QD.

10.1.2.6.1.2 Enrollment by Center

Enrollment was distributed among centers as listed in the table below:

Table HMCJ.14.1. Patient Allocation by Investigator
 All Randomized Patients
 6-Month Acute Therapy Phase

The FRQ Procedure
 Table of INVID by TREATMENT

INVID (Clinical Investigator Number)
 TREATMENT (Treatment)

Frequency Row Pct	PLACEBO	OLEGROD	OLEL100D	OLEL20/60 OD	Total
100	2	6	4	4	22
	11.02	22.73	27.27	18.18	
101	6	6	6	3	16
	22.22	22.22	27.27	16.67	
102	6	7	6	3	22
	27.27	21.62	27.27	13.64	
103	27.27	27.27	18.18	27.27	11
	27.27	27.27	18.18	27.27	
104	6	2	6	3	17
	18.18	11.02	27.27	16.67	
Total (Continued)	144	150	147	79	520

Table HMCJ.14.1. Patient Allocation by Investigator
 All Randomized Patients
 6-Month Acute Therapy Phase (Continued)

The FRQ Procedure
 Table of INVID by TREATMENT

INVID (Clinical Investigator Number)
 TREATMENT (Treatment)

Frequency Row Pct	PLACEBO	OLEGROD	OLEL100D	OLEL20/60 OD	Total
106	2	7	5	4	22
	27.27	11.02	22.73	18.18	
107	6	6	6	3	16
	22.22	22.22	27.27	16.67	
108	6	4	6	3	17
	22.22	23.03	27.27	17.46	
109	6	2	6	3	17
	27.27	11.02	27.27	16.67	
110	6	2	6	3	17
	27.27	11.02	27.27	16.67	
111	6	2	6	3	17
	27.27	11.02	27.27	16.67	
Total (Continued)	144	150	147	79	520

Table HMCJ.14.1. Patient Allocation by Investigator
 All Randomized Patients
 6-Month Acute Therapy Phase (Continued)

The FRQ Procedure
 Table of INVID by TREATMENT

INVID (Clinical Investigator Number)
 TREATMENT (Treatment)

Frequency Row Pct	PLACEBO	OLEGROD	OLEL100D	OLEL20/60 OD	Total
112	7	6	7	4	24
	29.17	25.00	29.17	16.67	
113	6	4	6	3	19
	22.22	16.67	27.27	16.67	
114	3	2	3	2	10
	18.00	10.00	18.00	10.00	
115	6	2	6	3	17
	27.27	11.02	27.27	16.67	
116	6	2	6	3	17
	27.27	11.02	27.27	16.67	
117	6	2	6	3	17
	27.27	11.02	27.27	16.67	
Total (Continued)	144	150	147	79	520

Table HMCJ.14.1. Patient Allocation by Investigator
 All Randomized Patients
 6-Month Acute Therapy Phase (Continued)

The FRQ Procedure
 Table of INVID by TREATMENT

INVID (Clinical Investigator Number)
 TREATMENT (Treatment)

Frequency Row Pct	PLACEBO	OLEGROD	OLEL100D	OLEL20/60 OD	Total
118	14.29	42.86	28.57	14.29	7
	14.29	42.86	28.57	14.29	
119	3	3	3	2	6
	22.22	16.67	22.22	16.67	
120	12	14	14	7	47
	27.80	39.17	29.17	24.58	
121	26.57	14.29	42.86	14.29	7
	26.57	14.29	42.86	14.29	
122	14.29	18.57	42.86	14.29	7
	14.29	18.57	42.86	14.29	
Total (Continued)	144	150	147	79	520

Table HMCJ.14.1. Patient Allocation by Investigator
 All Randomized Patients
 6-Month Acute Therapy Phase (Continued)

The FRQ Procedure
 Table of INVID by TREATMENT

INVID (Clinical Investigator Number)
 TREATMENT (Treatment)

Frequency Row Pct	PLACEBO	OLEGROD	OLEL100D	OLEL20/60 OD	Total
123	3	3	3	1	10
	10.43	10.00	10.00	10.00	
124	7	7	6	3	23
	10.43	10.43	24.09	13.04	
125	6	6	6	3	21
	14.79	24.09	24.09	13.04	
126	5	6	6	4	21
	17.78	19.33	22.22	16.67	
127	5	5	5	3	18
	27.50	27.50	27.50	16.67	
Total (Continued)	144	150	147	79	520

Table HMCJ.14.1. Patient Allocation by Investigator
 All Randomized Patients
 6-Month Acute Therapy Phase (Continued)

The FRQ Procedure
 Table of INVID by TREATMENT

INVID (Clinical Investigator Number)
 TREATMENT (Treatment)

Frequency Row Pct	PLACEBO	OLEGROD	OLEL100D	OLEL20/60 OD	Total
128	4	4	4	2	15
	26.67	26.67	33.33	13.33	
129	2	2	2	2	8
	25.00	25.00	25.00	25.00	
130	16	16	16	7	55
	28.57	28.57	28.57	14.29	
131	2	2	2	1	7
	22.22	22.22	44.44	11.11	
132	3	3	3	1	10
	17.50	17.50	17.50	12.50	
133	3	3	3	1	10
	17.50	17.50	17.50	12.50	
Total (Continued)	144	150	147	79	520

Table HMCJ.14.1. Patient Allocation by Investigator
 All Randomized Patients
 6-Month Acute Therapy Phase (Concluded)

The FRQ Procedure
 Table of INVID by TREATMENT

INVID (Clinical Investigator Number)
 TREATMENT (Treatment)

Frequency Row Pct	PLACEBO	OLEGROD	OLEL100D	OLEL20/60 OD	Total
134	2	3	2	1	8
	15.00	17.50	25.00	12.50	
135	2	2	2	2	8
	22.22	22.22	13.33	22.22	
136	0	3	0	0	3
	0.00	30.00	0.00	0.00	
137	3	5	3	1	12
	25.00	41.67	25.00	8.33	
138	2	2	2	0	6
	40.00	20.00	40.00	0.00	
Total	144	150	147	79	520

10.1.2.6.1.3 Subject Disposition

A total of 520 subjects were randomized in a 1:2:2:2 ratio.

	Placebo N = 144	DLX 20 QD N = 79	DLX 60 QD N = 150	DLX 120 QD N = 147
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%)		

	Placebo N = 144	DLX 20/60 QD N = 79	DLX 60 QD N = 150	DLX 120 QD N = 147
Completed 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%)

The applicant provided discontinuation tables by treatment visit. During the initial 3-Month Treatment Phase, across all treatment groups, the most frequent reasons for withdrawal were adverse event (n=79), lack of efficacy (n=39), subject decision (n=32), lost to follow-up (n=30), protocol violation (n=11), physician decision (n=3), and entry criteria exclusion (n=1).

For the entire 6-Month Therapy Phase, across all treatment groups, the most frequent reasons for withdrawal were adverse event (n=90), lack of efficacy (n=46), subject decision (n=44), lost to follow-up (n=40), protocol violation (n=14), physician decision (n=7), entry criteria exclusion (n=1), and sponsor decision (n=1).

10.1.2.6.2 Demographics

The table below illustrates demographic and baseline characteristics of the 4 treatment groups. Overall, most patients were Caucasian females, with a median age of 51 years, a median weight of 80 kilograms, and a median height of 163 cm. Approximately 25% had a concomitant diagnosis of major depressive disorder and 5% had an anxiety disorder.

**Table HMCJ.11.1. Patient Demographics
 All Randomized Patients**

Variable	PLACEBO (N=144)	DLX60QD (N=150)	DLX120QD (N=147)	DLX20/60QD (N=79)	Total (N=520)
Sex					
No. of Patients	144	150	147	79	520
Female	137 (95.14)	136 (90.67)	143 (97.28)	76 (96.20)	492 (94.62)
Male	7 (4.86)	14 (9.33)	4 (2.72)	3 (3.80)	28 (5.38)
Age in Years at Consent					
No. of Patients	144	150	147	79	520
Mean	50.28	51.75	51.04	50.93	51.02
Median	52.42	53.45	52.94	50.52	52.70
Standard Dev.	10.92	10.63	10.85	11.37	10.87
Minimum	18.93	24.57	23.31	20.93	18.93
Maximum	73.56	74.38	70.28	77.03	77.03
Race					
No. of Patients	144	150	147	79	520
African	5 (3.47)	3 (2.00)	4 (2.72)	4 (5.06)	16 (3.08)
Caucasian	119 (82.64)	127 (84.67)	126 (85.71)	66 (83.54)	438 (84.23)
East Asian	0 (0.00)	1 (0.67)	0 (0.00)	0 (0.00)	1 (0.19)
Hispanic	20 (13.89)	16 (10.67)	17 (11.56)	9 (11.39)	62 (11.92)
Native American	0 (0.00)	2 (1.33)	0 (0.00)	0 (0.00)	2 (0.38)
West Asian (Indian sub-continent)	0 (0.00)	1 (0.67)	0 (0.00)	0 (0.00)	1 (0.19)
Weight in Kg at Baseline					
No. of Patients	144	150	147	79	520
Mean	82.60	83.28	84.42	83.03	83.38
Median	80.06	79.83	78.93	78.47	79.38
Standard Dev.	21.29	19.53	22.82	21.87	21.29
Minimum	47.63	51.26	48.99	46.72	46.72
Maximum	172.72	158.76	170.10	157.85	172.72

**Table HMCJ.11.1. Patient Demographics
 All Randomized Patients (Concluded)**

Variable	PLACEBO (N=144)	DLX60QD (N=150)	DLX120QD (N=147)	DLX20/60QD (N=79)	Total (N=520)
Diagnosis of Major Depressive Disorder					
No. of Patients	144	150	147	79	520
No	109 (75.69)	115 (76.67)	113 (76.87)	57 (72.15)	394 (75.77)
Yes	35 (24.31)	35 (23.33)	34 (23.13)	22 (27.85)	126 (24.23)
Secondary Diagnosis of Anxiety					
No. of Patients	35	35	34	22	126
No	32 (91.43)	33 (94.29)	32 (94.12)	22 (100.00)	119 (94.44)
Yes	3 (8.57)	2 (5.71)	2 (5.88)	0 (0.00)	7 (5.56)
Previous Antidepressant Use					
No. of Patients	144	150	147	79	520
No	85 (59.03)	80 (53.33)	86 (58.50)	37 (46.84)	288 (55.38)
Yes	59 (40.97)	70 (46.67)	61 (41.50)	42 (53.16)	232 (44.62)
Height					
No. of Patients	144	148	147	78	517
Mean	163.53	163.07	163.04	163.63	163.28
Median	162.56	162.56	162.56	162.56	162.56
Standard Dev.	7.78	7.86	7.03	5.00	7.31
Minimum	127.00	137.16	139.70	149.86	127.00
Maximum	182.88	193.04	185.42	177.80	193.04

10.1.2.6.3 Dosing Information

The tables below illustrate exposure duration and compliance with medication across treatment groups for the 3-Month Therapy Phase and the 6-Month Therapy Phase. Groups were similar with respect to mean duration of exposure.

**Table HMCJ.12.1. Study Drug Exposure
 All Randomized Patients
 3-Month Therapy Phase**

Variable	PLACEBO (N=144)	DLX20QD (N=79)	DLX60QD (N=150)	DLX120QD (N=147)	Total (N=520)
Duration of Exposure (Days)					
NO. SUBJECTS	142	78	149	143	512
MEAN	78.89	90.71	81.94	87.43	83.96
STD	38.36	33.39	38.40	34.81	36.83
MAXIMUM	165.00	138.00	122.00	126.00	165.00
MEDIAN	103.00	105.00	104.00	104.00	104.00
MINIMUM	1.00	1.00	2.00	1.00	1.00
Patient Years	30.67	19.37	33.43	34.23	117.70
Duration of Exposure -n(%)					
NO. SUBJECTS	142	78	149	143	512
>0	142 (100.0)	78 (100.0)	149 (100.0)	143 (100.0)	512 (100.0)
>=7	137 (96.5)	77 (98.7)	140 (94.0)	134 (93.7)	488 (95.3)
>=14	134 (94.4)	72 (92.3)	131 (87.9)	130 (90.9)	467 (91.2)
>=28	118 (83.1)	68 (87.2)	123 (82.6)	124 (86.7)	433 (84.6)
>=49	105 (73.9)	66 (84.6)	117 (78.5)	121 (84.6)	409 (79.9)
>=77	91 (64.1)	66 (84.6)	105 (70.5)	109 (76.2)	371 (72.5)
>=105	56 (39.4)	41 (52.6)	60 (40.3)	67 (46.9)	224 (43.8)

**Table HMCJ.12.2. Study Drug Exposure
 All Randomized Patients
 6-Month Therapy Phase**

Variable	PLACEBO (N=144)	DLX60QD (N=150)	DLX120QD (N=147)	DLX20/60QD (N=79)	Total (N=520)
Duration of Exposure (Days)					
NO. SUBJECTS	142	149	143	78	512
MEAN	127.49	137.98	143.69	146.14	137.91
STD	78.15	77.67	72.40	69.52	75.38
MAXIMUM	224.00	237.00	224.00	222.00	237.00
MEDIAN	189.00	193.00	193.00	192.50	192.00
MINIMUM	1.00	2.00	1.00	1.00	1.00
Patient Years	49.57	56.29	56.26	31.21	193.32
Duration of Exposure -n(%)					
NO. SUBJECTS	142	149	143	78	512
>0	142 (100.0)	149 (100.0)	143 (100.0)	78 (100.0)	512 (100.0)
>=7	137 (96.5)	140 (94.0)	134 (93.7)	77 (98.7)	488 (95.3)
>=14	134 (94.4)	131 (87.9)	130 (90.9)	72 (92.3)	467 (91.2)
>=28	118 (83.1)	123 (82.6)	124 (86.7)	69 (87.2)	433 (84.6)
>=49	105 (73.9)	117 (78.5)	121 (84.6)	66 (84.6)	409 (79.9)
>=77	91 (64.1)	105 (70.5)	109 (76.2)	66 (84.6)	371 (72.5)
>=105	85 (59.3)	101 (67.8)	98 (69.5)	56 (71.8)	340 (66.4)

10.1.2.6.4 Protocol Violations

Protocol deviations were identified programmatically by searching the database for randomized subjects who had screening or baseline values falling outside of the ranges specified by inclusion or exclusion criteria (eg, values for age, weight, medical history, smoking history, laboratory parameters, etc). The database was also searched for subjects who used prohibited medications during the study and subjects who were withdrawn from the study due to protocol deviations. In addition, lists of protocol deviations were compiled by site monitors during routine center visits or during remote review of electronic data. All deviations identified by the methods described above were reviewed by Lilly for clinical significance. Those considered potentially significant are summarized in the table below.

Violation Type	Patient	Violation Details
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Exclusionary Con. Med. Taken	100/1003	CYCLOBENZAPRINE
	100/1027	ORPHENADRINE
	106/1600	CARISOPRODOL
	106/1600	DEXTROMETHORPHAN
	106/1600	TIZANIDINE
	106/1617	DEXTROMETHORPHAN
	106/1621	LIDOCAINE
	106/1626	METHOCARBAMOL
	107/1707	CYCLOBENZAPRINE
	107/1711	LIDOCAINE
	109/1907	CARBAMAZEPINE
	109/1907	VENLAFAXINE
	109/1920	HYPERICUM PERFORATUM
	110/2021	LIDOCAINE
	110/2056	AMITRIPTYLINE
	110/2060	FLUOXETINE
	111/2107	CARISOPRODOL
	112/2242	CYCLOBENZAPRINE
	115/2511	SERTRALINE
	118/2818	LIDOCAINE
	120/3013	TOPIRAMATE
	120/3054	DEXTROMETHORPHAN
	121/3103	ESCITALOPRAM
	124/3401	SERTRALINE
	124/3403	CITALOPRAM
	124/3403	TIZANIDINE
	124/3411	CYCLOBENZAPRINE
	124/3411	VENLAFAXINE
	126/3614	DEXTROMETHORPHAN
	126/3631	ORPHENADRINE
	128/3807	ORPHENADRINE
	128/3818	ORPHENADRINE
	128/3819	CYCLOBENZAPRINE
	128/3827	DEXTROMETHORPHAN
	128/3827	ORPHENADRINE
	128/3833	AMITRIPTYLINE
	130/4029	FLUOXETINE
	132/4222	METAXALONE
	132/4222	ROPINIROLE
	135/4538	ZIPRASIDONE
	135/4542	TRAZODONE
	135/4549	METAXALONE
	135/4553	TRAZODONE
	135/4568	PAROXETINE
	135/4575	TRAZODONE
	138/4804	CISATRACURIUM BESILATE
	138/4804	LIDOCAINE
	138/4804	SUXAMETHONIUM
	139/4902	BUTALBITAL
Inclusion/Exclusion	100/1018	Pt randomized with an ALT > 1.5 X ULN
	107/1701	Pt had previous duloxetine exposure
	107/1709	Pt did not receive > = 7 day washout from an antidepressant, antipsychotic, or anticonvulsant medication.
	110/2060	Pt did not receive > = 30 day washout from fluoxetine
	112/2213	Pt did not receive > = 7 day washout from an antidepressant, antipsychotic, or anticonvulsant medication.
	115/2509	Pt randomized with an ALT > 1.5 X ULN
	115/2512	Pt did not receive > = 7 day washout from an antidepressant,
	115/2513	Pt randomized with an ALT > 1.5 X ULN
	118/2818	Pt did not receive > = 7 day washout from an antidepressant,
	124/3418	Pt did not receive > = 7 day washout from an antidepressant,
	125/3506	Pt did not receive > = 7 day washout from an antidepressant,

	125/3511	Pt randomized with an RF > 15 IU ml
	125/3519	Pt did not receive > = 7 day washout from an antidepressant, antipsychotic, or anticonvulsant medication.
	125/3532	Pt did not receive > = 7 day washout from an antidepressant, antipsychotic, or anticonvulsant medication.
	126/3601	Pt had previous duloxetine exposure
	126/3602	Pt had previous duloxetine exposure
	126/3605	Pt did not receive > = 7 day washout from an antidepressant, antipsychotic, or anticonvulsant medication.
	126/3634	Pt did not receive > = 7 day washout from an antidepressant, antipsychotic, or anticonvulsant medication.
	126/3634	Pt did not receive > = 30 day washout from fluoxetine
	130/4001	Pt did not receive > = 7 day washout from an antidepressant, antipsychotic, or anticonvulsant medication.
	132/4214	Pt did not receive > = 7 day washout from an antidepressant, antipsychotic, or anticonvulsant medication.
	135/4521	Pt did not receive > = 7 day washout from an antidepressant, antipsychotic, or anticonvulsant medication.
	135/4525	Pt did not receive > = 7 day washout from an antidepressant, antipsychotic, or anticonvulsant medication.
	135/4528	Pt did not receive > = 7 day washout from an antidepressant, antipsychotic, or anticonvulsant medication.
	135/4530	Pt did not receive > = 7 day washout from an antidepressant, antipsychotic, or anticonvulsant medication.
	135/4534	Pt did not receive > = 7 day washout from an antidepressant,
	135/4538	Pt did not receive > = 7 day washout from an antidepressant,
	135/4542	Pt did not receive > = 7 day washout from an antidepressant,
	135/4550	Pt did not receive > = 30 day washout from fluoxetine
	135/4558	Pt did not receive > = 7 day washout from an antidepressant, antipsychotic, or anticonvulsant medication.
	135/4568	Pt did not receive > = 7 day washout from an antidepressant, antipsychotic, or anticonvulsant medication.
	135/4576	Pt did not receive > = 7 day washout from an antidepressant, antipsychotic, or anticonvulsant medication.
	135/4587	Pt did not receive > = 7 day washout from an antidepressant, antipsychotic, or anticonvulsant medication.
	138/4812	Pt did not receive > = 7 day washout from an antidepressant, antipsychotic, or anticonvulsant medication.
	142/5200	Pt randomized with an RF > 15 IU ml
Restricted Con. Med. Overused	106/1623	ZOLPIDEM
	110/2018	VICODIN
	110/2021	PROPACET
	111/2107	MORPHINE
	111/2107	OXYCOCET
	111/2107	PETHIDINE
	111/2107	VICODIN
	111/2116	PANADEINE CO
	112/2232	VICODIN
	119/2900	VICODIN
	120/3027	TYLENOL PM
	123/3304	OXYCODONE
	124/3406	OXYCOCET
	132/4201	MORPHINE
	132/4201	VICODIN
	135/4506	PANADEINE CO
	135/4542	OXYCODONE
	135/4549	ZOPICLONE
	135/4572	VICODIN
	138/4802	MORPHINE
	138/4806	VICODIN

Protocol violations included subjects who did not meet inclusion/exclusion criteria, generally with no implications for interpretation of efficacy results, as well as several subjects who took contraindicated medications during the treatment phase and overused restricted contraindicated medications during the treatment phase.

10.1.2.7 Efficacy Results

Applicant's Analysis

Co-Primary Efficacy Analyses – 3-month Therapy Phase: Patient's Global Impression of Improvement and Brief Pain Inventory Average Pain Score

The primary objective of the study was to assess the efficacy of duloxetine 120 mg QD compared with placebo on the treatment of FM during the 3-month therapy phase as measured by the PGI-Improvement and the BPI average pain score. The Applicant states that duloxetine 120 mg QD and duloxetine 60 mg QD showed a significantly greater mean decreased (improvement) compared with placebo. The table below shows the results of the BPI average pain score mean change from baseline to endpoint at the end of 3-months.

**Table HMCJ.11.9. Brief Pain Inventory Average Pain Score
 Mean Change from Baseline to Endpoint
 All Randomized Patients
 3-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
1) PLACEBO	139	6.57	1.70	7.0	4.0	10.0	5.19	2.52	5.0	0.0	10.0	-1.38	2.37	-1.0	-6.0	3.0
2) DLX20QD	77	6.74	1.62	7.0	4.0	10.0	4.74	2.37	5.0	0.0	10.0	-2.00	2.39	-2.0	-9.0	3.0
3) DLX60QD	144	6.46	1.43	6.5	4.0	10.0	4.53	2.28	5.0	0.0	10.0	-1.94	2.25	-2.0	-8.0	4.0
4) DLX120QD	142	6.41	1.59	6.0	4.0	10.0	4.18	2.44	4.0	0.0	10.0	-2.23	2.44	-2.0	-9.0	4.0

Interaction (Type II SS) Raw Data Treatment-by-Pooled Investigator F= 0.66 df= 42,441 p= .951

Main Effects (Type II SS) Raw Data
 Treatment F= 4.08 df= 3,483 p= .007
 Pooled Investigator F= 0.95 df= 14,483 p= .503

Least Squares Means for Change from Baseline
 1) PLACEBO -1.39 (SE= 0.20)
 2) DLX20QD -1.92 (SE= 0.27)
 3) DLX60QD -2.00 (SE= 0.20)
 4) DLX120QD -2.31 (SE= 0.20)

Pairwise Comparison of LS Means
 DLX20QD - PLACEBO diff= -0.53 Two-sided 95% CI : (-1.16, 0.10) t= -1.66 p= .097
 DLX60QD - PLACEBO diff= -0.62 Two-sided 95% CI : (-1.15, -0.09) t= -2.31 p= .022
 DLX120QD - PLACEBO diff= -0.93 Two-sided 95% CI : (-1.45, -0.40) t= -3.44 p= <.001
 DLX60QD - DLX20QD diff= -0.08 Two-sided 95% CI : (-0.71, 0.54) t= -0.27 p= .791
 DLX120QD - DLX20QD diff= -0.39 Two-sided 95% CI : (-1.02, 0.24) t= -1.23 p= .221
 DLX120QD - DLX60QD diff= -0.31 Two-sided 95% CI : (-0.83, 0.22) t= -1.15 p= .250

Type II sums of squares from ANCOVA Model = Treatment, Pooled Investigator, and Baseline for main effects p-values. Model = Treatment, Pooled Investigator, Baseline, and Treatment*Pooled Investigator for the interaction p-value. N = Number of patients with a baseline and at least one non-missing post-baseline value.

Report: RMP.FLJ0.HMCJSTAT.INTRM1(LOBP1A1)
 Program: RMP.FLJ0.HMCJ.SASPGM(LOBP1A1)
 Data: RMP.SAS.FLJ0.L.HMCJ03.ADS.INTRM1

The table below shows the results of the PGI-Improvement mean score at endpoint at the end of 3-months. The Applicant states that all duloxetine treatment groups showed a significantly greater patient-rated improvement at endpoint compared with placebo.

Appears This Way
 On Original

**Table HMCJ.11.10. Patient's Global Impressions of Improvement
 Mean Score at Endpoint
 All Randomized Patients
 3-Month Therapy Phase**

PGI-Improvement	Endpoint					
	N	Mean	SD	Median	Min	Max
1) PLACEBO	139	3.49	1.49	3.0	1.0	7.0
2) DLX20QD	77	2.97	1.46	3.0	3.0	6.0
3) DLX60QD	141	3.12	1.48	3.0	1.0	7.0
4) DLX120QD	141	3.00	1.54	3.0	1.0	7.0

Interaction (Type II SS)	Raw Data	Treatment-by-Pooled Investigator	F= 1.04	df= 42,436	p= .409
Main Effects (Type II SS)	Raw Data				
Treatment	F= 3.57	df= 3,478	p= .014		
Pooled Investigator	F= 3.00	df= 14,478	p= <.001		

Least Squares Means for Endpoint		
1) PLACEBO	3.39	(SE= 0.13)
2) DLX20QD	2.95	(SE= 0.17)
3) DLX60QD	3.04	(SE= 0.13)
4) DLX120QD	2.89	(SE= 0.13)

Pairwise Comparison of LS Means						
DLX20QD - PLACEBO	diff=	-0.55	Two-sided 95% CI :	(-0.95, -0.14)	ts= -2.64	ps= .009
DLX60QD - PLACEBO	diff=	-0.35	Two-sided 95% CI :	(-0.70, -0.01)	ts= -2.02	ps= .044
DLX120QD - PLACEBO	diff=	-0.50	Two-sided 95% CI :	(-0.84, -0.16)	ts= -2.86	ps= .004
DLX60QD - DLX20QD	diff=	0.19	Two-sided 95% CI :	(-0.21, 0.60)	ts= 0.93	ps= .351
DLX120QD - DLX20QD	diff=	0.05	Two-sided 95% CI :	(-0.36, 0.45)	ts= 0.23	ps= .820
DLX120QD - DLX60QD	diff=	-0.15	Two-sided 95% CI :	(-0.49, 0.19)	ts= -0.84	ps= .400

Type II sums of squares from ANCOVA Model = Treatment, Pooled Investigator, and Baseline PGI-S for main effects p-values. Model = Treatment, Pooled Investigator, Baseline PGI-S, and Treatment*Pooled Investigator for interaction p-value. N = Number of patients with baseline PGI-S and at least one non-missing post-baseline PGI-I value.

Report: RMP.FLJG.HMCJSTAT.INTRM1(LOPGIALL)
 Program: RMP.FLJG.HMCJ.SASPGM(LOPGIALL)
 Date: RMP.SAS.FLJG.L.WCHMCJ.ADS.INTRM1

Secondary Endpoints

Secondary Gatekeeper Analyses

Using a gatekeeper strategy, secondary objectives were sequentially tested as follows:

- Comparison of duloxetine 60 mg QD and placebo on BPI average pain score mean change and the endpoint of the PGI-I at 3 months.
- Comparison of duloxetine 120 mg QD and placebo on the BPI average pain score mean change and the endpoint of the PGI-I at 6 months.
- Comparison of duloxetine 60 mg QD and placebo on the BPI average pain score mean change and the endpoint PGI-I at 6 months
- Comparison of the duloxetine 120 mg QD and placebo on the BPI average pain score mean change and the endpoint PGI-I at 6 months.
- Comparison of duloxetine 60 mg QD and placebo on the SDS total score mean change at 6 months.
- Comparison of duloxetine 120 mg QD and placebo on the SDS total score mean change at 3 months.
- Comparison of duloxetine 60 mg QD and placebo on the SDS total score mean change at 3 months.

The following table shows the mean change analysis of the BPI average pain score for all randomized patients during the 6-month therapy phase. The Applicant states that all duloxetine treatment groups showed a significantly greater mean decrease (improvement) compared with placebo.

Table HMCJ.11.11. 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	
1) PLACEBO	139	6.57	1.70	7.0	4.0	10.0	5.17	2.56	5.0	0.0	10.0	-1.40	2.53	-1.0	-9.0	3.0	
2) DLX60QD	144	6.46	1.41	6.5	4.0	10.0	4.56	2.49	5.0	0.0	10.0	-1.90	2.52	-2.0	-8.0	4.0	
3) DLX120QD	142	6.41	1.59	6.0	4.0	10.0	4.27	2.49	4.0	0.0	10.0	-2.14	2.30	-2.0	-9.0	4.0	
4) DLX20/60QD	77	6.74	1.62	7.0	4.0	10.0	4.47	2.50	4.0	0.0	10.0	-2.27	2.51	-2.0	-9.0	3.0	

Interaction (Type II SS) Raw Data Treatment-by-Pooled Investigator F= 0.82 df= 42,441 p= .783

Main Effects (Type II SS) Raw Data
 Treatment F= 1.48 df= 3,483 p= .016
 Pooled Investigator F= 1.52 df= 11,483 p= .098

Least Squares Means for Change from Baseline
 1) PLACEBO -1.43 (SE= 0.21)
 2) DLX60QD -1.99 (SE= 0.21)
 3) DLX120QD -2.25 (SE= 0.21)
 4) DLX20/60QD -2.22 (SE= 0.21)

Pairwise Comparison of LS Means
 DLX60QD - PLACEBO diff= -0.57 Two-sided 95% CI : (-1.12, -0.02) t= -2.05 p= .041
 DLX120QD - PLACEBO diff= -0.83 Two-sided 95% CI : (-1.38, -0.28) t= -2.97 p= .003
 DLX20/60QD - PLACEBO diff= -0.79 Two-sided 95% CI : (-1.45, -0.14) t= -2.38 p= .018
 DLX120QD - DLX60QD diff= -0.26 Two-sided 95% CI : (-0.81, 0.29) t= -0.94 p= .348
 DLX20/60QD - DLX60QD diff= -0.22 Two-sided 95% CI : (-0.87, 0.43) t= -0.67 p= .503
 DLX20/60QD - DLX120QD diff= 0.04 Two-sided 95% CI : (-0.61, 0.69) t= 0.11 p= .909

Type II sums of squares from ANCOVA Model = Treatment, Pooled Investigator, and Baseline for main effects p-values. Model = Treatment, Pooled Investigator, Baseline, and Treatment*Pooled Investigator for the interaction p-value. N = Number of patients with a baseline and at least one non-missing post-baseline value.

Report: EMP.F130.HMCJSTAT.INTRM1(L08P1A12)
 Program: EMP.F130.HMCJ.SASPGM(L08P1A12)
 Data: EMP.SAS.F130.L.HMCJ.ADS.INTRM1

The following table shows the PGI-I mean score at endpoint for all randomized patient during the 6-month therapy phase. The Applicant states that duloxetine 120 mg QD and 20/60 mg QD showed a significantly greater patient-rated improvement at endpoint compared with placebo.

Table HMCJ.11.12. Patient's Global Impressions of Improvement Mean Score at Endpoint All Randomized Patients 6-Month Therapy Phase

PGI-Improvement	Endpoint					
	N	Mean	SD	Median	Min	Max
1) PLACEBO	138	3.44	1.48	3.0	1.0	7.0
2) DLX60QD	141	3.24	1.54	3.0	1.0	7.0
3) DLX120QD	141	3.01	1.53	3.0	1.0	7.0
4) DLX20/60QD	77	2.91	1.48	3.0	1.0	6.0

Interaction (Type II SS) Raw Data Treatment-by-Pooled Investigator F= 0.82 df= 42,436 p= .783

Main Effects (Type II SS) Raw Data
 Treatment F= 3.25 df= 3,476 p= .022
 Pooled Investigator F= 2.18 df= 11,476 p= .082

Least Squares Means for Endpoint
 1) PLACEBO 3.37 (SE= 0.13)
 2) DLX60QD 3.09 (SE= 0.13)
 3) DLX120QD 2.93 (SE= 0.13)
 4) DLX20/60QD 2.80 (SE= 0.17)

Pairwise Comparison of LS Means
 DLX60QD - PLACEBO diff= -0.28 Two-sided 95% CI : (-0.64, 0.06) t= -1.61 p= .108
 DLX120QD - PLACEBO diff= -0.45 Two-sided 95% CI : (-0.80, -0.10) t= -2.52 p= .012
 DLX20/60QD - PLACEBO diff= -0.58 Two-sided 95% CI : (-1.09, -0.16) t= -2.74 p= .006
 DLX120QD - DLX60QD diff= -0.16 Two-sided 95% CI : (-0.51, 0.19) t= -0.91 p= .362
 DLX20/60QD - DLX60QD diff= -0.29 Two-sided 95% CI : (-0.71, 0.12) t= -1.38 p= .169
 DLX20/60QD - DLX120QD diff= -0.13 Two-sided 95% CI : (-0.54, 0.28) t= -0.62 p= .538

Type II sums of squares from ANCOVA Model = Treatment, Pooled Investigator, and Baseline PGI-I for main effects p-values. Model = Treatment, Pooled Investigator, Baseline PGI-I, and Treatment*Pooled Investigator for interaction p-value. N = Number of patients with baseline PGI-I and at least one non-missing post-baseline PGI-I value.

Report: EMP.F130.HMCJSTAT.INTRM1(L08P1A12)
 Program: EMP.F130.HMCJ.SASPGM(L08P1A12)
 Data: EMP.SAS.F130.L.HMCJ.ADS.INTRM1

The table below shows the mean change analysis for the FIQ for all randomized patient in the 3-month therapy phase. The Applicant states that all duloxetine groups showed a significantly greater mean decrease (improvement) compared with placebo on the FIQ total score.

**Table HMCJ.14.7. Fibromyalgia Impact Questionnaire
 Mean Change from Baseline to Endpoint
 All Randomized Patients
 3-Month Acute Therapy Phase**

FIQ Total Score	Baseline					Endpoint					Change					
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	133	52.73	11.01	53.4	18.6	76.6	43.04	16.96	45.6	3.0	79.1	-9.68	15.79	-7.1	-51.5	20.3
2) DLX20QD	75	53.66	11.44	55.1	22.0	76.0	38.88	17.43	42.4	2.0	79.6	-14.77	16.03	-11.7	-58.4	11.8
3) DLX60QD	136	51.25	11.90	51.7	18.2	77.3	36.90	16.70	37.2	0.0	77.2	-14.35	15.70	-12.9	-61.4	10.1
4) DLX120QD	140	51.69	14.17	53.9	13.6	79.4	37.99	16.98	39.4	0.0	77.0	-13.70	17.62	-12.0	-62.1	24.6

Interaction (Type II SS) Raw Data Treatment-by-Pooled Investigator F= 0.97 df= 42,423 p= .537

Main Effects (Type II SS) Raw Data
 Treatment F= 1.28 df= 3,465 p= .021
 Pooled Investigator F= 1.90 df= 14,465 p= .024

Least Squares Means for Change from Baseline
 1) PLACEBO -10.06 (SE= 1.42)
 2) DLX20QD -14.60 (SE= 1.83)
 3) DLX60QD -15.82 (SE= 1.40)
 4) DLX120QD -14.50 (SE= 1.38)

Pairwise Comparison of LS Means
 DLX20QD - PLACEBO diff= -4.54 Two-sided 95% CI = (-8.09, -0.20) t= -2.06 p= .040
 DLX60QD - PLACEBO diff= -5.36 Two-sided 95% CI = (-9.04, -1.69) t= -2.87 p= .004
 DLX120QD - PLACEBO diff= -4.44 Two-sided 95% CI = (-8.09, -0.80) t= -2.40 p= .017
 DLX60QD - DLX20QD diff= -0.82 Two-sided 95% CI = (-5.15, 3.51) t= -0.37 p= .710
 DLX120QD - DLX20QD diff= 0.10 Two-sided 95% CI = (-4.21, 4.41) t= 0.05 p= .964
 DLX120QD - DLX60QD diff= -0.92 Two-sided 95% CI = (-2.70, 4.54) t= 0.50 p= .618

Type II sums of squares from ANCOVA Model = Treatment, Pooled Investigator, and Baseline for main effects p-values. Model = Treatment, Pooled Investigator, Baseline, and Treatment*Pooled Investigator for the interaction p-value. N = Number of patients with a baseline and at least one non-missing post-baseline value.

Report: RMP.FIJO.HMCJSTAT.INTRM1(LOFQ011)
 Program: RMP.FIJOHMCJ.SASPNW(LOFQ011)
 Date: RMP.SAS.FIJS.L.HCMCJ.ADS.INTRM1

The table below shows the mean change analysis for the CGI-Severity score for all randomized patients during the 3-month acute therapy phase. The Applicant states that duloxetine 60 mg QD and duloxetine 120 mg QD showed a significantly greater mean decrease (improvement) compared with placebo while duloxetine 20 mg QD did not.

**Table HMCJ.14.9. Clinical Global Impressions of Severity
 Mean Change from Baseline to Endpoint
 All Randomized Patients
 3-Month Acute Therapy Phase**

CGI-Severity	Baseline					Endpoint					Change					
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	134	4.47	0.95	4.0	2.0	7.0	3.79	1.21	4.0	1.0	7.0	-0.68	1.10	-0.5	-4.0	3.0
2) DLX20QD	76	4.43	0.93	4.0	2.0	7.0	3.51	1.11	4.0	1.0	6.0	-0.92	1.17	-1.0	-4.0	2.0
3) DLX60QD	132	4.23	0.81	4.0	2.0	6.0	3.33	1.08	3.0	1.0	6.0	-0.91	1.09	-1.0	-4.0	2.0
4) DLX120QD	139	4.41	0.77	4.0	3.0	6.0	3.37	1.12	4.0	1.0	6.0	-1.04	1.17	-1.0	-4.0	1.0

Interaction (Type II SS) Raw Data Treatment-by-Pooled Investigator F= 1.29 df= 42,419 p= .109

Main Effects (Type II SS) Raw Data
 Treatment F= 4.34 df= 3,461 p= .005
 Pooled Investigator F= 2.53 df= 14,461 p= .002

Least Squares Means for Change from Baseline
 1) PLACEBO -0.69 (SE= 0.10)
 2) DLX20QD -0.96 (SE= 0.13)
 3) DLX60QD -1.07 (SE= 0.10)
 4) DLX120QD -1.10 (SE= 0.09)

Pairwise Comparison of LS Means
 DLX20QD - PLACEBO diff= -0.26 Two-sided 95% CI = (-0.55, 0.02) t= -1.78 p= .076
 DLX60QD - PLACEBO diff= -0.38 Two-sided 95% CI = (-0.63, -0.13) t= -2.96 p= .003
 DLX120QD - PLACEBO diff= -0.41 Two-sided 95% CI = (-0.65, -0.16) t= -3.27 p= .001
 DLX60QD - DLX20QD diff= -0.11 Two-sided 95% CI = (-0.41, 0.18) t= -0.75 p= .451
 DLX120QD - DLX20QD diff= -0.14 Two-sided 95% CI = (-0.43, 0.15) t= -0.97 p= .331
 DLX120QD - DLX60QD diff= -0.03 Two-sided 95% CI = (-0.28, 0.22) t= -0.24 p= .807

Type II sums of squares from ANCOVA Model = Treatment, Pooled Investigator, and Baseline for main effects p-values. Model = Treatment, Pooled Investigator, Baseline, and Treatment*Pooled Investigator for the interaction p-value. N = Number of patients with a baseline and at least one non-missing post-baseline value.

Report: RMP.FIJO.HMCJSTAT.INTRM1(LOC08A11)
 Program: RMP.FIJOHMCJ.SASPNW(LOC08A11)
 Date: RMP.SAS.FIJS.L.HCMCJ.ADS.INTRM1

Sheehan Disability Scale (SDS)

The table below shows the mean change analysis of the SDS Global Functioning Impairment total score for all randomized patients during the 3-month therapy phase. The Applicant states that no significant treatment group differences were observed.

Table HMCJ.11.14. Sheehan Disability Scale Global Functioning Impairment Total Score Mean Change from Baseline to Endpoint All Randomized Patients 3-Month Therapy Phase

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	125	16.76	6.69	16.0	0.0	30.0	13.06	8.61	13.0	0.0	30.0	-3.70	7.28	-3.0	-25.0	16.0
2) DLX120QD	73	18.53	7.09	19.0	0.0	30.0	12.76	8.21	13.0	0.0	30.0	-5.77	8.21	-4.5	-24.0	12.0
3) DLX60QD	134	17.31	6.92	18.0	1.0	30.0	11.91	7.67	11.0	0.0	30.0	-5.51	7.72	-5.0	-30.0	12.0
4) DLX120QD	134	16.48	7.90	18.0	0.0	30.0	12.03	8.52	12.0	0.0	30.0	-4.45	8.23	-3.0	-25.0	16.0

Interaction (Type II SS) Raw Data Treatment-by-Pooled Investigator F= 0.93 df= 42,405 p= .605

Main Effects (Type II SS) Raw Data
 Treatment F= 0.81 df= 3,447 p= .460
 Pooled Investigator F= 1.99 df= 14,447 p= .018

Least Squares Means for Change from Baseline
 1) PLACEBO -4.35 (SE= 0.68)
 2) DLX120QD -5.39 (SE= 0.86)
 3) DLX60QD -5.71 (SE= 0.66)
 4) DLX120QD -5.60 (SE= 0.66)

Pairwise Comparison of LS Means
 DLX120QD - PLACEBO diff= -1.04 Two-sided 95% CI : (-3.11, 1.03) t= -0.99 p= .323
 DLX60QD - PLACEBO diff= -1.35 Two-sided 95% CI : (-3.10, 0.39) t= -1.52 p= .128
 DLX120QD - PLACEBO diff= -0.65 Two-sided 95% CI : (-2.39, 1.09) t= -0.73 p= .465
 DLX60QD - DLX120QD diff= -0.21 Two-sided 95% CI : (-2.25, 1.72) t= -0.20 p= .761
 DLX120QD - DLX120QD diff= 0.39 Two-sided 95% CI : (-1.65, 2.43) t= 0.38 p= .705
 DLX120QD - DLX60QD diff= 0.71 Two-sided 95% CI : (-1.00, 2.41) t= 0.81 p= .417

Type II sums of squares from ANCOVA Model = Treatment, Pooled Investigator, and Baseline for main effects p-values. Model = Treatment, Pooled Investigator, Baseline, and Treatment*Pooled Investigator for the interaction p-value. N = Number of patients with a baseline and at least one non-missing post-baseline value.

Report: RMP.F130.HMCJSTAT.INTERM1 (LOSHR11)
 Program: RMP.F130.HMCJ.SASPGM (LOSHR11)
 Data: RMP.SAS.F130.L.HMCJ.ADS.INTERM1

The table below shows the mean change analysis of the 17-item Hamilton Depression Rating Scale (HAMD-17) total score for all randomized patient during the 3-month therapy phase. The Applicant states that duloxetine 60 mg QD showed a significantly greater mean decrease (improvement) compared with placebo.

Table HMCJ.14.19. 17-Item Hamilton Depression Rating Scale Total Score Mean Change from Baseline to Endpoint All Randomized Patients 3-Month Acute Therapy Phase

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	123	19.64	6.60	10.0	0.0	24.0	8.74	5.94	7.0	0.0	23.0	-1.92	5.82	-2.0	-16.0	13.0
2) DLX120QD	72	10.71	5.59	10.0	0.0	23.0	7.83	6.26	6.0	0.0	27.0	-2.88	5.80	-3.0	-15.0	14.0
3) DLX60QD	128	9.84	6.21	9.0	0.0	24.0	6.63	5.22	5.0	0.0	34.0	-3.21	5.92	-3.0	-18.0	27.0
4) DLX120QD	128	10.12	6.16	9.0	0.0	24.0	7.30	5.53	6.0	0.0	23.0	-2.81	6.09	-2.0	-21.0	20.0

Interaction (Type II SS) Raw Data Treatment-by-Pooled Investigator F= 0.49 df= 41,391 p= .997

Main Effects (Type II SS) Raw Data
 Treatment F= 2.38 df= 3,432 p= .069
 Pooled Investigator F= 4.14 df= 14,432 p= <.001

Least Squares Means for Change from Baseline
 1) PLACEBO -2.27 (SE= 0.46)
 2) DLX120QD -3.06 (SE= 0.58)
 3) DLX60QD -3.84 (SE= 0.46)
 4) DLX120QD -3.40 (SE= 0.46)

Pairwise Comparison of LS Means
 DLX120QD - PLACEBO diff= -0.79 Two-sided 95% CI : (-2.17, 0.61) t= -1.11 p= .269
 DLX60QD - PLACEBO diff= -1.57 Two-sided 95% CI : (-2.76, -0.38) t= -2.59 p= .010
 DLX120QD - PLACEBO diff= -1.13 Two-sided 95% CI : (-2.31, 0.06) t= -1.96 p= .053
 DLX60QD - DLX120QD diff= -0.79 Two-sided 95% CI : (-2.17, 0.60) t= -1.12 p= .265
 DLX120QD - DLX120QD diff= -0.34 Two-sided 95% CI : (-1.72, 1.04) t= -0.49 p= .625
 DLX120QD - DLX60QD diff= 0.44 Two-sided 95% CI : (-0.73, 1.62) t= 0.74 p= .458

Type II sums of squares from ANCOVA Model = Treatment, Pooled Investigator, and Baseline for main effects p-values. Model = Treatment, Pooled Investigator, Baseline, and Treatment*Pooled Investigator for the interaction p-value. N = Number of patients with a baseline and at least one non-missing post-baseline value.

Report: RMP.F130.HMCJSTAT.INTERM1 (LOH17A11)
 Program: RMP.F130.HMCJ.SASPGM (LOH17A11)
 Data: RMP.SAS.F130.L.HMCJ.ADS.INTERM1

Reviewer's Analysis

Evaluation of Pain, Patient Global Improvement, FIQ Total Score and FIQ Pain Score

The primary efficacy analysis in Study HMCJ was based on the mean change from baseline to endpoint in BPI average pain score. As a co-primary to the BPI the PGI-Improvement was also collected.

Using BOCF and LOCF/BOCF approaches to missing data imputation, both duloxetine 60 mg QD and 120 mg QD were associated improvement in pain over placebo (see table below).

Although the unadjusted p-value for duloxetine at 20 mg QD suggests that this dose failed, as the Applicant believes, the treatment effect at this dose is similar to the other doses, suggesting that this dose may work.

Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint at Endpoint: All Randomized Patients in the 3-Month Therapy Phase of Placebo-Controlled Study HMCJ						
Study	Treatment Group	BPI Average Pain Score (BOCF)			BPI Average Pain Score (LOCF/BOCF)	
		Baseline	LSMean Change	p-value	LSMean Change	p-value
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

†unadjusted p-value.
 Dr. Buenconsejo's Table.

PGI-Improvement results are similar to BPI average pain scores. The table below shows the results for PGI-I and again indicates that duloxetine 20 mg QD has a similar treatment effect to the successful doses of 60 mg QD and 120 mg QD.

PGI-Improvement at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Study HMCJ						
Study	Treatment Group	N	PGI Improvement Score (LOCF)		PGI Improvement Score (WOCF)	
			LSMean Change	p-value	LSMean Change	p-value
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.

Dr. Buenconsejo plotted a continuous responder curve for study HMCJ. In this plot, the patients who drop out are considered non-responders. The x-axis shows the percent reduction in pain from baseline and the y-axis shows the percentage of patients achieving that level of pain