Summary ID# 11198

Clinical Study Summary: Study F1J-MC-HMFG

Duloxetine 60 to 120 mg versus Placebo in the Treatment of Patients with Osteoarthritis Knee Pain

Date summary approved by Lilly: 17 November 2008

Title of Study: Duloxetine 60 to 120 mg Versus Placebo in the Treatment of Patients with Osteoarthritis Knee Pain	
Investigators: This multicenter study included 21 principal investigators.	
Study Centers: This study was conducted at 21 study centers in 5 countries.	
Length of Study: Date of first patient enrolled: 27 February 2007 Date of last patient completed: 04 May 2008	**Phase of Development:** 3

Objectives

Primary:

To assess the efficacy of duloxetine 60 to 120 mg once daily (QD) compared with placebo on the reduction of pain severity as measured by the Brief Pain Inventory (BPI) 24-hour average pain score (referred to as the BPI average pain score hereafter) in patients with osteoarthritis (OA) knee pain during a 13-week, double-blind, treatment period.

Secondary:

A gatekeeper strategy was employed to sequentially test the following secondary objectives:

- To evaluate duloxetine 60 to 120 mg QD versus placebo on patients' perceived improvement during the 13-week treatment period, as measured by Patient Global Impressions of Improvement (PGI-Improvement);
- To evaluate duloxetine 60 to 120 mg QD versus placebo on the change in patients' functioning during the 13-week treatment period, as measured by the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) physical function subscale.

Additional secondary objectives were as follows:

- To assess the efficacy of duloxetine 60 to 120 mg QD versus placebo during the 13-week treatment period, as measured by:
  - Weekly mean of the 24-hour average pain and worst pain score,
  - Clinical Global Impressions of Severity (CGI-S),
  - WOMAC pain and stiffness subscales,
  - BPI - Severity and Interference,
  - Response to treatment, as defined by a 30% reduction of BPI average pain score.

• To assess the impact of treatment with duloxetine 60 to 120 mg QD versus placebo during the 13-week treatment period on patient-reported health outcomes, as measured by:
  o Medical Outcomes Study Short Form-36 (SF-36),
  o EuroQoL Questionnaire - 5 Dimension (EQ-5D) version of the EuroQoL instrument.
• To evaluate whether reduction in pain, as assessed by the BPI average pain intensity scores during the treatment period, is a direct analgesic effect of duloxetine and is independent of treatment effect on mood, as measured by the total score of the Beck Depression Inventory-II (BDI-II), or anxiety, as measured by the Hospital Anxiety and Depression Scale (HADS) anxiety subscale (HADS-A).
• To assess the safety of duloxetine versus placebo during the treatment period on discontinuation rates, treatment-emergent adverse events (TEAEs), laboratory assessments, and vital signs.
• To assess the effect of treatment with duloxetine 120 mg QD in patients who did not respond to duloxetine 60 mg QD for 6 weeks, as measured by reduction in BPI average pain score, response to treatment, and adverse events (AEs) reported as reasons for discontinuations.

Study Design: A multicenter, randomized, double-blind, parallel, placebo-controlled clinical trial with 3 study periods (screening, treatment, and taper), conducted in outpatients treated for knee pain due to OA. At Visit 4 (after 6 weeks of duloxetine 60 mg QD treatment), patients in the duloxetine treatment group who met the dose escalation criterion (experienced <30% reduction from baseline to Visit 4 in BPI average pain score [nonresponders]), and who tolerated the 60-mg QD dose were escalated to a 120-mg QD dose. See Figure HMFG.1 for study design diagram.
Number of Patients: Planned: 230 (115 per treatment group) Randomized (Week 0, Visit 2): 256 (128 per treatment group) Completed (Week 7, Visit 4): 219 (117 on placebo and 102 on duloxetine) Completed (Week 13, Visit 5): 204 (111 on placebo and 93 on duloxetine 60/120 mg)
Diagnosis and Main Criteria for Inclusion: Male or female outpatients at least 40 years of age who met the American College of Rheumatology (ACR) clinical and radiographic criteria for the diagnosis of OA of the knee with pain for ≥14 days of each month for 3 months prior to study entry and with a weekly mean of the 24-hour average pain severity ≥4 on a 11-point Likert scale collected from patient diary.
Test Product, Dose, and Mode of Administration: Duloxetine 30 mg QD (titration purposes only), 60 mg QD, or 120 mg QD given orally as one or two 30-mg or 60-mg capsule(s).
Reference Therapy, Dose, and Mode of Administration: Placebo QD given orally as 1 or 2 capsules.
Duration of Treatment: 13-week treatment period (including 1 week of titration for duloxetine-treated patients at 30 mg duloxetine per day), followed by a 2-week taper period.

Variables:

Efficacy:

Change from baseline on the BPI 24-hour average pain score

PGI-Improvement ratings

Change from baseline on the WOMAC physical function subscale score

Change from baseline in weekly mean of the 24-hour average pain and worst pain scores (11-point Likert scale) collected from the diary

Change from baseline on the CGI-S score

Change from baseline on the WOMAC pain and stiffness subscale scores

Change from baseline on the BPI-Severity and Interference scores (Severity scores included 4 questions assessing worst pain, least pain, and average pain in the past 24 hours, and the pain right now; Interference scores assessed the interference of pain in the past 24 hours for general activity, mood, walking ability, normal work, relationships with other people, sleep, enjoyment of life, and the average score of these 7 Interference items)

Percentage of patients who had response to treatment (response defined as a 30% reduction of the BPI average pain score; additional analyses were performed on the percentage of patients who had a 50% reduction of the BPI average pain score)

Change from baseline in BDI-II and HADS-A scores

Health Outcomes:

Change from baseline to endpoint in the SF-36 subscale scores (a self-reported survey that consists of 36 questions covering overall mental and physical health components, as well as 8 health domains [subscales], including 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)

Change from baseline to endpoint in the EQ-5D index scores

Safety:

Treatment period discontinuation rates

TEAE rates

Change from baseline to endpoint in laboratory values

Change from baseline to endpoint in vital signs values, orthostatics, and weight

Frequency of treatment-emergent abnormal laboratory values

Frequency of treatment-emergent abnormal vital signs and orthostatics

Percentage of patients with sustained elevation in blood pressure (a patient was considered to have met this criteria after randomization if sitting diastolic blood pressure was ≥90 mm Hg and had increased from baseline [defined as the highest of the measures at all the visits before randomization] 10 mm Hg for at least 3 consecutive visits, or if sitting systolic blood pressure was ≥140 mm Hg and had increased from baseline [defined as the highest of the measures at all the visits before randomization] 10 mm Hg for at least 3 consecutive visits)

Evaluation Methods:

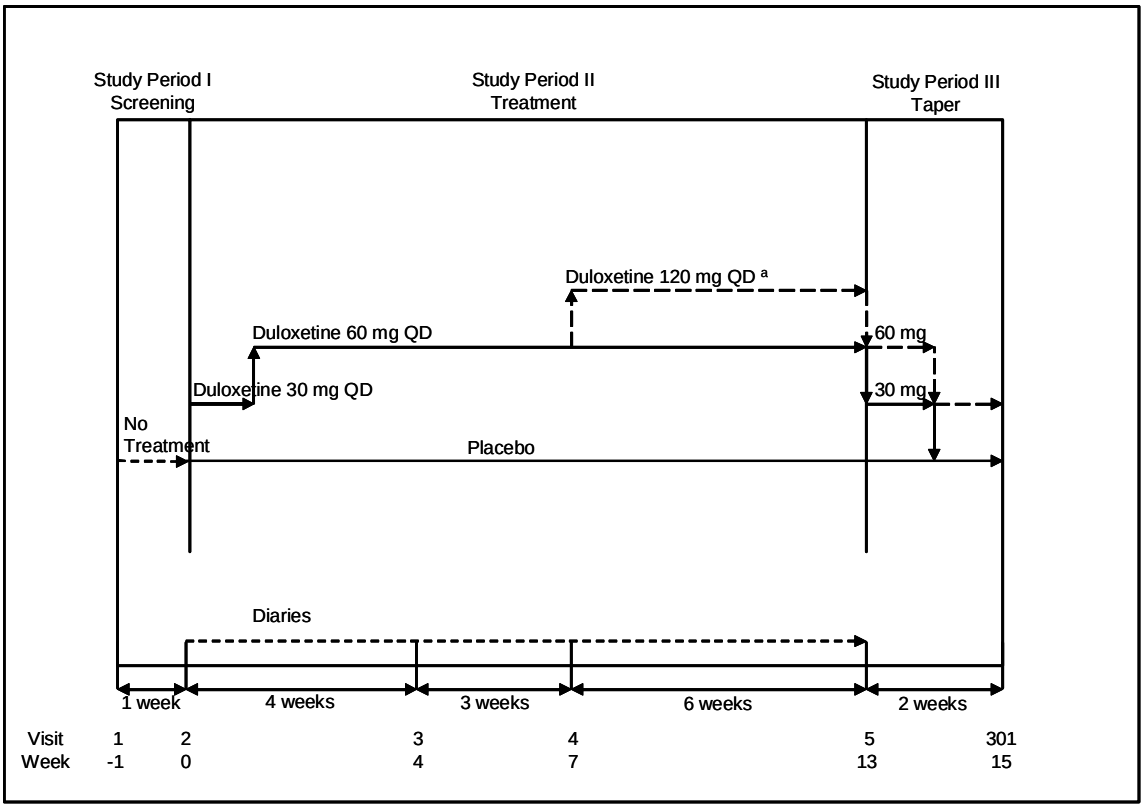
Statistical: Unless otherwise specified, analyses were conducted on an intent-to-treat basis. Treatment effect and interaction effect were evaluated based on a 2-sided significance level of 0.05. No adjustments for multiple comparisons were made. A likelihood-based, mixed-effects model repeated measures (MMRM) analysis was used to analyze the primary efficacy variable (BPI 24-hour average pain score). All patients with data from baseline and at least 1 postbaseline visit were included in the analysis. The model included fixed categorical effects of treatment, nonsteroidal anti-inflammatory drug (NSAID) use, investigator, visit, and treatment-by-visit interactions, as well as the continuous fixed covariates of baseline score and baseline-by-visit interactions. Mean change in the primary efficacy variable was also analyzed using a last-observation-carried-forward (LOCF) approach. When an analysis of variance (ANOVA) model was used to analyze continuous variables, the model contained terms of treatment and investigator. For efficacy variables, the stratifying variable of NSAID use was added to the analysis of covariance (ANCOVA) with baseline values added as a covariate to the above ANOVA model. Type III sum of squares for the least-squares mean (LS Mean) was used for statistical comparison using ANOVA or ANCOVA when there was no interaction term involved. Type II sum of squares was used for the LS Mean when an interaction term was included. Categorical variables were compared between treatment groups using a Fisher's exact test. A gatekeeper strategy was used to sequentially test the secondary objectives to compare improvement between duloxetine- and placebo-treated patients on the PGI-Improvement and the WOMAC physical function score, using the ANCOVA model and LOCF approach. Three regression models were used to estimate the direct effect of treatment and the indirect effects through change in BDI and change in HADS-A on the change in the 24-hour average pain score.

Safety analyses included all randomized patients.

Unless otherwise specified, patients who took duloxetine 60 mg QD and 120 mg QD were combined into 1 duloxetine treatment group for all analyses.

Based on data from 2 previously completed studies in the chronic pain program for duloxetine, this study with 115 patients per treatment arm was planned to have:

- ≥91% power to detect a treatment-group difference of 0.97 in the mean change from baseline to endpoint in the BPI average pain score between duloxetine and placebo treatment groups. This sample size was determined using a 2-sided 2-sample t-test with α=0.05, and assuming a common standard deviation of 2.2;
- 54% power to detect a treatment-group difference of 0.63 in the mean change from baseline to endpoint in the BPI average pain score between the duloxetine and placebo treatment groups. This sample size was determined using a 2-sided 2-sample t-test with α=0.05, and assuming a common standard deviation of 2.3.



[a] Non-responders at Visit 4 will titrate up to 120 mg QD

Figure HMFG.1. Study design for Study F1J-MC-HMFG.

Summary:

Patient Disposition:

At treatment Week 0 (Visit 2), a total of 256 patients were randomly assigned in a 1:1 ratio to duloxetine (n=128) and placebo (n=128). At the end of treatment (Week 13), a total of 111 (86.7%) placebo-treated patients and 93 (72.7%) duloxetine-treated patients completed the treatment period. Overall, a statistically significantly larger percentage (27.3%) of duloxetine patients discontinued the study due to any reason compared with placebo patients (13.3%, p=.008). The most frequent cause of discontinuation for both treatment groups was an AE, and a statistically significant larger percentage (p=.002) of duloxetine-treated patients (18% [24 patients]) discontinued due to an AE compared with the percentage of placebo-treated patients (5.5% [7 patients]).

Patient Demographics:

Table HMFG.1 presents patient demographic and disease characteristics at baseline. The majority of patients were female and Caucasian. The mean age of patients was 62.5 years. No statistically significant differences in demographic and disease characteristics between treatment groups were observed except for gender; the placebo-treated patients

group had a statistically significantly (p=.012) higher percentage of females (83.6%) compared with the duloxetine-treated patients (69.5%).

Table HMFG.1. Patient Demographics and Other Baseline Characteristics
All Randomly Assigned Patients
Treatment Period

Variable	Placebo n=128	DLX 60/120QD n=128	p-Value*
Age (in years)			.196
Mean	61.90	63.16	
SD	9.20	8.75	
BMI (kg/m*m)			.720
Mean	29.65	29.44	
SD	4.52	4.66	
Gender (%)			.012
Female	107 (83.6)	89 (69.5)	
Male	21 (16.4)	39 (30.5)	
Race (%)			.091
African	3 (2.3)	0 (0.0)	
Caucasian	124 (96.9)	126 (98.4)	
East Asian	1 (0.8)	0 (0.0)	
Hispanic	0 (0.0)	2 (1.6)	
Weekly mean of 24-hour average pain severity			.828
Mean	6.07	6.02	
SD	1.26	1.18	
BPI Average Pain Score			.797
Mean	6.14	6.07	
SD	1.27	1.39	
CGI-Severity			.722
Mean	3.34	3.34	
SD	1.33	1.21	
Duration of osteoarthritis since diagnosis (in years)			.482
Mean	5.62	6.16	
SD	6.20	5.88	
Duration of OA pain (in years)			.177
Mean	6.74	8.14	
SD	6.58	7.64	

Abbreviations: BPI = Brief Pain Inventory, BMI = body mass index, CGI = Clinical Global Impressions, DLX = duloxetine, N = number of randomly assigned patients, OA = osteoarthritis, QD = once daily, SD = standard deviation.

*Frequencies were analyzed using Fisher's exact test. Means were analyzed using Type III sum of squares ANOVA: Model = Treatment and Pooled Investigator.

Primary Efficacy:

The primary efficacy analysis was the MMRM analysis on the BPI average pain score. Statistically significantly greater reductions in the average pain score (p-values <.001) were observed at all post-treatment visits; namely, Visits 3, 4, and 5 (that is, treatment weeks 4, 7, and 13, respectively) in the duloxetine-treated patients (LS Mean changes of -1.80, -2.47, and -2.72) compared with the placebo-treated patients (LS Mmean changes of -1.12, -1.41, and -2.27).

Secondary Efficacy and Health Outcomes:

For the 30% response rate at endpoint (based on the percent change of BPI average pain score using the LOCF approach during the treatment period), a statistically significantly greater percentage of patients met the 30% response criteria (p<.001) with duloxetine (65.3%) compared with placebo (44.1%).

In the gatekeeper analyses, the LOCF analysis of PGI-Improvement showed the duloxetine-treated patients had a lower mean score at endpoint compared with the placebo-treated patients (2.85 and 3.09, respectively), but no statistically significant difference was observed. For the LOCF analysis in the WOMAC assessment of physical functioning subscale, there was a statistically significant (p=.016) improvement (lower score) in the duloxetine-treated patients (21.27) compared with the placebo-treated patients (26.07).

Duloxetine-treated patients also demonstrated statistically significant improvement (greater decrease in scores) compared with placebo-treated patients in mean change from baseline analyses for the following secondary efficacy variables: weekly mean of 24-hour average pain score (LS Mean changes were -2.32 and -1.73; p=.008), weekly mean of 24-hour worst pain score (LS Mean changes were -2.45 and -1.98; p=.047), CGI-S (LS Mean changes were -0.70 and -0.40; p=.009), and most parameters of BPI including worst pain, least pain, average pain, pain right now, general activity interference, and normal work interference (p-values $\leq$.050).

Path analysis was implemented to assess the relative contributions of duloxetine's effect on mood and anxiety symptoms towards the observed total effect using the BPI average pain score, the BDI-II, and the HADS-A subscale score. The results of the path analysis showed that the direct treatment effect of the duloxetine group (95.48% of the total effect) was statistically significant (p=.002). This observation demonstrated that the improvement in the BPI average pain score was due to a direct analgesic effect of duloxetine and was not dependent upon the improvement in mood (that is, depression and/or anxiety symptoms).

In the SF-36 Health Outcomes measure for all randomly assigned patients, the duloxetine-treated patients showed statistically significantly greater improvement compared with the placebo-treated patients on the SF-36 physical component summary (LS Mean changes 7.82 and 4.41, respectively; p<.001) as well as the subscales of bodily

pain (LS Mean changes 1.64 and 1.04, respectively; p=.004), physical functioning (LS Mean changes 3.30 and 2.16, respectively; p=.019), and physical role (LS Mean changes 1.13 and 0.59, respectively; p=.006). Statistically significantly greater improvements from baseline to endpoint in the EQ-5D index scores were also observed in the subgroup of duloxetine-treated patients who completed the study compared with placebo-treated patients. LS Mean changes for the UK-based index scores were 0.17 for the duloxetine group and 0.11 for the placebo group (p=.027), and LS Mean changes for the US-based index scores were 0.11 for the duloxetine group and 0.08 for the placebo group(p=.040).

A total of 33 duloxetine-treated patients did not respond to duloxetine 60 mg QD at Visit 4 (nonresponders), and thus increased their duloxetine dose to 120 mg QD. For these patients, treatment with 120 mg QD resulted in a statistically significant decrease (improvement) in the BPI average pain score during the 6 weeks of duloxetine 120 mg QD treatment (mean change of -0.76, p =.040).

There were no statistically significant differences between treatment groups on secondary endpoints other than specified above.

Safety:

Overall, the mean study drug exposure was 80.97 days. A statistically significantly (p=.002) lower number of mean days of study drug exposure was observed for the duloxetine-treated patients (76.65) compared with the placebo-treated patients (85.32).

Table HMFG.2 contains an overview of AEs reported during the study. No deaths were reported during the study. A total of 5 serious adverse events (SAEs) were reported by 3 duloxetine-treated patients (drug intolerance, memory impairment, supraventricular tachycardia) and 2 placebo-treated patients (atrial fibrillation, pyelonephritis acute). An SAE was any AE from this study that resulted in 1 of the following outcomes: death, initial or prolonged inpatient hospitalization, a life-threatening experience (that is, immediate risk of dying), persistent or significant disability/incapacity, congenital anomaly/birth defect, or was considered significant by the investigator for any other reason. None of the SAEs reported were considered by the investigator to be related to study drug. No SAEs were reported during the drug-taper period. Overall, a statistically significantly higher percentage of duloxetine-treated patients discontinued due to an AE compared with placebo-treated patients (p=.002).

Table HMFG.2. Overview of Adverse Events Number and Percentage of Patients All Randomly Assigned Patients

Adverse Event[a]	Placebo N=128 (%)	DLX60/120QD N=128 (%)
Deaths	0 (0)	0 (0)
Serious adverse events	3 (1.6)	2 (2.3)
Discontinuations due to an adverse event	7 (5.5)	24 (18.8)
Treatment-emergent adverse events	42 (32.8)	65 (50.8)

Abbreviations: DLX60/120 = duloxetine 60 and/or 120 mg once daily (QD).

[a] Patients may be counted in more than 1 category.

Table HMFG.3 summarizes all TEAEs occurring in at least 5% of patients in any treatment group during the treatment period. A statistically significant difference (p=.005) was observed between treatment groups in the overall number of patients reporting ≥1 TEAE during the treatmeant period as well as for all 3 of the TEAEs that were reported by at least 5% of patients in any treatment group.

Table HMFG.3. Treatment-Emergent Adverse Events Occurring in at Least 5% of Patients in Any Treatment Group All Randomly Assigned Patients Treatment Period

Preferred Term	Placebo (N=128) n (%)	DLX 60/120QD (N=128) n (%)	p-Value
Patients with ≥1 TEAE	42 (32.8)	65 (50.8)	.005
Nausea	3 (2.3)	13 (10.2)	.018
Constipation	2 (1.6)	10 (7.8)	.034
Hyperhidrosis	0 (0.0)	7 (5.5)	.014

Abbreviations: DLX =duloxetine, N = number of randomly assigned patients; n = number of patients with a TEAE, TEAE = treatment-emergent adverse event.

As shown in Table HMFG.4, in the mean change from baseline to endpoint analysis of chemistry and hematology analytes, statistically significant differences in alkaline phosphatase, aspartate amino transamine (AST), and gammaglutamyl transpeptidase (GGT) levels were observed between the treatment groups; duloxetine-treated patients experienced mean increases while placebo-treated patients experienced mean decreases. Also, a statistically significantly greater mean decrease in chloride was observed in the duloxetine-treated patients compared with the placebo-treated patients.

Table HMFG.4. Laboratory Data – Chemistry Analytes Mean Change from Baseline to Endpoint All Randomly Assigned Patients

Laboratory Analytes*	Placebo Mean change (SD)	DLX 60/120QD Mean change (SD)	p-Value
Alkaline phosphatase	-3.43 Units/L (14.56)	2.38 Units/L (15.74)	<.001
Aspartate amino transamine	-1.37 Units/L (7.26)	1.44 Units/L (8.32)	.010
Gammaglutamyl transpeptidase	-2.10 Units/L (19.12)	5.33 Units/L (20.40)	.023
Chloride	-0.08 mmol/L (2.66)	-0.83 mmol/L (2.62)	.042

*Table includes only the laboratory analytes that showed statistically significant differences between treatment groups in the mean change from baseline to endpoint.

Abbreviations: DLX =duloxetine, L = liter, mmol = millimole, SD = standard deviation.

A statistically significantly greater number of the duloxetine-treated patients had a treatment-emergent abnormal (high) AST value at endpoint compared with the placebo-treated patients (11 patients versus 2 patients; p=.010). No other statistically significant differences between treatment groups were observed at endpoint or at any time in the study. None of the patients with abnormal liver function test results developed an abnormal total bilirubin level.

There was a statistically significant difference between treatment groups in mean change from baseline to endpoint in pulse rate and body weight. For pulse rate, duloxetine-treated patients had a mean increase in pulse rate of 2.55 beats per minute (bpm), while the placebo-treated patients showed a mean decrease of -0.06 bpm (p=.005). For body weight, duloxetine-treated patients had a mean decrease in weight of -0.65 kg, compared with placebo-treated patients who had a mean increase of 0.47 kg ($p \leq .001$).

There were no statistically significant differences between treatment groups in the incidences of orthostatic hypotension or the incidences of sustained elevations in blood pressure.