

Summary ID# 10258

Clinical Study Summary: Study F1J-MC-HMEM

Maintenance of Effect of Duloxetine 60 mg Once Daily in Patients with Diabetic Peripheral Neuropathic Pain

Date summary approved by Lilly: 30 October 2008

Title of Study: Maintenance of Effect of Duloxetine 60 mg Once Daily in Patients with Diabetic Peripheral Neuropathic Pain	
Investigators: This multicenter study included 21 principal investigators.	
Study Centers: This study was conducted at 21 study centers in 4 countries.	
Length of Study: 18 months Date of first patient enrolled: 27 April 2006 Date of last patient completed: 30 October 2007	Phase of Development: 4
<p>Objectives:</p> <p><u>Primary:</u></p> <p>To evaluate whether an effect of duloxetine 60 mg once daily (QD) was maintained over 6 months of therapy in patients with diabetic peripheral neuropathic pain (DPNP) as measured by change on the Brief Pain Inventory (BPI) 24-hour average pain item from baseline of the maintenance therapy arm (Visit 4) to endpoint. Only patients who achieved a $\geq 30\%$ reduction on the BPI 24-hour average pain item after 8 weeks of acute therapy were included in the analysis.</p> <p><u>Secondary:</u></p> <ul style="list-style-type: none"> to evaluate the efficacy of duloxetine 60 mg QD after 6 months of maintenance therapy in patients who achieved a $\geq 30\%$ reduction on the BPI 24-hour average pain item (responders) after 8 weeks of acute therapy on the following efficacy measures: <ul style="list-style-type: none"> percentage of patients with a $\geq 50\%$ reduction from Visit 2 on the BPI 24-hour average pain item, BPI - Severity and Interference scores, sensory portion of the Short-Form McGill Pain Questionnaire (SF-MPQ), Patient's Global Impression of Improvement (PGI-Improvement), Clinical Global Impression of Severity (CGI-Severity). to evaluate the efficacy of duloxetine 120 mg QD after 6 months of rescue therapy in patients who did not achieve a $\geq 30\%$ reduction on the BPI 24-hour average pain item (nonresponders) after 8 weeks of 60 mg acute therapy on the following efficacy measures: <ul style="list-style-type: none"> percentage of patients with a $\geq 50\%$ reduction from Visit 2 on the BPI 24-hour average pain item, BPI-Severity and Interference scores, sensory portion of the SF-MPQ, PGI-Improvement, CGI-Severity. to evaluate the safety of duloxetine 60 mg QD during 8 weeks of acute therapy, duloxetine 60 mg QD during 6 months of maintenance therapy, and duloxetine 120 mg QD during 6 months of rescue therapy as measured by: <ul style="list-style-type: none"> discontinuation rates, treatment-emergent adverse events (TEAEs), vital signs (including pulse and blood pressure). 	
<p>Study Design: This was a Phase 4, multicenter, single-arm, open-label, uncontrolled trial. Following 8 weeks of acute therapy with duloxetine 60 mg QD (Visits 2 to 4), patients who were identified as responders continued on the 60 mg QD dose in a 26-week (6-month) maintenance arm, while patients who were identified as nonresponders entered a 26-week rescue arm that included a duloxetine dose of 120 mg QD. Responders were defined as patients with a $\geq 30\%$ reduction on the BPI 24-hour average pain item at the end of the acute therapy (Visit 4); all other patients were considered nonresponders. See Figure HMEM.1 for study design diagram.</p>	

Number of Patients:

Planned: A total of 212 patients were planned for this study.

Enrolled: 216 patients were enrolled.

Completed: 184 patients completed the acute therapy. Of these, 103 patients continued in the maintenance arm, while 69 patients proceeded with the rescue arm. A total of 77 and 33 patients completed the study during the maintenance and rescue therapies, respectively. In addition, 12 patients who began the maintenance therapy increased to 120 mg QD at either Visits 5, 6, or 7; of these patients, 9 completed the rescue therapy.

Diagnosis and Main Criteria for Inclusion: Patients must have had pain due to bilateral peripheral neuropathy caused by type 1 or type 2 diabetes mellitus. Pain must have begun in the feet, with relatively symmetrical onset. Daily pain should have been present for at least 6 months. The diagnosis must have been confirmed by a score of at least 3 on the Michigan Neuropathy Screening Instrument (MNSI). In addition, baseline BPI 24-hour average pain score had to be ≥ 4 and glycosylated hemoglobin had to be $<12\%$.

Test Product, Dose, and Mode of Administration: Duloxetine 30 mg or 60 mg given orally once daily every morning as 1 capsule. Duloxetine 120 mg given orally once daily every morning as 2 (60 mg) capsules.

Reference Therapy, Dose, and Mode of Administration: N/A

Duration of Treatment: For Study Period II, patients were to take duloxetine 30 mg QD for 1 week before increasing the dose to 60 mg QD for the duration of the acute therapy (8 weeks total). For Study Period III, responders continued on a 60 mg QD (maintenance dose) for 26 weeks, while nonresponders, or those who worsened after beginning Study Period III, had their duloxetine dose increased to 120 mg QD (rescue dose) for all, or the remainder of, that study period. Finally, prior to completing the study, patients were tapered off study medication (Study Period IV, 2 weeks total) as follows: all patients previously taking duloxetine 60 mg QD were to take duloxetine 30 mg QD for 2 weeks. All patients previously taking duloxetine 120 mg QD were to take duloxetine 60 mg QD for 1 week and then duloxetine 30 mg QD for the second week.

Variables:**Efficacy:**Primary:

Mean change on the BPI 24-hour average pain item from baseline of the maintenance therapy (Visit 4 [Week 8]) to endpoint (Visit 8 [Week 34]) of the 26-week maintenance therapy

Secondary:

Measures were based on the 26-week maintenance/rescue (or management of decline in effectiveness of 60 mg QD after entering maintenance/rescue) therapy. For these measures, baseline equaled Visit 4 for patients who entered the maintenance/rescue therapy, or, for patients who lost effectiveness on 60 mg QD maintenance therapy and switched to 120 mg QD rescue therapy at Visit 5, 6, or 7, baseline equaled the visit that the duloxetine dose was increased.

- percentage of patients with a $\geq 50\%$ reduction from Visit 2 on the BPI 24-hour average pain item
- change from baseline to endpoint in the BPI-Severity and BPI-Interference scores
- change from baseline to endpoint in the sensory component of the SF-MFQ score
- all postbaseline data (mean score at each visit and endpoint) for the PGI-Improvement scale (where PGI-Improvement scores range from 1 [very much better] to 7 [very much worse])
- change from baseline to endpoint in the CGI-Severity score

Safety:

Frequencies of reported TEAEs, serious adverse events (SAEs), and discontinuations due to adverse events (AEs)

Change from baseline to endpoint during each dosing period for vital signs (weight, sitting heart rate, and blood pressure)

Change in the patient-reported Beck Depression Inventory-II (BDI-II) score (assessed symptoms of depression and risk of suicide at each visit)

Evaluation Methods:Statistical:

All analyses were conducted on an intent-to-treat basis, meaning that data were analyzed for all patients meeting criteria to enter the maintenance arm, even if the patient did not take the assigned treatment, did not receive the correct treatment, or did not comply with the protocol. Unless otherwise specified, the data summaries and the statistical evaluation of the safety and efficacy of the study refer to the time period before study drug tapering occurred. For analyses regarding efficacy variables, the within-group changes from baseline to endpoint were evaluated using a Student's t-test. To evaluate the maintenance effect of duloxetine 60 mg QD, change from baseline to endpoint on the BPI average pain item was summarized along with a 1-sided 97.5% confidence interval (CI). When the upper bound of the 97.5% CI was less than or equal to the prespecified noninferiority margin of 1.5 points on the BPI 24-hour average pain item scale, the null hypothesis that duloxetine treatment effect on pain reduction on DPNP patients was not maintained in the 26-week maintenance arm was rejected at the significance level of 0.025. For analyses regarding safety variables, a Student's t-test was used to test the within-group change from baseline to endpoint unless the assumption of a t-test appeared to be violated, in which case the Wilcoxon signed-rank procedure was used. Comparisons were not made between different duloxetine dose groups. Statistical significance was evaluated at the level of 0.05 unless specified otherwise.

Sample size was determined using a 1-sided noninferiority test with ≤ 0.025 and a margin of 1.5 points on the BPI pain scale; this sample size allowed for at least 80% probability that the upper limit of the 1-sided 97.5% CI did not exceed 1.5. Additional assumptions included: a mean change of the BPI 24-hour average pain item score of 0.7 during the 26-week maintenance therapy; standard deviation of the change would be 2.6; 55% of the patients would meet entry criteria for the maintenance therapy arm; and discontinuation rates would be 22% and 45% for the acute therapy arm and maintenance therapy arm, respectively.

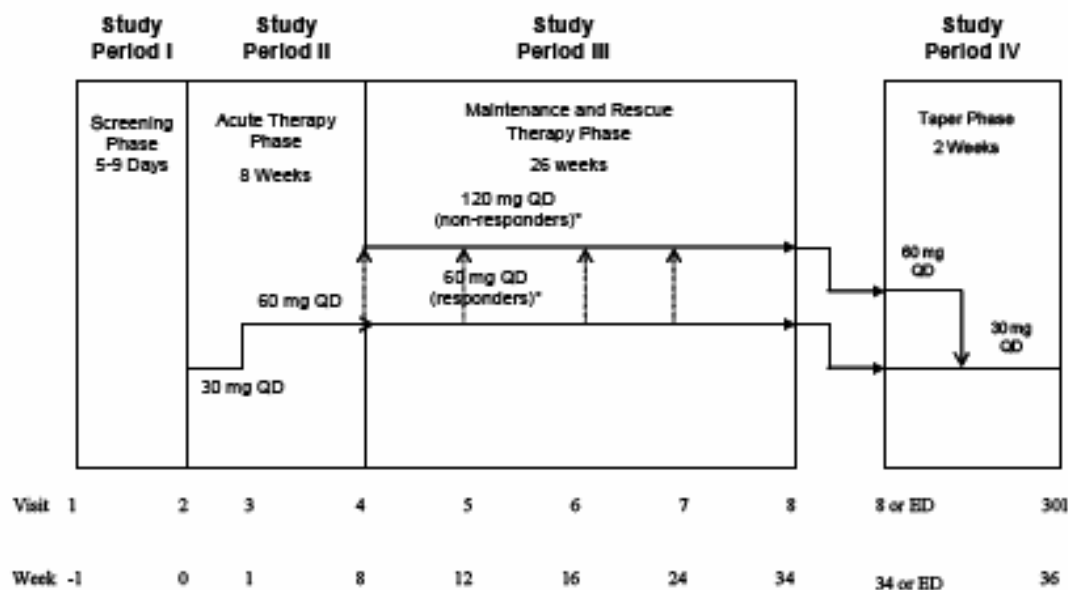


Figure HMEM.1. Study design for Study F1J-MC-HMEM.

Patient Disposition:

A total 216 patients were screened and enrolled into the acute phase of the study. One hundred eighty-four patients completed the acute phase. Of these, 115 patients continued into the maintenance arm of the study at 60 mg QD, while 69 patients entered the rescue arm at a dose of 120 mg QD. Of the 115 patients entering the maintenance arm at 60 mg QD, 103 remained at this dose level for the remainder of their time in the study and 77 completed all 26 maintenance weeks. Twelve patients had their dose of duloxetine increased to the 120 mg QD dose at Visit 5, 6, or 7; of these, 9 patients completed the study. Of the 69 patients in the rescue arm on 120 mg QD, 33 completed the study.

The primary reason for discontinuation from the study during the acute therapy arm and for patients who entered the maintenance arm on duloxetine 60 mg QD without dosage increase for the remaining study visits was AEs (20 [9.3%] and 14 [13.6%] patients, respectively). For patients who entered the rescue arm at the dose of 120 mg QD and for patients who increased to 120 mg QD during the maintenance arm, the most common reason for discontinuation was lack of efficacy (24 [34.8%] and 3 [25.0%] patients, respectively). Treatment compliance for each visit interval was defined as taking between 80% and 120% of the study drug prescribed for that interval. Overall, the compliance rate was 71.8%; however, at each visit compliance ranged between 91.7% and 94.0%.

Patient Demographics:

Demographic and disease characteristics at baseline for all randomized patients (enrolled in the acute phase) are summarized in Table HMEM.1 below. The average age was 63.3 years, the average weight was 84.0 kg, most patients were Caucasian (80.1%), and 51.9% of patients were males. The majority of the patients had a diagnosis of type 2 diabetes mellitus (94.4%) and most (63.9%) were diagnosed over 2 years ago, with a mean duration of 14.4 years. Diabetic neuropathic pain had been present for greater than 1 year for the majority (82.4%) of patients; the mean duration was 4.2 years. The average BPI-Severity score assessing the patients' pain over the previous 24 hours was 5.88. In Table HMEM.1, demographic characteristics and baseline disease characteristics are also provided separately for patients entering the maintenance/rescue arms on duloxetine 60 mg QD and duloxetine 120 mg QD. Demographic characteristics and baseline disease characteristics were comparable for each subset of patients.

**Table HMEM.1. Patient Demographic and Disease Characteristics at Baseline
All Enrolled Patients**

Variable	All Patients Enrolled (Acute Phase) N=216	Patients Entering Maintenance on Duloxetine 60 mg QD n=115	Patients Entering Rescue on Duloxetine 120 mg QD n=69
Gender [n (%)]			
Male	112 (51.9)	58 (50.4)	34 (49.3)
Female	104 (48.1)	57 (49.6)	35 (50.7)
Race [n (%)]			
Caucasian	173 (80.1)	85 (73.9)	58 (84.1)
West Asian	33 (15.3)	24 (20.9)	8 (11.6)
African	6 (2.8)	3 (2.6)	2 (2.9)
Hispanic	4 (1.9)	3 (2.6)	1 (1.4)
Age (years)			
Mean (SD)	63.3 (9.45)	62.6 (9.38)	63.5 (9.06)
Height as Visit 1 (cm)			
Mean (SD)	166.7 (10.39)	166.2 (10.45)	166.3 (10.59)
Weight at Visit 2 (kg)			
Mean (SD)	84.0 (18.36)	83.3 (17.26)	83.2 (20.70)
Type of diabetes mellitus [n (%)]			
Type 1	12 (5.6)	5 (4.3)	3 (4.3)
Type 2	204 (94.4)	110 (95.7)	66 (95.7)
Duration of diabetes (years)			
≤2 Years	78 (36.1)	42 (36.5)	25 (36.2)
>2 Years	138 (63.9)	73 (63.5)	44 (63.8)
Duration of neuropathic pain (years)			
≤1 Year	38 (17.6)	18 (15.7)	15 (21.7)
>1 Year	178 (82.4)	97 (84.3)	54 (78.3)
BPI 24-hour average pain severity			
Mean (SD)	5.88 (1.45)	5.95 (1.38)	5.74 (1.34)

Abbreviation: BPI = Brief Pain Inventory, N = number of randomized patients, n = number of patients in this category, QD = once daily, SD = standard deviation.

Summary:Primary Efficacy:

Since this was an uncontrolled study, the primary endpoint measured changes from baseline to endpoint within the treatment group. Of the 115 patients who began maintenance therapy on duloxetine 60 mg QD, 114 had a postbaseline value, and 103 remained on this dose throughout Study Period III.

In the 114 patients that began maintenance therapy and had a postbaseline value, the mean pain level at baseline (Visit 4) was 1.76 and at endpoint was 2.11. During the maintenance therapy, the change on BPI 24-hr average pain score from baseline to endpoint was 0.35 with 0.79 as the upper bound of the 97.5% CI, which was less than the prespecified noninferiority margin of 1.5 ($p < .001$), indicating statistically significant maintenance of effect for duloxetine 60 mg QD.

Repeated measures analysis of least squares mean for BPI 24-hour average pain score showed numerical changes from baseline (Visit 4) of 1.04, 0.49, 0.36, and 0.19 at Visits 5, 6, 7, and 8, respectively. The increases at Visits 5 and 6 were statistically significant ($p < .001$ and $p = .017$, respectively).

Secondary Efficacy:

Of the 114 patients who entered the maintenance arm on duloxetine 60 mg QD and who had baseline and postbaseline BPI scores, 76 (66.7%) had at least a 50% reduction in pain at endpoint from Visit 2. No statistically significant change was observed for any of the BPI-Severity and BPI-Interference items except for the severity of pain right now (mean change, 0.48, $p = .026$) and the interference with normal work (0.63, $p = .016$) scores. PGI-Improvement scores decreased (improved) during the maintenance phase with the means ranging from 2.36 at Visit 5 to 1.79 at Visit 8; the overall endpoint score was 2.32, which corresponds to the category of “much better.”

Of the 66 patients who entered the rescue arm on duloxetine 120 mg QD and who had baseline and postbaseline BPI scores, 21 (31.8%) had at least a 50% reduction in pain at endpoint from Visit 2. In this group, BPI-Severity scores indicated a statistically significant pain reduction (average pain, mean change -1.39, $p < .001$; worst pain, mean change -1.33, $p < .001$; least pain, mean change -0.93, $p = .016$; and pain right now, mean change -1.12, $p = .011$), while BPI-Interference scores were statistically significantly improved for general activity (mean change -1.01, $p = .021$), walking ability (mean change -1.15, $p = .009$), and normal work (mean change -0.97, $p = .022$) scores. PGI-Improvement scores decreased (improved) during the rescue therapy with the means ranging from 2.87 at Visit 5 to 2.41 at Visit 8. The overall PGI-Improvement endpoint score was 3.04, which corresponds to the category of “little better.” Finally, the change (improvement) from baseline (3.40) to endpoint (2.94) in the CGI-Severity score was statistically significantly different (-0.46, $p = .003$).

SF-MPQ scores did not change statistically significantly in either treatment phase.

Safety:

One sudden death occurred during the study in the duloxetine 60 mg QD group; the death was considered related to the patient's underlying medical condition and was not attributed to the study drug. Overall, 20 (9.3%) patients experienced a total of 27 SAEs. Table HMEM.2 contains an overview of AEs reported during the study. TEAEs were defined as events that first occurred or worsened after enrollment (Visit 2) through the taper phase and included the first week of the study, when patients were receiving duloxetine 30 mg QD. The only AE reported as a reason for discontinuation by $\geq 1\%$ of all randomized patients for the acute and maintenance/rescue therapy period was nausea; nausea was reported as the reason for discontinuation by 3 patients in the 60 mg QD group and 1 patient in the 120 mg QD group. Most patients reported that their most severe TEAE was mild or moderate in severity.

**Table HMEM.2. Overview of Adverse Events
Number and Percentage of Patients
All Randomized Patients**

Adverse Event ^a	Number (%) of Patients			
	All Enrolled Patients N=216	All Patients on Duloxetine 60 mg QD N=216	All Patients on Duloxetine 120 mg QD N=81	Patients at Taper Phase N=132
Deaths	1 (0.5)	1 (0.5)	0 (0)	0 (0)
Serious adverse events	20 (9.3)	18 (8.3)	2 (2.5)	3 (2.3)
Discontinuations due to an adverse event	40 (18.5)	35 (16.2)	5 (6.2)	1 (0.8)
Treatment-emergent adverse events	NA	139 (64.4)	39 (48.1)	NA

Abbreviations: N = number of randomized patients, NA = not analyzed, QD = daily.

^a Patients may be counted in more than 1 category.

Table HMEM.3 summarizes TEAEs that occurred in at least 2% of patients by decreasing frequency.

Table HMEM.3. Treatment-Emergent Adverse Events Occurring in at Least 2% of Patients by Decreasing Frequency and Preferred Term Patients on 60 mg QD and 120 mg QD

Preferred Term	All Patients on Duloxetine 60 mg QD (N=216) n (%)	All Patients on Duloxetine 120 mg QD (N=81) n (%)
Patients with ≥ 1 TEAE	139 (64.4)	39 (48.1)
Nausea	41 (19.0)	1 (1.2)
Somnolence	18 (8.3)	1 (1.2)
Hyperhidrosis	14 (6.5)	1 (1.2)
Dry mouth	13 (6.0)	1 (1.2)
Anorexia	12 (5.6)	0
Asthenia	11 (5.1)	1 (1.2)
Fatigue	11 (5.1)	0
Headache	11 (5.1)	3 (3.7)
Constipation	9 (4.2)	0
Vertigo	9 (4.2)	2 (2.5)
Back pain	8 (3.7)	0
Chills	7 (3.2)	0
Diarrhea	7 (3.2)	7 (8.6)
Dizziness	7 (3.2)	1 (1.2)
Erectile dysfunction	7 (3.2)	0
Vomiting	7 (3.2)	1 (1.2)
Decreased appetite	6 (2.8)	0
Insomnia	6 (2.8)	1 (1.2)
Muscle spasms	6 (2.8)	0
Pain in extremity	6 (2.8)	2 (2.5)
Abdominal pain upper	5 (2.3)	4 (4.9)
Influenza	5 (2.3)	0
Nasopharyngitis	5 (2.3)	1 (1.2)
Pruritus	5 (2.3)	1 (1.2)
Hypertension	4 (1.9)	2 (2.5)
Arthralgia	3 (1.4)	2 (2.5)
Arteriosclerosis	1 (0.5)	2 (2.5)
Diabetic foot	1 (0.5)	2 (2.5)
Excoriation	0	2 (2.5)

Abbreviations: N = total number of patients, n = number of patients in this category, QD = once daily, TEAE = treatment-emergent adverse event.

Within the 60 mg QD group, statistically significant changes in vital signs from baseline to endpoint were as follows:

- mean heart rate increased from baseline (76.19 bpm to 78.58 bpm, $p \leq .001$),
- mean systolic blood pressure decreased from baseline (139.00 mm Hg to 134.77 mm Hg, $p \leq .001$), and
- mean body weight decreased from baseline (84.18 kg to 82.89 kg, $p \leq .001$).

No other statistically significant changes in vital signs were seen in the 60 mg QD group, and no statistically significant changes in vital signs were seen in the 120 mg QD group or during the taper phase.