Summary ID# 9072

Clinical Study Summary: Study F1J-MC-HMEF

Duloxetine 60/120 mg versus Placebo in the Treatment of Fibromyalgia

Date summary approved by Lilly: 27 May 2008

Title of Study: Duloxetine 60/120 mg versus Placebo in the Treatment of Fibromyalgia	
Investigator(s): This multicenter study included 36 principal investigator(s).	
Study Center(s): This study was conducted at 36 study center(s) in five countries	
Length of Study: 1 year and 2.5 months Date first patient entered: 13 September 2005 Date first patient enrolled: 19 September 2005 Date last patient completed acute therapy phase: 06 December 2006 Date last patient completed extension therapy phase: 27 June 2007	**Phase of Development:** 3
Objectives: **Acute Therapy Phase** The primary objective of this study was to assess the efficacy of duloxetine 60/120 mg once daily (QD) compared with placebo on the treatment of pain in patients with American College of Rheumatology (ACR)-defined primary fibromyalgia (FM), with or without major depressive disorder (MDD), during the acute therapy phase of the study. The primary objective was evaluated by the following coprimary measures: change in pain severity as measured by the average pain item of the Brief Pain Inventory (BPI-Modified Short Form) score and the endpoint of patient-reported improvement as collected by the Patient's Global Impressions of Improvement (PGI-Improvement) scale. **Extension Therapy Phase** The primary objective was to test the maintenance of efficacy of duloxetine 60 mg in the treatment of pain in the extension phase.	
Study Design: Study F1J-MC-HMEF was a Phase 3, multicenter, randomized, parallel, double-blind, placebo-controlled trial.	
Number of Patients: Planned: 320 Randomized: 330 (162 duloxetine, 168 placebo) Completed acute therapy phase: 204 (101 duloxetine, 103 placebo) Completed extension therapy phase	

Completed the extension therapy phase: 140 (65 placebo-DLX60mgQD, 11 DLX60QD-DLX60QD, 1 DLX60/120/60QD-DX60QD, 63 DLX60/120/120QD-DLX120QD) Completed the taper phase: 170 (6 placebo, 95 duloxetine 60 mg QD, 69 duloxetine 120 mg)
Diagnosis and Main Criteria for Inclusion: The population for this study included patients with fibromyalgia (FM), as defined by the American College of Rheumatology (ACR), with or without major depressive disorder (MDD). Were male or female outpatients ≥18 years of age.
Test Product, Dose, and Mode of Administration: Duloxetine 60 or 120 mg/day, given orally once a day as capsules.
Duration of Treatment: 1 week screening period, 27 weeks of double-blind therapy (acute therapy phase), 29 weeks of double-blind therapy (extension therapy phase), 2 week taper phase
Reference Therapy, Dose, and Mode of Administration: Placebo given orally once a day as capsules.

Measures:

Efficacy:

Brief Pain Inventory (BPI-Modified Short Form) Severity (worst pain, least pain, average pain, and pain right now) and average interference score
Patient's Global Impressions of Improvement
Fibromyalgia Impact Questionnaire (FIQ)
Clinical Global Impressions of Severity (CGI-Severity)
Tender Point Pain Threshold
Area under the curve (AUC) of pain relief, based on the BPI average pain score
Multidimensional Fatigue Inventory (MFI) Dimensions
17-item Hamilton Depression Rating Scale ($HAMD_{17}$)
Beck Depression Inventory-II (BDI-II)

Health Outcomes:

Sheehan Disability Scale (SDS)
36-item Short Form Health Survey
EuroQoL Questionnaire – 5 Dimension

Safety:

Reasons for Discontinuation
Serious Adverse Events
Treatment-Emergent Adverse Events
Laboratory Tests
Vital signs and weight
ECG (acute therapy phase only)

Bioanalytical: Plasma concentrations of duloxetine

Pharmacokinetic/Pharmacodynamic: Average steady state duloxetine plasma concentration at 60 mg QD and 120 mg QD. Average pain score on Brief Pain Inventory, area under the curve of pain relief, and PGI-Improvement score.

Evaluation Methods:

Statistical: All analyses were conducted on an intent-to-treat (ITT) basis. Treatment effects were evaluated based on a two-sided significance level of 0.05 and interaction effects at a significance level of 0.10. Unless otherwise specified, when a total score was calculated from individual items, it was considered missing if any of the individual items were missing. When an average score was computed from individual items, it was calculated from existing values. An analysis of covariance model containing main effects of treatment and investigator, also the baseline value as a continuous covariate were used to analyze efficacy variables. The difference in the least-squares means (LSMeans) based on type II sums of squares were used to evaluate treatment differences compared with placebo. Categorical variables were compared between treatment groups using Fisher's exact test.

Bioanalytical: Plasma samples were analyzed for duloxetine using a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) method.

Pharmacokinetic/Pharmacodynamic: Duloxetine plasma concentration data collected from this study was pooled with pharmacokinetic data from previous studies and was analyzed using population pharmacokinetic modeling with nonlinear mixed effects modeling program (NONMEM). Potentially important patient factors, such as age, body weight, gender, ethnic origin, smoking status and other factors such as disease condition, dose, dosing regimen were investigated to assess their influence on key pharmacokinetic parameters. The relationships between predicted average steady state duloxetine concentration and primary efficacy measures (BPI-average pain score and PGI-Improvement) were determined using linear and logistic models using NONMEM and S plus program.

Summary:

Patient Demographics

A total of 162 patients were randomly assigned to duloxetine treatment and 168 patients were randomly assigned to placebo treatment in this study. Table HMEF.1 summarizes baseline patient demographics.

Table HMEF.2 summarizes the patient demographics for the extension therapy phase.

Table HMEF.1. Patient Demographic Characteristics at Baseline

Variable	PLC	DLX60/120	Total	p-Value
Gender [n (%)]				
No. of Patients	168	162	330	.188
Female	160 (95.24%)	148 (91.36%)	308 (93.33%)	
Male	8 (4.76%)	14 (8.64%)	22 (6.67%)	
Age (yrs)				
No. of Patients	168	162	330	.718
Mean	50.17	50.69	50.43	
Median	51.41	51.05	51.12	
Standard Deviation	11.36	10.05	10.72	
Minimum	19.90	22.51	19.90	
Maximum	83.22	82.12	83.22	
Race [n (%)]				
No. of Patients	168	162	330	.555
Caucasian	149 (88.7%)	150 (92.6%)	299 (90.6%)	
African	1 (0.6%)	2 (1.23%)	3 (0.91%)	
Hispanic	15 (8.9%)	10 (6.2%)	25 (7.6%)	
Native American	1 (0.60%)	0 (0.0%)	1 (0.30%)	
East Asian	1 (0.30%)	0 (0.0%)	1 (0.30%)	
West Asian	1 (0.30%)	0 (0.0%)	1 (0.30%)	
Weight (kg)				
No. of Patients	166	161	327	.739
Mean	77.03	77.71	77.37	
Median	74.00	76.00	75.00	
Standard Deviation	19.24	16.79	18.05	
Minimum	47.00	48.00	47.00	
Maximum	143.00	134.00	143.00	
Diag. of Major Depression [n(%)]				
No. of Patients	168	162	330	1.00
No	130 (77.4%)	126 (77.8%)	256 (77.6%)	
Yes	38 (22.6%)	38 (22.2%)	74 (22.4%)	
Secondary Diag. of Anxiety [n (%)]				
No. of Patients	167	155	322	.675
No	165 (98.8%)	152 (98.1%)	317 (98.5%)	
Yes	2 (1.2%)	3 (1.9%)	5 (1.6%)	
Previous Antidepressant Use [n (%)]				
No. of Patients	168	162	330	.824
No	96 (57.1%)	90 (55.6%)	186 (56.4%)	
Yes	72 (42.9%)	72 (44.4%)	144 (43.6%)	

Table HMEF.1. Patient Demographic Characteristics at Baseline (concluded)

Height (cm)				
No. of Patients	168	161	329	.314
Mean	162.72	163.56	163.13	
Median	162.50	163.00	163.00	
Standard Deviation	6.64	8.07	7.38	
Minimum	147.00	147.00	147.00	
Maximum	183.00	184.00	184.00	

Abbreviations: Diag=diagnosis; DLX=duloxetine; No.=number; PLC=placebo and yrs=years.

Table HMEF.2. Patient Demographic Characteristics at Visit 2
All Randomized Patients Who Entered the Extension Phase
Extension Phase

Variable	PLC-DLX60	DLX60-DLX60	DLX60/120/-DLX60	DLX60/120/120 QD-DLX120QD	**Total**
Gender [n (%)]					
No. of Patients	103	17	2	82	204
Female	101 (98.06)	17(100.00)	2(100.00)	74 (90.24)	194 (95.10)
Male	2 (1.94)	0 (0.00)	0 (0.00)	8 (9.76)	10 (4.90)
Age (yrs)					
No. of Patients	103	17	2	82	204
Mean	50.45	53.89	54.38	49.88	50.55
Median	52.16	54.84	54.38	49.95	51.79
Standard Deviation	10.79	10.07	6.90	9.09	10.05
Minimum	24.24	26.76	49.50	32.18	24.24
Maximum	73.84	72.15	59.26	75.34	75.34
Race [n (%)]					
No. of Patients	103	17	2	82	204
Caucasian	94 (91.26)	16 (94.12)	2(100.00)	78 (95.12)	1 (0.49)
African	0 (0.00)	1 (5.88)	0 (0.00)	0 (0.00)	1 (0.49)
Hispanic	7 (6.80)	0 (0.00)	0 (0.00)	4 (4.88)	11 (5.39)
Native American	1 (0.97)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.49)
West Asian	1 (0.97)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.49)
Weight (kg)					
No. of Patients	102	17	2	81	202
Mean	75.29	76.76	78.50	75.40	75.49
Median	72.00	78.00	78.50	73.00	72.50
Standard Deviation	17.74	12.62	14.85	15.14	16.23
Minimum	48.00	30.00	68.00	48.00	48.00
Maximum	143.00	106.00	89.00	124.00	143.00

Table HMEF.2. Patient Demographic Characteristics at Visit 2
All Randomized Patients Who Entered the Extension Phase
Extension Phase (concluded)

Diag. of Major Depression [n(%)]					
No. of Patients	103	17	2	82	204
No	80 (77.67)	15 (88.24)	2(100.00)	60 (73.17)	157 (76.96)
Yes	23 (22.33)	2 (11.76)	0 (0.00)	22 (26.83)	47 (23.04)
Secondary Diag. of Anxiety [n (%)]					
No. of Patients	102	17	2	79	200
No	101 (99.02)	17(100.00)	2(100.00)	78 (98.73)	198 (99.00)
Yes	1 (0.98)	0 (0.00)	0 (0.00)	1 (1.27)	2 (1.00)
Previous Antidepressant Use [n (%)]					
No. of Patients	103	17	2	82	204
No	56 (54.37)	11 (64.71)	2 (100.00)	40 (48.78)	109 (53.43)
Yes	47 (45.63)	6 (35.29)	0 (0.00)	42 (51.22)	95 (46.57)
Height (cm)					
No. of Patients	103	17	2	81	203
Mean	162.03	165.71	161.50	162.78	162.63
Median	162.00	165.00	161.50	163.00	162.00
Standard Deviation	5.93	6.72	4.95	8.47	7.13
Minimum	147.00	155.00	158.00	147.00	147.00
Maximum	180.00	181.00	165.00	184.00	184.00

Abbreviations: Diag=diagnosis; DLX=duloxetine; No.=number; PLC=placebo and yrs=years.

The primary objective of this study was to assess the efficacy of duloxetine 60/120 mg once daily (QD) compared with placebo on the treatment of patients with FM during the acute therapy phase as measured by the Brief Pain Inventory-Modified Short Form (BPI) average pain score and Patient's Global Impressions of Improvement (PGI-Improvement). Duloxetine-treated patients showed greater improvement than did placebo-treated patients on the BPI (p=.052) and the PGI-Improvement (p=064), but the differences were not statistically significant (Table HMEF.3).

Sixteen patients in the DLX60QD-DLX60QD treatment group met the criteria for evaluation of maintenance of effect (30% reduction on BPI average pain score at the entry of the extension phase). There was a mean increase on the BPI average pain score, but it was not statistically significant. The upper bound of the 90% confidence interval was not <0.5, thus the FM patients did not meet the criteria for maintenance in the extension therapy phase.

Table HMEF.4 summarizes efficacy measures with statistically significant mean change from baseline to endpoint during the acute therapy phase. Versus placebo, patients treated with duloxetine 60 mg QD experienced statistically significant improvement on the following scales: BPI least pain (p=.046); BPI average interference (p=.009); PGI-Improvement for all qualified patients (p=.011); FIQ pain score (p=.030); CGI-Severity (p=.007); MFI mental fatigue scale (p0.022) and the BDI-II (p=.017). There were no other statistically significant differences noted in any other efficacy measures during the acute therapy phase.

There were four treatment groups in the extension therapy phase: patients randomized to the duloxetine 60 mg once daily during the acute therapy phase and ending the acute therapy phase at 60 mg once daily were continued at 60 mg once daily for the extension phase (DLX60QD-DLX60QD); patients randomized to the duloxetine 60 to 120 mg once daily during the acute therapy phase and ending the acute therapy phase at 60 mg once daily were continued at 60 mg once daily for the extension phase (DLX60/120/60QD-DLX60Q); patients randomized to the duloxetine 60 to 120 mg once daily during the acute therapy phase and ending the acute therapy phase at 120 mg once daily were continued at 120 mg once daily for the extension phase (DLX60/120/120QD-DLX120); and patients randomized to the placebo group during the acute therapy phase were then given 60 mg of duloxetine once daily in the extension phase (Placebo-DLX60QD).

Table HMEF.5 summarizes efficacy measures with statistically significant mean change from baseline to endpoint during the extension therapy phase. The placebo–duloxetine 60 mg once daily (placebo-DLX60QD) treatment group experienced a significant mean decrease on the PGI-Improvement scale (p<.001). The placebo-DLX60QD treatment group experienced a significant increase in mean tender point threshold (p=.001) and a significant decrease in count of low threshold (p=.002). The placebo-DLX60QD treatment group experienced a significant mean decrease on the BDI-II total score (p=.007). There were no other significant differences noted in any other efficacy measures during the extension therapy phase.

Table HMEF.3. Primary and Secondary Gatekeeper Efficacy Measures Acute Therapy Phase

Scale				
BPI Average Score – Mean Change from Baseline to Endpoint* – Acute *Therapy Phase	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Change Mean (SD)**	**p-Value**
PLC (N=167)	6.45 (1.47)	5.34 (2.43)	-1.11 (2.38)	
DLX60/120 (N=158)	6.59 (1.51)	4.94 (2.38)	-1.66 (2.44)	.053
PGI-Improvement – Mean at Endpoint – Acute Therapy Phase		**Endpoint Mean (SD)**		**p-Value**
PLC (N=165)		3.75 (1.37)		
DLX60/120 (N=157)		3.45 (1.56)		.064
Secondary Gate Keeper Analysis				
***SDS Global Functional Impairment Total Score* – Acute Therapy Phase**	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Change Mean (SD)**	**p-Value**
PLC (N=160)	18.20 (7.12)	15.43 (8.22)	-2.77 (6.97)	
DLX60/120 (N=143)	16.54 (7.57)	14.61 (8.76)	-1.93 (7.63)	.993

Abbreviations: BPI= Brief Pain Inventory-Modified Short Form; PGI-I= Patient's Global Impressions of Improvement; SD=standard deviation; SDS=Sheehan Disability scale.

Table HMEF.4. Secondary Efficacy Measures with Statistically Significant Mean Change from Baseline to Endpoint Acute Therapy Phase

Scale				
BPI Least Pain Score	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Change Mean (SD)**	**p-Value**
PLC (N=167)	5.14 (1.94)	4.35 (2.37)	-0.80 (2.30)	
DLX60/120 (N=158)	4.94 (2.09)	3.79 (2.43)	-1.15 (2.64)	.046
BPI Average Interference	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Change Mean (SD)**	**p-Value**
PLC (N=167)	5.70 (1.96)	4.66 (2.62)	-1.05 (2.46)	
DLX60/120 (N=158)	5.58 (2.09)	3.96 (2.49)	-1.62 (2.41)	.009
PGI-I – Mean at Endpoint All Qualified Patients		**Endpoint Mean (SD)**		**p-Value**
PLC (N=129)		3.54 (1.35)		
DLX60/120 (N=125)		3.11 (1.42)		p= .011
FIQ Pain Score – Mean Change from Baseline to Endpoint	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Change Mean (SD)**	**p-Value**
PLC (N=163)	7.26 (1.74)	6.21 (2.60)	-1.05 (2.70)	
DLX60/120 (N=154)	7.42 (1.68)	5.66 (2.72)	-1.76 (2.92)	.030
CGI-S – Mean Change from Baseline to Endpoint	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Change Mean (SD)**	**p-Value**
PLC (N=163)	3.73 (1.21)	3.49 (1.41)	-0.24 (1.30)	
DLX60/120 (N=155)	3.78 (1.21)	3.22 (1.28)	-0.56 (1.28)	.007

Table HMEF.4. Secondary Efficacy Measures with Statistically Significant Mean Change from Baseline to Endpoint Acute Therapy Phase (concluded)

MFI – Mean Change from Baseline to Endpoint				
MFI Mental Fatigue	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Change Mean (SD)**	**p-Value**
PLC (N=163)	13.14 (4.55)	12.83 (5.01)	-0.31 (3.99)	
DLX60/120 (N=152)	12.75 (4.49)	11.65 (4.71)	-1.10 (4.33)	.022
BDI-II Total Score – Mean Change from Baseline to Endpoint	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Change Mean (SD)**	**p-Value**
PLC (N=164)	14.65 (10.16)	12.95 (11.10)	-1.70 (7.83)	
DLX60/120 (N=151)	14.55 (10.00)	11.04 (8.54)	-3.51 (8.49)	.017

Abbreviations: BDI-II=Beck Depression Inventory-II; BPI= Brief Pain Inventory-Modified Short Form; CGI-Severity= Clinical Global Impressions of Severity; DLX=duloxetine; FIQ= Fibromyalgia Impact Questionnaire ; MFI=Multidimensional Fatigue Inventory; PGI-I= Patient's Global Impressions of Improvement; PLC=placebo; SD=standard deviation.

Table HMEF.5. Secondary Measures with Statistically Significant Mean Change from Baseline to Endpoint Extension Therapy Phase

Scale				
BPI – Mean Change from Baseline to Endpoint				
BPI Average Interference	**Baseline**	**Endpoint**	**Change**	**p-Value**
PLC-DLX60 (N=101)	4.07	3.58	-0.49	.029
PGI-I – Mean Change from Baseline to Endpoint	**Baseline**	**Endpoint**	**Change**	**p-Value**
PLC-DLX60 (N=101)	3.34	2.81	-0.52	<.001
Tender Point Pain Thresholds – Mean Change from Baseline to Endpoint				
Mean Tender Point Threshold	**Baseline**	**Endpoint**	**Change**	**p-Value**
PLC-DLX60 (N=99)	2.58	2.83	0.25	.001
Count of Low Threshold	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Change Mean (SD)**	**p-Value**
PLC-DLX60 (N=99)	15.78 (3.28)	14.95 (4.02)	-0.83 (2.58)	.002
BDI-II Total Score – Mean Change from Baseline to Endpoint	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Change Mean (SD)**	**p-Value**
PLC-DLX60 (N=100)	11.86 (10.63)	9.76 (8.52)	-2.10 (7.64)	.007

Abbreviations: BDI-II=Beck Depression Inventory-II; BPI= Brief Pain Inventory-Modified Short Form; DLX=duloxetine; PGI-I= Patient's Global Impressions of Improvement; PLC=placebo; and SD=standard deviation..

Duloxetine-treated patients experienced a significant improvement for the 36-item Short-Form Health Survey (SF-36) mental component summary and the mental health domain compared with placebo-treated patients on the mean change from baseline to endpoint for all randomized patients in the acute therapy phase (Table HMEF.6). There were no other statistically significant health outcomes analyses during the acute therapy phase. Table HMEF.7 summarizes the health outcome measures with statistically significant mean change during the extension therapy phase.

Table HMEF.6. Health Outcome Measures with Statistically Significant Mean Change from Baseline to Endpoint Acute Therapy Phase

Scale				
SF-36 – Mean Change from Baseline to Endpoint				
SF-36 Mental Component Summary	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Change Mean (SD)**	**p-Value**
PLC (N=162)	45.28 (11.94)	45.77 (12.66)	0.49 (11.10)	
DLX60/120 (N=146)	45.18 (11.90)	48.05 (11.75)	2.87 (11.52)	.027
SF-36 Mental Health	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Change Mean (SD)**	**p-Value**
PLC (N=162)	63.98 (19.97)	64.69 (21.97)	0.72 (17.16)	
DLX60/120 (N=148)	64.03 (19.74)	69.76 (21.12)	5.73 (19.59)	.005

Abbreviations: DLX=duloxetine; SF-36= 36-Item Short-Form Health Survey; PLC=placebo; and SD=standard deviation.

Table HMEF.7. Health Outcome Measures with Statistically Significant Mean Change from Baseline to Endpoint Extension Therapy Phase

Scale				
SDS – Mean Change from Baseline to Endpoint				
SDS Global Functioning Impairment Score	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Change Mean (SD)**	**p-Value**
PLC-DLX60 (N=101)	14.39 (8.41)	12.72 (8.28)	-1.67 (6.36)	.010
SDS School/Work Score	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Change Mean (SD)**	**p-Value**
PLC-DLX60 (N=96)	5.06 (2.89)	4.52 (2.96)	-0.54 (2.41)	.030
SDS Social Life/Leisure Activities Score	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Change Mean (SD)**	**p-Value**
PLC-DLX60 (N=101)	4.61 (3.08)	4.08 (2.83)	-0.53 (2.52)	.035
SDS Family Life/Home Responsibilities Score	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Change Mean (SD)**	**p-Value**
PLC-DLX60 (N=101)	4.78 (2.830	4.23 (2.91)	-0.55 (2.31)	.018
SF-36 – Mean Change from Baseline to Endpoint				
SF-36 Mental Health	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Change Mean (SD)**	**p-Value**
PLC-DLX60 (N=96)	67.08 (21.27)	72.42 (18.42)	5.33 (19.28)	.008
SF-36 Vitality	**Baseline Mean (SD)**	**Endpoint Mean (SD)**	**Change Mean (SD)**	**p-Value**
PLC-DLX60 (N=96)	31.35 (22.79)	35.57 (23.74)	4.33 (19.65)	P=.030

Abbreviations: DLX=duloxetine; SF-36= 36-Item Short-Form Health Survey; PLC=placebo; SD=standard deviation; and SDS=Sheehan Disability Scale.

Safety

There were no deaths in this study. There was no significant difference between duloxetine and placebo in the overall rate of discontinuation, but discontinuation due to lack of efficacy was statistically significantly more frequent for placebo.

Table HMEF.8 summarizes treatment-emergent adverse events (TEAEs) ≥5% that occurred in all randomly assigned patients during the acute therapy phase. Duloxetine-treated patients experienced an overall higher percentage of TEAEs compared with placebo. Events with a statistically higher incidence in duloxetine-treated patients included: nausea, headache, dry mouth, diarrhea, constipation, hyperhidrosis, somnolence, decreased appetite, dysgeusia, and nocturia compared with placebo-treated patients. In duloxetine-treated patients, TEAEs reported by ≥10% of patients were (in decreasing frequency): nausea, headache, dry mouth, diarrhea, constipation, dizziness,

fatigue and hyperhidrosis. Headache was the only TEAE reported by ≥10% of placebo-treated patients.

Forty-nine patients (14.8%) discontinued the study because of an AE during the acute therapy phase. No significant treatment group differences were observed in the incidence of AEs as the reason for discontinuation. No significant treatment group differences in SAEs were observed for all randomized patients during the acute therapy phase. A total of 10 SAEs were reported by 8 patients (4 placebo [arthralgia, abdominal pain upper, cystocele and non-cardiac chest pain] and 4 duloxetine [arthralgia, gait disturbance, lung infection pseudomonal, muscular weakness, paraesthesia, and pseudoneurologic symptom). In the opinion of the investigator the events of arthralgia (duloxetine) and paraesthesia were considered possibly related to study drug.

Table HMEF.9 presents statistically significant results in mean change from baseline to endpoint for chemistry analytes during the acute therapy phase.

Table HMEF.10 presents statistically significant results in mean change from baseline to endpoint for hematology analytes during the acute therapy phase.

Table HMEF.11 presents statistically significant results in mean change from baseline to endpoint for fasting lipid profile analytes during the acute therapy phase.

Table HMEF.12 presents statistically significant results in mean change from baseline to endpoint for vital signs and weight during the acute therapy phase.

Table HMEF.13 shows the ECG measures that showed a statistically significant change from baseline to endpoint during the acute therapy phase.

Table HMEF.8. Treatment-Emergent Adverse Events ≥5% By Decreasing Frequency All Randomized Patients Acute Therapy Phase

Preferred Term	PLACEBO (N=168) n	(%)	DLX60/120QD (N=162) n	(%)	Total (N=330) n	(%)	p-Value*
Patients with >= 1 Treatment-Emergent Event	135	(80.4)	143	(88.3)	278	(84.2)	.051
Nausea	16	(9.5)	43	(26.5)	59	(17.9)	<.001
Headache	18	(10.7)	35	(21.6)	53	(16.1)	.010
Dry mouth	9	(5.4)	31	(19.1)	40	(12.1)	<.001
Diarrhoea	10	(6.0)	26	(16.0)	36	(10.9)	.004
Constipation	9	(5.4)	26	(16.0)	35	(10.6)	.002
Dizziness	12	(7.1)	20	(12.3)	32	(9.7)	.137
Fatigue	9	(5.4)	18	(11.1)	27	(8.2)	.070
Back pain	11	(6.5)	13	(8.0)	24	(7.3)	.674
Hyperhidrosis	4	(2.4)	17	(10.5)	21	(6.4)	.003
Insomnia	12	(7.1)	9	(5.6)	21	(6.4)	.654
Upper respiratory tract infection	7	(4.2)	12	(7.4)	19	(5.8)	.242
Arthralgia	5	(3.0)	9	(5.6)	14	(4.2)	.284
Nasopharyngitis	9	(5.4)	5	(3.1)	14	(4.2)	.415
Somnolence	2	(1.2)	12	(7.4)	14	(4.2)	.006
Dyspepsia	4	(2.4)	9	(5.6)	13	(3.9)	.164

N = Number of randomized patients; n = Number of patients with treatment-emergent adverse event.
*Frequencies are analyzed using Fisher's exact test.
MedDRA Version: 9.1

Table HMEF.9. Chemistry Analytes with Statistically Significant Mean Change From Baseline to Endpoint All Randomized Patients Acute Therapy Phase

				Change to		
		Baseline		Endpoint		
Lab Test	**Therapy (N)**	**Mean**	**SD**	**Mean**	**SD**	**p-Value**
ALKALINE PHOSPHATASE (Units/Liter)	PLC (164)	75.890	24.477	-2.445	9.940	
	DLX60/120 (155)	74.800	22.086	2.381	11.976	<.001
ALT/SGPT (Units/Liter)	PLC (164)	19.494	7.822	-0.933	5.700	
	DLX60/120 (155)	21.187	9.392	6.916	50.134	.042
BILIRUBIN, TOTAL (micromole/Liter)	PLC (164)	7.622	3.492	0.271	2.538	
	DLX60/120 (155)	7.613	3.588	-0.345	2.958	.021
CHOLESTEROL (millimole/Liter)	PLC (164)	5.486	1.076	-0.226	0.745	
	DLX60/120 (155)	5.658	1.110	-0.043	0.706	.019
URIC ACID (micromole/Liter)	PLC (164)	288.494	71.111	3.909	42.923	
	DLX60/120 (155)	303.735	74.466	-19.503	43.356	<.001

Table HMEF.10. Hematology Analytes with Statistically Significant Mean Change From Baseline to Endpoint All Randomized Patients Acute Therapy Phase

				Change to		
		Baseline		Endpoint		
Lab Test	**Therapy (N)**	**Mean**	**SD**	**Mean**	**SD**	**p-Value**
MCH (femtomole[Fe])	PLC (152)	1.803	0.122	-0.012	0.058	
	DLX60/120 (140)	1.807	0.111	0.003	0.056	.037
PLATELET COUNT (BILL/L)	PLC (150)	280.393	65.207	-13.840	40.195	.001
	DLX60/120 (140)	286.207	35.546	4.200	46.172	

Table HMEF.11. Fasting Lipid Profile Analytes with Statistically Significant Mean Change From Baseline to Endpoint All Randomized Patients Acute Therapy Phase

				Change to		
		Baseline		Endpoint		
Lab Test	**Therapy (N)**	**Mean**	**SD**	**Mean**	**SD**	**p-Value**
HDL CHOLESTEROL-DEXTRAN PRECIP. millimole/Liter	PLC (159)	1.511	0.395	-0.034	0.251	
	DLX60/120 (145)	1.519	0.374	0.028	0.251	.017
LDL CHOLESTEROL (DIRECT) millimole/Liter	PLC (159)					
	DLX60/120 (146)	3.544	1.003	-0.249	0.698	
		3.591	1.046	-0.112	0.652	.041

Table HMEF.12. Vital Signs (Sitting) and Weight with Statistically Significant Mean Change From Baseline to Endpoint All Randomized Patients Acute Therapy Phase

Pulse Rate (bpm)	**Baseline**	**Endpoint**	**Change**	**p-Value**
PLC (N=167)	73.06	71.53	-1.53	
DLX60/120 (N=159)	73.88	74.94	1.06	.017
Diastolic Blood Pressure (mm Hg)	**Baseline**	**Endpoint**	**Change**	**p-Value**
PLC (N=167)	77.15	75.87	-1.28	
DLX60/120 (N=159)	77.21	79.08	1.87	.004

Table HMEF.13. Electrocardiograms with Statistically Significant Mean Change from Baseline to Endpoint All Randomized Patients Acute Therapy Phase

Acute Therapy Phase				
Heart Rate	**Baseline**	**Endpoint**	**Change**	**p-Value**
PLC (N=149)	68.81	67.59	-1.22	
DLX60/120 (N=136)	68.12	70.84	2.72	<.001
PR Interval	**Baseline**	**Endpoint**	**Change**	**p-Value**
PLC (N=149)	157.87	159.71	1.85	
DLX60/120 (N=136)	156.80	151.96	-4.84	<.001
QT Interval	**Baseline**	**Endpoint**	**Change**	**p-Value**
PLC (N=149)	396.43	401.45	5.02	
DLX60/120 (N=136)	396.43	393.47	-2.96	.002
RR Interval (msec)	**Baseline**	**Endpoint**	**Change**	**p-Value**
PLC (N=149)	888.92	905.95	17.03	
DLX60/120 (N=136)	898.82	864.42	-34.40	<.001

There were no deaths during the extension therapy phase. A total of 31 (15.2%) patients discontinued due to an adverse event during the extension phase. The most commonly reported reasons for discontinuation due to adverse events were diarrhea and nausea. A total of 10 SAEs were reported by 8 patients (2 DLX60-DLX60 [fall and patella fracture] and 8 DLX60/120/120-DLX120 [arrhythmia, arthralgia, Haematoma, odema mouth, pulmonary embolism, road traffic accident, stress, squamous cell carcinoma of skin]). In the opinion of the investigator the events of none of the SAEs reported were considered related to study drug.

A TEAE was defined as an event that first occurred or else worsened in the extension phase. Table HMEF.14 summarizes TEAEs by decreasing frequency $\leq$5% during the extension phase. Overall, dry mouth and nausea were experienced by >10% of patients. In the placebo-DLX60QD treatment group, dry mouth, nausea, headache, and hyperhidrosis were experienced by >10% of patients. In the DLX60QD-DLX60QD treatment group, dyspepsia and nasopharyngitis were experienced by >10% of patients. Constipation, vertigo and abdominal distension were experienced by >10% of patients in the duloxetine 60/120/60 mg once daily to duloxetine 60 mg once daily

(DLX60/120/60QD-DLX60QD) treatment group. There were no TEAEs reported in >10% of patients in the DLX60/120/120QD-DLX120QD treatment group.

Table HMEF.15 presents statistically significant results in mean change from baseline to endpoint for chemistry analytes during the extension therapy phase.

Table HMEF.16 presents statistically significant results in mean change from baseline to endpoint for hematology analytes during the extension therapy phase.

Table HMEF.17 presents statistically significant results in mean change from baseline to endpoint for fasting lipid profile analytes during the extension therapy phase.

Table HMEF.18 presents statistically significant results in mean change from baseline to endpoint for vital signs and weight during the extension therapy phase. Statistically significant increases in pulse rate and diastolic blood pressure were observed.

Table HMEF.14. Treatment-Emergent Adverse Events By Decreasing Frequency
All Randomized Patients Who Entered the Extension Phase
Extension Therapy Phase

Preferred Term	PLACEBO->DLX60QD (N=103) n (%)	DLX60QD->DLX60QD (N=17) n (%)	DLX60/120/60QD ->DLX60QD (N=2) n (%)	DLX60/120/120QD ->DLX120 (N=82) n (%)	Total (N=204) n (%)
Patients with >= 1 Treatment-Emergent Event	79 (76.7)	6 (35.3)	2(100.0)	62 (75.6)	149 (73.0)
Dry mouth	17 (16.5)	0 (0.0)	0 (0.0)	4 (4.9)	21 (10.3)
Nausea	20 (19.4)	0 (0.0)	0 (0.0)	1 (1.2)	21 (10.3)
Headache	11 (10.7)	0 (0.0)	0 (0.0)	5 (6.1)	16 (7.8)
Hyperhidrosis	14 (13.6)	0 (0.0)	0 (0.0)	2 (2.4)	16 (7.8)
Constipation	10 (9.7)	0 (0.0)	1 (50.0)	3 (3.7)	14 (6.9)
Diarrhoea	9 (8.7)	0 (0.0)	0 (0.0)	4 (4.9)	13 (6.4)
Dizziness	9 (8.7)	0 (0.0)	0 (0.0)	2 (2.4)	11 (5.4)
Insomnia	10 (9.7)	0 (0.0)	0 (0.0)	1 (1.2)	11 (5.4)
Hypertension	4 (3.9)	0 (0.0)	0 (0.0)	5 (6.1)	9 (4.4)
Muscle spasms	5 (4.9)	2 (11.8)	0 (0.0)	1 (1.2)	8 (3.9)
Nasopharyngitis	3 (2.9)	0 (0.0)	0 (0.0)	5 (6.1)	8 (3.9)
Neck pain	6 (5.8)	0 (0.0)	0 (0.0)	1 (1.2)	7 (3.4)
Paraesthesia	3 (2.9)	1 (5.9)	0 (0.0)	2 (2.4)	6 (2.9)
Vomiting	3 (2.9)	1 (5.9)	0 (0.0)	2 (2.4)	6 (2.9)
Dyspepsia	1 (1.0)	2 (11.8)	0 (0.0)	1 (1.2)	4 (2.0)
Fall	1 (1.0)	1 (5.9)	0 (0.0)	1 (1.2)	3 (1.5)
Vertigo	1 (1.0)	0 (0.0)	1 (50.0)	1 (1.2)	3 (1.5)
Abdominal distension	1 (1.0)	0 (0.0)	1 (50.0)	0 (0.0)	2 (1.0)
Excoriation	1 (1.0)	1 (5.9)	0 (0.0)	0 (0.0)	2 (1.0)
Gastrooesophageal reflux disease	1 (1.0)	1 (5.9)	0 (0.0)	0 (0.0)	2 (1.0)
Irritable bowel syndrome	0 (0.0)	1 (5.9)	0 (0.0)	1 (1.2)	2 (1.0)
Osteitis	1 (1.0)	1 (5.9)	0 (0.0)	0 (0.0)	2 (1.0)
Dysgeusia	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	1 (0.5)

Treatment groups: treatment in the Acute Therapy Phase (placebo or randomized/highest/last dose of duloxetine)
-> duloxetine dose in the Extension Phase.
N = Number of patients who entered the Extension Phase, n = Number of patients with treatment-emergent adverse event.
MedDRA Version: 9.1

Table HMEF.15. Chemistry Analytes with Statistically Significant Mean Change From Baseline to Endpoint Patients Who Entered the Extension Therapy Phase

		Baseline		Endpoint		Change		
Lab Test	**Therapy (N)**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p-Value**
ALKALINE PHOSPHATASE (Units/Liter)	PLC-DLX60 (93)	72.10	21.37	75.92	23.2	3.83	9.98	<.001
AST/SGPT (Units/Liter)	PLC-DLX60 (93)	17.70	6.29	23.12	31.34	5.42	30.82	<.001
	DLX60/120/120-DLX120 (78)	22.46	9.47	28.04	35.12	6.95	46.84	.011
ALT/SGOT (Units/Liter)	PLC-DLX60 (93)	17.70	6.29	23.12	31.34	3.00	16.80	.001
BILIRUBIN, TOTAL (micromole/Liter)	PLC-DLX60 (93)	8.09	3.90	7.37	3.17	-0.72	2.83	.017
CALCIUM (millimole/Liter)	PLC-DLX60 (93)	2.44	0.09	2.41	0.09	-0.03	0.09	<.001
	DLX60/120/120-DLX120 (78)	2.44	0.10	2.40	0.09	-0.04	0.09	<.001
CHOLESTEROL (micromole/Liter)	PLC-DLX60 (93)	5.36	0.98	5.65	0.96	0.29	0.67	<.001
URIC ACID (micromole/Liter)	PLC-DLX60 (93)	285.91	76.31	273.24	82.20	-12.68	41.77	.002
UREA NITROGEN (micromole/Liter)	DLX60-DLX60 (16)	4.76	1.16	5.73	1.23	0.98	0.89	<.001

Table HMEF.16. Hematology Analytes with Statistically Significant Mean Change From Baseline to Endpoint Patients Who Entered the Extension Therapy Phase

		Baseline		Endpoint		Change		
Lab Test	**Therapy (N)**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p-Value**
BASOPHILS (BILL/L)	PLC-DLX60 (82)	0.05	0.03	0.05	0.02	0.00	0.03	.042
	DLX60/120/120-DLX120 (73)	0.05	0.02	0.06	0.03	0.01	0/02	.020
EOSINOPHILS (BILL/L)	PLC-DLX60 (82)	0.13	0.09	0.16	0.10	0.02	0.07	.002
ERYTHROCYTE COUNT (TRIL/L)	PLC-DLX60 (82)	4.64	0.37	4.59	0.33	-0.05	0.24	.025
	DLX60/120/120-DLX120 (73)	4.66	0.37	4.58	0.30	-0.08	0.24	0.12
LEUKOCYTE COUNT (BILL/L)	PLC-DLX60 (82)	6.26	1.61	6.60	1.75	0.34	1.20	.021
MEAN CELL HEMOGLOBIN (femtomole[Fe])	PLC-DLX60 (82)	1.80	0.13	1.83	0.13	0.02	0.06	<.001
	DLX60/120/120-DLX120 (73)	1.81	0.12	1.84	0.13	0.03	0.07	<.001
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC) (MMOL/LITER [Fe])	PLC-DLX60 (82)	20.04	0.74	20.23	0.73	0.19	0.72	.024
	DLX60/120/120-DLX120 (73)	20.15	0.78	20.33	0.77	0.18	0.77	.048
NEUTROPHILS, SEGMENTED (BILL/L)	PLC-DLX60 (82)	3.73	1.34	4.03	1.34	0.30	1.01	.013
PLATELET COUNT (BILL/L)	PLC-DLX60 (82)	268.93	61.13	280.96	59.96	12.04	41.02	.006
MEAN CELL VOLUME (FEMTOLITER)	DLX60-DLX60 (16)	88.63	6.12	90.38	5.18	1.75	3.59	.049
MONOCYTES (BILL/L)	DLX60-DLX60 (16)	0.30	0.10	0.34	0.09	0.05	0.08	.023

Table HMEF.17. Fasting Lipid Profile Analytes with Statistically Significant Mean Change From Baseline to Endpoint Patients Who Entered the Extension Therapy Phase

		Baseline		Endpoint		Change		
Lab Test	**Therapy (N)**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p-Value**
HDL CHOLESTEROL-DEXTRAN PRECIP (millimole/Liter)	PLC-DLX60 (91)	1.50	0.36	1.56	0.39	0.06	0.22	.002

Table HMEF.18. Vital Signs and Weight with Statistically Significant Mean Change From Baseline to Endpoint Patients Who Entered the Extension Therapy Phase

		Baseline		Endpoint		Change		
	Therapy (N)	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p-Value**
Pulse Rate (bpm)	PLC-DLX60 (103)	70.60	10.17	75.45	9.89	4.84	10.17	<.001
Weight (kg)	DLX60-DLX60 (17)	76.53	14.17	78.18	14.82	1.65	2.69	.023
	DLX60/120/120-DLX120 (82)	74.96	14.75	76.24	15.02	1.28	3.11	<.001

Pharmacokinetic/Pharmacodynamic Results

Consistent with the results of statistical analysis on the coprimary efficacy measures, duloxetine treated patients had higher reduction in BPI-average pain score relative to placebo treated patients. Further, there is a duloxetine concentration-dependent increase in BPI-average pain score such that when duloxetine dose is doubled from 60 mg (typical Cav,ss = 72 ng/mL) to 120 mg (Cav,ss = 189 ng/mL at 120 mg), there is a 49% increase in BPI pain score reduction (that is, from -1.08 to -1.62) and a 22% increase in $AUC_{pain\ relief}$ (that is, from 224 to 272). Similarly, the probability of PGI-improvement score of either 1 or 2 (that is, very much better or much better) increased from 18.8 % in placebo treated patients to 57.6 % in duloxetine treated patients in a concentration-dependent manner. The probability of PGI-improvement score of either 3, 4 or 5 (that is, little better, no change or little worse, respectively) decreased from 70% in patients treated with placebo to a maximum of 39.6 % in duloxetine treated patients and for PGI-Improvemnt of 6 or 7 (that is, much worse or very much worse, respectively) decreased nearly 5-fold in duloxetine treated patients (2.74%) relative to placebo treated patients (14.2%).

