2. Synopsis

Clinical Study Synopsis: Study F1J-MC-HMEN

Title of Study: Effect of Duloxetine 60 mg to 120 mg Once Daily in Patients with Chronic Low Back Pain	
Investigator(s): This multicenter study included 20 principal investigator(s).	
Study Center(s): This study was conducted at 20 study center(s) in 5 countries.	
Publication(s) Based on the Study: None at this time.	
Length of Study: 9 months/years Date first patient enrolled: 24 January 2007 Date last patient completed for interim analysis:: 19 December 2007	Phase of Development: 3

Objectives: The primary objective of this study was to assess the efficacy of duloxetine 60 mg once daily (QD) to 120 mg QD compared with placebo on the reduction of pain severity as measured by the Brief Pain Inventory (BPI) 24-hour average pain scores (for simplicity, it is referred to as the BPI average pain score hereafter) in patients with chronic low back pain (CLBP) during a 13-week, double-blind acute treatment period.

Secondary Gatekeeper:

A gatekeeper strategy was employed for sequentially testing the secondary objectives. The following are the secondary gatekeeper objectives for the study:

- to evaluate duloxetine 60 mg QD to 120 mg QD versus placebo on patients' perceived improvement as measured by Patient Global Impression of Improvement (PGI-Improvement).
- to evaluate duloxetine 60 mg QD to 120 mg QD versus placebo on the improvement of functioning as measured by the Roland-Morris Disability Questionnaire (RMDQ-24), a questionnaire addressing intensity of CLPB and its interference with activities of daily living.

Additional secondary objectives included:

- To assess the efficacy of duloxetine 60 mg QD to 120 mg QD versus placebo during the acute treatment phase as measured by: weekly mean of 24-hour average pain, night pain, and worst pain scores (measured using 11-point Likert scale) computed from electronic diary scores, BPI – Severity and Interference, Clinical Global Impressions of Severity (CGI-Severity), response to treatment, as defined by a 30% reduction of BPI average pain scores, response to treatment, as defined by a 50% reduction of BPI average pain scores, Athens Insomnia Scale (AIS).
- To assess the impact of treatment with duloxetine 60 mg QD to 120 mg QD versus placebo during the acute treatment phase on patient-reported health outcomes, as measured by: 36-item Short-Form Health Survey (SF-36), EuroQoL Questionnaire – 5 Dimension (EQ-5D) version of the instrument, Work Productivity and Activity Impairment Instrument (WPAI).
- To evaluate whether reduction in pain (as assessed by the average pain intensity scores during the acute treatment phase) is a direct analgesic effect of duloxetine 60 mg QD to 120 mg QD and is independent of treatment effect on mood (as measured by the total score of the Beck Depression Inventory [BDI-II] and anxiety (as measured by the Hospital Anxiety Depression Scale anxiety subscale [HADS-A]).
- To evaluate the safety of duloxetine 60 mg QD to 120 mg QD versus placebo as measured by discontinuation rates, treatment-emergent adverse events (TEAEs), laboratory assessments, vital signs, and orthostatics during the acute treatment phase.

Study Design: A double-blind, randomized, parallel, outpatient study.

Number of Patients:
Planned: Approximately 230 patients; 115 per treatment group
Randomized: 115 duloxetine, 121 placebo
Completed: 84 duloxetine, 98 placebo

Diagnosis and Main Criteria for Inclusion: Patients had to have a clinical diagnosis of CLBP. Pain had to be present on most days for at least 6 months and either restricted to low back or associated with radiation to the proximal portion of the lower limb only (Class 1 and 2 per Quebec Task Force on Spinal Disorders). Patients had to have no radicular signs, evidence of spinal stenosis or painful conditions that can interfere with assessment of CLBP. Patients with MDD or baseline 24-hour average pain <4 were excluded.

Test Product, Dose, and Mode of Administration: duloxetine hydrochloride 60 to 120 mg/day, given QD as 1 or 2 x 60 mg capsules

Duration of Treatment: 13 weeks

Reference Therapy, Dose, and Mode of Administration: placebo given QD

Variables:
Efficacy:
Primary: BPI average pain scores
Secondary Gatekeepers:
PGI-Improvement
RMDQ-24
Additional Secondary Objectives:
Weekly average pain, night pain and worst pain scores (computed from electronic diary)
BPI – Severity and Interference scores
CGI-Severity
Percentage of patients who have response to treatment (defined as 30% and 50 % reduction of BPI average pain scores)
AIS
Health Outcomes:
SF-36
EQ-5D
WPAI
Safety:
Frequencies of Reasons for Discontinuation
Frequencies of Adverse Events
Frequencies of Serious Adverse Events
Frequencies of TEAEs
Changes in Laboratory Tests
Changes in Vital signs and weight
Changes in orthostatics
Others:
BDI-II
HADS-A

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 0.05. . A likelihood-based, mixed-effects model repeated measures (MMRM) analysis was used to analyze the primary efficacy variable (BPI average pain score). All patients with data from baseline and at least 1 post-baseline visit were included in the analysis. The model included fixed categorical effects of treatment, nonsteroidal anti-inflammatory drug (NSAID) use (Yes/No), investigator, visit and treatment-by-visit interactions, and continuous fixed covariates of baseline score and baseline-by-visit interaction. Mean change in the primary efficacy variable was also analyzed using a last-observation-carried-forward (LOCF) approach and baseline-observation-carried –forward (BOCF) approach. When an analysis of variance (ANOVA) model was used to analyze a continuous variable, the model contained the terms of treatment and investigator. The analysis of covariance (ANCOVA) model, in general, referred to the ANOVA model with baseline values added as a covariate. The stratifying variable of NSAID use (Yes/No) was added to the above ANCOVA model for all efficacy analyses. Type III sum-of-squares for the least-squares means (LSMean) 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 LSMean when an interaction term was included. Overall treatment group differences were examined using an ANOVA model for continuous variables and Fisher's exact test for the categorical variables.

A gatekeeper strategy was employed to sequentially test the secondary objectives that there is no treatment-group difference between the duloxetine treatment group (60 to 120 mg) and placebo-treated patients on the endpoint PGI-Improvement and change from baseline to endpoint on the RMDQ-24 total score, using the ANCOVA model and LOCF approach.

Summary:

Efficacy:

No significant treatment group differences were noted in patient demographics, baseline illness characteristics, historical illness, secondary conditions, previous drug therapy, and concomitant therapy were observed. There was a difference in the alcohol consumption (duloxetine-treated patients reported taking a significantly higher number of beers per week and placebo-treated patients reported taking a significantly higher number of glasses of wine per week) at baseline; however, this difference was not considered clinically relevant.

Duloxetine at 60/120 mg once daily (QD) demonstrated efficacy in the treatment of patients with chronic low back pain (CLBP). Significantly greater pain reduction compared to placebo was demonstrated on the primary efficacy measure (the mixed models repeated measures [MMRM] analysis on the average pain score of the Brief Pain Inventory [BPI]) during a 13-week, double-blind, acute therapy phase in patients with CLBP. The repeated measures analysis using the patient diary demonstrated a significantly greater reduction in pain in the first week after starting the 60 mg dose and continued throughout the 13 weeks of the acute therapy phase.

Duloxetine demonstrated superiority to placebo in most secondary analyses including 8 out of remaining 10 BPI items, weekly 24-hour average pain score, weekly 24-hour worst pain, weekly 24-hour night pain, Patient's Global Impressions of Improvement

(PGI-Improvement) rating, Roland-Morris Disability Questionnaire (RMDQ-24). Clinical Global Impressions of Severity (CGI-Severity) rating did not show significant difference in the mean change from baseline to endpoint between the treatment groups, although repeated measures analysis showed significantly greater improvement for the duloxetine treatment group at Visit 4 and Visit 5, but not Visit 3. No difference in the mean change of Athens Insomnia Scale (AIS) between the treatment groups was found. A significantly greater improvement in quality of life in the duloxetine treatment group compared with placebo, as measured by the EuroQoL Questionnaire – 5 Dimension (EQ-5D), was observed only in the subgroup of patients who completed the study. Overall, there was no significant difference between the treatment groups in the mean change in 36-item Short-Form Health Survey (SF-36), although three individual items, including bodily pain, demonstrated difference in favor of duloxetine. There was a significantly greater improvement in the duloxetine treatment group on the work activity impairment score compared with the placebo treatment group using the Work Productivity and Activity Impairment Instrument (WPAI). . The path analysis indicated that the direct analgesic effect of duloxetine on pain was predominant.

This study provides substantial evidence that duloxetine at 60/120 mg QD was effective in the treatment of patients with CLBP.

Safety:

Duloxetine 60/120 mg QD was well tolerated and safely administered in patients with CLBP. No deaths occurred during the study. Few serious adverse events (SAEs) occurred during the acute therapy phase (4 patients in the duloxetine treatment group and 1 patient in the placebo treatment group) and few patients discontinued because of adverse events (13.9% of patients in the duloxetine group compared with 5.8 % of patients in the placebo group). There were no significant treatment group differences in the incidence of individual adverse events reported as the reason for discontinuation. The treatment-emergent adverse events (TEAEs) that occurred with significant overall treatment-group differences (with patients in the duloxetine treatment groups experiencing the highest percentage of events) were nausea, fatigue, and hyperhidrosis. Most TEAEs were mild or moderate in severity. Significantly more duloxetine-treated patients reported TEAEs as severe but this finding was not driven by any single event.

Clinical laboratory assessments and vital signs were stable relative to baseline and no clinically relevant differences were detected between treatment groups.

This study demonstrates that treatment with duloxetine at 60/120 mg QD is safe in the treatment of patients with CLBP.

Conclusions: This study provides substantial evidence that treatment with duloxetine at 60/120 mg QD is safe and effective in the treatment of chronic low back pain for up to 13 weeks. This was demonstrated by significant pain reduction on the primary and most secondary efficacy measures as well as safe administration and good tolerability during the study.