2. HMGC Synopsis

Clinical Study Report Synopsis: Study F1J-MC-HMGC

Title of Study: Effect of Duloxetine 60 mg Once Daily versus Placebo in Patients with Chronic Low Back Pain	
Number of Investigator(s): This multicenter/ study included 27 principal investigator(s).	
Study Center(s): This study was conducted at 27 study centers in 6 countries.	
Publication(s) Based on the Study: None at this time.	
Length of Study: Date of first patient visit: 15 September 2008 Date of last patient visit: 6 July 2009	**Phase of Development:** 3

Objectives:

The primary objective of this study was to assess the efficacy of duloxetine 60 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 (for simplicity, it is referred hereafter as the BPI average pain) in patients with chronic low back pain (CLBP) during a 12-week, double-blind treatment period.

Secondary Gatekeeper Objectives:

A gatekeeper strategy (Westfall and Krishen 2001) was employed for sequentially testing the secondary objectives. The secondary gatekeeper objectives for the study were:

- to evaluate duloxetine 60 mg QD versus placebo on patients' perceived improvement as measured by Patient's Global Impressions of Improvement (PGI–Improvement) (Guy 1976),
- to evaluate duloxetine 60 mg QD versus placebo on the improvement of functioning as measured by the Roland Morris Disability Questionnaire (RMDQ–24) (Roland and Morris 1983).

Additional Secondary Objectives:

- to assess the efficacy of duloxetine 60 mg QD versus placebo during the treatment phase as measured by:
  - BPI–Severity and Interference ratings collected from patient responses at scheduled office visits (except for average pain stated as primary),
  - weekly mean of 24-hour average pain, average pain at night, and worst daily pain ratings (measured using 11-point Likert scale) computed from daily electronic diary,
  - response to treatment, defined as 30% reduction of the BPI average pain,
  - response to treatment, defined as 50% reduction of the BPI average pain,
  - sustained response to treatment, defined as BPI average pain of at least a 30% reduction from baseline to endpoint; a 30% reduction from baseline at an earlier visit than the last visit, and which remains at least at a 20% reduction from baseline in every visit in between (if there are any intervening visits),

Additional Secondary Objectives (continued):

- cumulative distribution of BPI average pain reduction, as measured by the percentage of patients who have reached each threshold of BPI average pain reduction from baseline endpoint (from >0% to 100% by 10% incremental increases),
- Clinical Global Impressions of Severity (CGI–Severity), and
- Profile of Mood States – Brief Form (POMS–Brief Form).

- to assess the impact of treatment with duloxetine 60 mg QD versus placebo during the treatment phase on patient-reported health outcomes, as measured by:
  - 36-item Short-Form Health Survey (SF–36),
  - European Quality of Life Questionnaire – 5 Dimension (EQ–5D) version of the European Quality of Life instrument, and
  - Work Productivity and Activity Impairment Instrument (WPAI)
- to evaluate the safety of duloxetine 60 mg QD versus placebo during the treatment phase as measured by:
  - discontinuation rates of patients,
  - incidence rates of treatment-emergent adverse events (TEAEs),
  - changes in laboratory test values,
  - changes in vital signs and weight, and
  - Columbia Suicide Severity Rating Scale (C–SSRS).

Study Design: A Phase 3 study to assess the efficacy of duloxetine 60 mg daily compared with placebo in the reduction of chronic low back pain during a 12-week, double-blind, randomized comparison study followed by a 1-week taper phase in patients diagnosed with chronic low back pain.

Number of Patients:
Planned: 200 duloxetine 60 mg QD, 200 placebo
Randomized: 198 duloxetine 60 mg QD, 203 placebo
Treated (at least 1 dose): 197 duloxetine 60 mg QD, 200 placebo
Completed: 147 duloxetine 60 mg QD, 156 placebo

Diagnosis and Main Criteria for Inclusion: Patients were eligible to be included in the study only if they met **all** of the following criteria:

- Male or female outpatients at least 18 years of age with chronic low back pain as their primary painful condition and who had provided informed consent by signing the appropriate informed consent document(s). Patients had to be competent and able to give their own informed consent.
- Based upon medical history, neurological examination and medical records, had low back pain (T-6 or below) present on most days for the preceding 6 months or longer and fulfilled all disease diagnostic criteria (described in Section 9.3).
- Had ratings equal to or greater than 4 on the BPI average pain at both Visits 1 and 2.

Study Drug, Dose, and Mode of Administration: duloxetine 60 mg given orally once daily as 1 capsule during acute treatment phase; duloxetine 30 mg given orally once daily as 1 capsule during taper phase

Reference Therapy, Dose, and Mode of Administration: placebo, given orally once daily as 1 capsule during both acute treatment and taper phases

Duration of Treatment:
duloxetine 60 mg once daily for 12 weeks (acute treatment), duloxetine 30 mg once daily for 1 week (taper) placebo once daily for 13 weeks (acute treatment and taper)

Variables:

Efficacy:

- BPI 24-hour average pain item (primary)
- The Brief Pain Inventory (BPI) – (Severity and Interference)
- The PGI-Improvement scale
- The Roland-Morris Disability Questionnaire (RMDQ-24)
- The weekly mean of 24-hour average daily plan, average pain at night, and worst daily pain (recorded on 11-point Likert scale using electronic patient diaries
- The Clinical Global Impressions of Severity (CGI-Severity) scale
- The Profile of Mood States – Brief Form (POMS – BF)

Health Outcomes:

- 36-item Short-Form Health Survey (SF-36)
- The EuroQoL Questionnaire – 5 Dimension (EQ-5D)
- Work Productivity and Activity Impairment Instrument (WPAI)

Variables (continued):

Safety:

- baseline ECG and x-ray
- discontinuation rates of patients
- incidence rates of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- changes in laboratory test values
- changes in vital signs and weight
- Columbia Suicide Severity Rating Scale (C–SSRS)

Statistical Evaluation Methods:

In this study, approximately 400 patients were to be randomized to the 2 treatment groups (200 patients per arm). This study had at least 90% power to detect a treatment group difference of 0.76 point in the mean change from baseline to endpoint in the BPI average pain between duloxetine and placebo treatment groups. The sample size was determined using a two-sided two-sample t-test with α=0.05, and assuming a common standard deviation of 2.26 and a discontinuation rate of 6% (dropout without post-treatment BPI).

This study also had at least 89% power to detect a treatment group difference of 17% in the response rates ($\geq$30% reduction from baseline) based on the BPI average pain between duloxetine and placebo treatment groups. The sample size was determined using a two-sided Fisher's exact test with α=0.05, and assuming the 38% and 55% response rates for placebo-treated patients and duloxetine-treated patients, respectively, and a discontinuation rate of 6% (dropout without post-treatment BPI).

Efficacy:

The primary efficacy measure was the BPI average pain. The primary efficacy analysis was to test the null hypothesis that the difference in the BPI average pain between the duloxetine and placebo treatment groups at the last visit of the treatment phase was zero.

The null hypothesis was tested by a likelihood-based, mixed-effects model repeated measures (MMRM) analysis on all the data after randomization. The model included the fixed categorical effects of treatment, investigator, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline rating and baseline-by-visit interaction. The unstructured covariance matrix was used to estimate within-patient errors in the model of the repeated measures analyses for all efficacy variables.

Statistical Evaluation Methods (continued):

Efficacy (continued)

The Kenward-Roger method was used to estimate denominator degrees of freedom. Type III sum-of-squares for the least-squares means was used. Analyses were implemented using SAS PROC MIXED. A contrast statement associated with the model performed primary treatment comparison between the duloxetine and placebo groups at the last visit of the treatment phase.

A gatekeeper strategy was employed for sequentially testing the secondary hypotheses to be eligible for possible label inclusion in the proposed clinical trial section of the label. If the primary hypotheses were statistically significant at the 0.05 two-sided level, the first secondary gatekeeper hypothesis was tested. If this comparison was statistically significant at the 0.05 two-sided level, subsequent secondary hypotheses were tested in sequence until a null hypothesis in the sequence failed to be rejected. The sequential testing was conducted in the following order:

- The comparison between duloxetine 60 mg QD and placebo on the endpoint PGI–Improvement.
- The comparison between duloxetine 60 mg QD and placebo on the change from baseline to endpoint on the RMDQ–24 total score.

For each variable, the hypothesis that there was no treatment-group difference between the duloxetine treatment group and the placebo group was evaluated by the analysis of covariance (ANCOVA) model using LOCF endpoint. The PGI–Severity was collected at baseline and used as a covariate in the model that analyzed the endpoint of PGI–Improvement.

Additional analyses of primary efficacy variable and secondary efficacy variables were conducted. Categorical variables were analyzed using the Fisher's exact test and continuous variables were analyzed using the ANOVA model. For continuous efficacy variables measured at each visits, MMRM analysis was also conducted.

Health Outcomes:

Patient self-reported health outcomes were assessed at Visit 2, Visit 3 (EQ-5D and WPAI), and at the last visit in the treatment phase by:

- 36-item Short-Form Health Survey (SF–36),
- European Quality of Life Questionnaire – 5 Dimension (EQ–5D), and
- Work Productivity and Activity Impairment Instrument (WPAI).

The mean change from baseline to endpoint for these measures was analyzed by the ANCOVA model.

Safety:

Treatment group differences in the incidence rates of death, SAEs, discontinuations due to adverse events, TEAEs, and treatment-emergent abnormal laboratory values at endpoint were evaluated using Fisher's exact test. Moreover, TEAEs were summarized by their maximum severity and system organ class (SOC) and analyzed by the Fisher's exact test. Mean change from baseline to endpoint in vital signs, weight, and laboratory values were analyzed using the analysis of variance (ANOVA) model.

Suicide-related thoughts and behaviors based on the Columbia Suicide Severity Rating Scale (C–SSRS) were summarized and compared between treatment groups.

Similar analyses were performed for both the acute treatment phase and for the taper phase.

Summary:
No significant treatment group differences were noted in patient demographics, baseline illness characteristics (except CGI-S), historical illness, secondary conditions, and previous drug therapy (except cyclobenzaprine) were observed. Significantly more placebo-treated patients reported the use of a rescue analgesic compared with duloxetine-treated patients.

Duloxetine at 60 mg QD demonstrated efficacy in the treatment of patients with CLBP. A significantly greater pain reduction compared with placebo was demonstrated on the primary efficacy measure (BPI average pain rating) during a 12-week, double-blind, therapy phase in patients with CLBP.

Duloxetine demonstrated significant superiority to placebo in the PGI-Improvement secondary gatekeeper analysis but not on the measure of physical function (RMDQ-24). Duloxetine also showed greater improvement than placebo in most other secondary measures including the BPI severity and interference items, 50% response rate based on average pain, weekly mean of 24-hour average pain, worst pain, and night pain rating, and POMS. The Clinical Global Impressions of Severity rating did not show a significant difference in the mean change from baseline to endpoint between the treatment groups. A significant improvement in quality of life in the duloxetine treatment group compared with placebo, as measured by the EQ-5D, was observed in both the UK and US index scores.

A total of 197 patients were exposed to duloxetine for a mean of 72 days, which was similar to the 200 patients exposed to placebo for a mean of 76 days. No deaths occurred during the study. During the double-blind treatment period, 5 patients assigned to duloxetine reported an SAE, the incidence of which was significantly more frequent than patients assigned to placebo (0 events); however, no individual SAE term was reported more than once. One SAE (placebo-treated patient) was reported during the taper phase. No suicidal ideation or suicidal behaviors were reported during the study.

Significantly more patients reported adverse events as the reason for discontinuation with duloxetine (15.2%) than with placebo (5.4%) during the double-blind treatment period. Nausea was the only adverse event term that was reported significantly more frequently as a reason for discontinuation with duloxetine (6.1%) than with placebo (1.0%).

No significant treatment group differences were observed in patients with at least 1 TEAE during the double-blind treatment period, with 63.1% of patients assigned to duloxetine and 55.2% of patients assigned to placebo experiencing at least 1 TEAE. For individual events, statistically significantly more patients assigned to duloxetine than placebo reported the following TEAEs: nausea (17.7% vs. 3.0%), dry mouth (6.6% vs. 2.0%), and somnolence (4.5% vs. 1.0%). The majority of all TEAEs (87.3%) were reported as mild or moderate in severity, and no single event was reported as severe significantly more frequently with duloxetine than placebo. In general, the onset of the 5 most frequently reported TEAEs was earlier for patients assigned to duloxetine than placebo, with time to resolution similar between treatment groups.

During the double-blind treatment period, significant differences in mean change analysis of some laboratory tests (such as ALKPH, ALT, AST, albumin, total protein, creatinine, uric acid) were observed between treatment groups; however, these findings, due to either the magnitude or direction of change, were considered not clinically relevant. While patients experienced abnormal increases in ALT and AST levels more frequently with duloxetine (7.6% and 8%, respectively) than placebo (3.5% and 3.2% respectively), no simultaneous abnormal increases in total or direct bilirubin levels were observed in either treatment group. One patient experienced an ALT elevation of 3X ULN; however, the patient's ALT level decreased to near normal values (36 units/liter; normal range limit: 35 U/L) during follow-up visits and was not accompanied by increases in bilirubin levels. Analyses of changes in fasting glucose and glycosylated hemoglobin levels indicated no clinically relevant changes (i.e., all changes were <4.5 mmol/L fasting glucose) and no significant differences between treatment groups. No differences in either sustained elevation in blood pressure or treatment-emergent orthostatic hypotension were observed between treatment groups.

Conclusions:

This study provides substantial evidence that duloxetine at 60 mg QD was effective in the treatment of patients with CLBP. Overall, duloxetine was well tolerated by patients with CLBP over 12 weeks of treatment. The safety profile observed during this study was similar to that observed in previously reported duloxetine studies.