2. HMGR Synopsis

Clinical Study Report Synopsis: Study F1J-US-HMGR

Title of Study: A Phase 4, 8-Week, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Efficacy of Duloxetine 60 mg Once Daily in Outpatients with Major Depressive Disorder and Associated Painful Physical Symptoms

Number of Investigators: This multicenter study included 47 principal investigators.

Study Centers: This study was conducted at 47 study centers in 5 countries.

Publication(s) Based on the Study: None at this time.

Length of Study:	**Phase of Development:** 4
Date of first subject enrolled: 09 November 2009 Date of last subject completed: 26 October 2010	

Objectives:

Primary Objective: To test the hypothesis that duloxetine given 60 mg (30 mg for first week) once daily (QD), orally, for 8 weeks was superior to placebo QD, orally, for 8 weeks in the treatment of adult outpatients with major depressive disorder (MDD) and associated painful physical symptoms. The primary objective was evaluated from 2 perspectives: the reduction of pain severity and the improvement in depressive symptoms. The Brief Pain Inventory Short Form (BPI-SF) average pain question rating and the Montgomery-Åsberg Depression Rating Scale (MADRS) total score were used as co-primary efficacy measures.

Gatekeeper Objectives: A gatekeeper strategy was employed for sequentially testing the secondary hypotheses that duloxetine 60 mg QD was superior to placebo QD in the treatment of adult outpatients with MDD and associated painful physical symptoms. For these objectives, duloxetine and placebo were compared in a stepwise fashion, in the order indicated below. Testing stopped when a measure failed to show statistical significance favoring duloxetine ($p>.05$). The a priori statistical analysis plan (SAP) included minor changes in wording of the second gatekeeper objective and the addition of 3 gatekeeper objectives. The purpose of 1 of the added gatekeeper objectives was to evaluate improvement in MDD over an extended period of time. The purposes of the other 2 were to evaluate timing for onset of efficacy for treatment of MDD. The following gatekeeper objectives are verbatim from the a priori SAP:

- mean change from baseline to 8-week endpoint in Sheehan Disability Scale (SDS) global functional impairment score
- percentage of patients with MADRS total score ≤12 at 8-week endpoint
- percentage of patients with MADRS total score ≤12 at last 2 non-missing acute study visits
- mean change from baseline to 4-week endpoint in MADRS total score
- mean change from baseline to 2-week endpoint in MADRS total score

Additional Secondary Objectives:

To test the hypothesis that duloxetine 60 mg QD was superior to placebo QD in the treatment of adult outpatient subjects with MDD and associated painful physical symptoms, as measured by the following:

- mean change from baseline to 8-week endpoint in SDS individual item scores
- mean change from baseline to 8-week endpoint in BPI-SF Severity and Interference Scores
- mean Patient Global Impression of Improvement (PGI-I) Score at 8-week endpoint

To assess the safety of duloxetine 60 mg QD versus placebo QD during the 8-week treatment phase, as measured by the following:

- treatment-emergent adverse events (TEAEs)
- rates and reasons for early discontinuations
- vital signs
- laboratory assessments
- suicide-related events (behavior and/or ideation) as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)

Study Design: This study was a Phase 4, multicenter, randomized, double-blind, parallel, placebo-controlled, fixed-dose, study with 3 study periods (screening phase, double-blind treatment phase that included a 1-week escalation phase, and an optional blinded taper phase) examining efficacy and safety of duloxetine 60 mg QD in adult outpatient subjects with MDD and associated painful physical symptoms.

Number of Subjects:

Planned: 520 subjects (260 randomized to duloxetine, 260 randomized to placebo)
Randomized: 262 duloxetine, 266 placebo
Treated (at least 1 dose): 262 duloxetine, 266 placebo
Completed Double-blind period: 192 duloxetine, 204 placebo

Diagnosis and Main Criteria for Inclusion: Subjects ≥18 years old who met criteria for MDD as defined in the Diagnostic and Statistical Manual, Fourth Edition, Text Revision (DSM-IV-TR) and confirmed by the Mini International Neuropsychiatric Interview (MINI) with at least 1 previous episode of depression.

Inclusion Criteria included the following:

- Current episode of MDD with a MADRS total score of ≥20 at Visits 1 and 2
- Prior episode of depression in the subject's medical history
- Painful physical symptoms with a score of ≥3 on the BPI-SF average pain question at Visits 1 and 2
- Clinical Global Impression of Severity (CGI-S) score ≥4 at Visits 1 and 2

Exclusion Criteria included the following:

- Any current (within the past 6 months) DSM-IV-TR primary Axis I diagnosis other than MDD
- Lack of response of any (*lifetime of subject)* episode of major depression to 2 or more adequate courses of antidepressant therapy, defined as a clinically appropriate dose for a minimum of 4 weeks or, in the judgment of the investigator, the subject meets criteria for treatment-resistant depression
- Having pain of a known origin
- Subjects meeting criteria for fibromyalgia as defined by the American College of Rheumatology, which includes the presence of chronic widespread pain and tenderness in all 4 body quadrants (above and below waist, and on the left and right sides of the body) for ≥3 months and at least 11 of 18 tender point sites

Study Drug, Dose, and Mode of Administration:
Duloxetine 60 mg given orally as 1 capsule QD (duloxetine 30 mg given orally as 1 capsule QD during Week 1 of double-blind treatment phase and during the optional 2-week taper phase).

Reference Therapy, Dose, and Mode of Administration: Placebo, given orally as 1 capsule QD

Duration of Treatment:
Double-blind Treatment Phase: 8 weeks
Optional Taper Phase: 2 weeks

Variables:

Efficacy:

The co-primary objectives were the reduction of average pain severity and the improvement in depressive symptoms. The primary efficacy evaluations were to compare the efficacy of duloxetine 60 mg QD with placebo in mean change from baseline over the 8-week double-blind treatment period in BPI-SF average pain rating, and mean change from baseline to the 8-week endpoint in MADRS total score.

Secondary efficacy variables included:

- BPI-SF Severity and Interference Scores
- SDS global functional impairment score (gated)
- Remission rate (depressive symptoms; MADRS total score)
- Response (depressive and pain symptoms, that is MADRS total score and BPI-SF average pain rating)
- PGI-I

Safety variable included:

- C-SSRS
- Self-Harm Supplemental Form (SHSF) and Self-Harm Follow-up Form (SHFF)
- Concomitant therapies
- Adverse events (AEs) and serious adverse events (SAEs)
- Laboratory data
- Vital signs (sitting pulse and blood pressure)

Statistical Evaluation Methods:

Efficacy:

All analyses were conducted on an intent-to-treat (ITT) basis, unless otherwise specified, meaning that data were analyzed by the treatment groups to which subjects were randomly assigned even if the subject did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Efficacy analyses included all subjects who had both a baseline and at least 1 postbaseline observation, unless otherwise specified. All randomized subjects were included in all safety analyses.

Assuming an effect size of 0.29, this study is estimated to have 90% power to detect a treatment difference between duloxetine 60 mg QD and placebo in mean change from baseline in BPI-SF average pain over 8 weeks of treatment with 251 patients in each treatment arm using a 2-sided t-test at an alpha level of 0.05.

Unless otherwise stated, tests of treatment effects were conducted at a 2-sided alpha level of 0.05, and tests of interaction effects were conducted at a 2-sided alpha level of 0.10. No adjustments for multiple comparisons were made. The primary analyses of mean change from baseline in BPI-SF average pain rating and the MADRS total score over 8 weeks of treatment were analyzed using a restricted maximum likelihood based mixed-effects model repeated measures (MMRM) approach. 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 score and baseline score-by-visit interaction. The main effect of treatment was selected for use as the primary analysis for the BPI-SF because a relatively rapid onset of treatment effect that afterward remains fairly constant over time is expected. Because the effect of treatment seen in MDD symptom reduction was expected to steadily improve over time, the comparison of Week 8 values between treatments was selected as the primary comparison. For MADRS total score, visit-wise comparisons at Week 2 and Week 4 served as the primary evidence for gated secondary objective 4 and 5.

The mean change in MADRS total score and BPI-SF average pain rating were also analyzed using a fixed-effects analysis of covariance (ANCOVA) model which included treatment, investigator and baseline score, employing last-observation-carried-forward (LOCF). SDS global functional impairment score, SDS individual item scores and BPI-SF Interference items, were analyzed using the MMRM approach, as well as the ANCOVA model described above. Percentages of subjects that met remission/response criteria at 8-week endpoint were analyzed using a LOCF approach and the Cochran Mantel-Haenszel (CMH) test with stratification by investigator. The visit-wise remission/response rates were analyzed using a categorical MMRM model that included the fixed, categorical effects of treatment, investigator, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariate of baseline score. Percentages of subjects who met remission criteria at Weeks 4 and 8 or the last 2 study visits, were analyzed using CMH test with stratification by investigator. PGI-I was analyzed using the MMRM approach where the model included the fixed, categorical effects of treatment, investigator, visit, and treatment-by-visit interaction, as well as an ANOVA model, used to compare scores at 8-week LOCF endpoint, which included treatment and investigator.

For the safety variables of discontinuations due to AEs, TEAEs, SAEs, abnormal vital signs (endpoint and anytime), sustained hypertension, and abnormal laboratory values (endpoint), the percentage of subjects who met criteria were compared between treatment groups using Fisher's exact test. Adverse event (AE) reporting was based on preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA). The change from baseline in vital signs and weight was analyzed using the MMRM model as the primary analysis. C-SSRS outcomes during treatment were analyzed using Fisher's exact test.

Summary:

A total of 262 subjects were randomly assigned to duloxetine treatment and 266 subjects were randomly assigned to placebo treatment. There was a similar distribution of subjects by gender (approximately 69% female in each group) and the overall mean age was 45.9 years. There were no statistically significant differences between treatment groups in any of the subject demographic variables or baseline characteristics. Finally, no statistically significant differences between the treatment groups were observed in frequency of compliance (where compliance for each visit interval was defined as taking between 80% and 120% of the study drug prescribed for that interval); overall, 84.2% of the patients were compliant with study drug administration during the double-blind treatment phase.

Duloxetine 60 mg QD demonstrated efficacy in the treatment of pain and depression in subjects with at least moderate pain associated with depression. Subjects who were treated with duloxetine had a statistically significantly greater reduction (improvement) in their BPI average pain rating compared with subjects treated with placebo ($p<.001$, main effect of treatment) over the 8-week double-blind treatment period. Subjects who were treated with duloxetine had a statistically significantly greater reduction (improvement) in their depressive symptoms as measured by the MADRS total score compared with subjects treated with placebo at the 8-week endpoint ($p<.001$), as well as at Weeks 2 and 4 (p-values $\leq.001$). Sensitivity analyses (LOCF approach) conducted for both the change from baseline in the BPI average pain rating and the change from baseline in the MADRS total score also showed statistically significant improvement in the subjects treated with duloxetine compared with subjects treated with placebo at the 8-week LOCF endpoint (p-values <.001).

Results from all 5 gatekeeper analyses (mean change from baseline to 8-week endpoint in SDS global functional impairment score; percentage of patients with MADRS total score ≤12 at 8-week endpoint; percentage of patients with MADRS total score ≤12 at the last 2 non-missing acute study visits; mean change from baseline to 4-week endpoint in MADRS total score; mean change from baseline to 2-week endpoint in MADRS total score) showed statistical significance favoring duloxetine versus placebo (p-values $\leq.019$).

Duloxetine-treated subjects had statistically significantly greater improvement in their BPI average pain rating at Weeks 1, 2, 4, and 8 compared with subjects treated with placebo (p-values ≤.005). Duloxetine-treated subjects also had a statistically significantly greater improvement in all BPI pain ratings and most interference items compared with placebo (MMRM approach) with the exception of interference with walking at Week 4, interference with ability to sleep at Weeks 1, 2, 4, and 8 (p-values >.05).

The duloxetine treatment group had statistically significantly greater mean changes (reductions) in SDS Global Function Impairment total score over the 8-week treatment period and at each timepoint (p-values ≤.019). For the majority of the SDS Items scores, the duloxetine treatment group had statistically significantly greater reductions at the 8-week endpoint (p-values ≤.040), as well as over the 8-week treatment period and at Weeks 2 and 4 (p-values ≤.048). SDS items that did not show a statistically significantly greater mean change for duloxetine compared with placebo at measured timepoints include Item 1 (Week 8), Item 4 (Weeks 1, 2, 4, and overall), and Item 5 (Week 1).

Duloxetine-treated subjects showed statistically significantly greater improvement in PGI-I scores compared with placebo-treated subjects using the MMRM approach both over the 8-week treatment period and at each timepoint starting at Week 1 and continuing through Week 8, (p-values ≤.021). These findings were further supported by the LOCF sensitivity analysis.

There were no deaths reported during the study. A total of 7 SAEs were reported by 6 subjects. Four duloxetine-treated subjects reported 1 SAE each (syncope, inguinal hernia, respiratory tract infection, and suicide attempt), while 1 duloxetine-treated subject reported 2 SAEs (clostridial infection and diverticulitis) and 1 placebo-treated subject reported 1 SAE (therapeutic agent toxicity). No SAEs were reported as emerging during the Taper Phase. Two duloxetine-treated subjects had elevated alanine transaminase (ALT) ≥3 times the ULN at any postbaseline time point during the study; however, neither subject met the hepatic algorithm criteria, as both subjects also had elevated baseline ALT values. Both subjects had follow-up ALT levels that returned to, or were trending towards, their baseline ALT values. A total of 30 subjects discontinued the study because of an AE. Duloxetine-treated subjects reported AEs as the reason for discontinuation statistically significantly more frequently than placebo-treated subjects (21 versus 9 subjects; p=.024). The reasons for discontinuation from the study during the drug-tapering phase were not captured. Of the 528 subjects randomly assigned in the study, 302 (57.2%) reported 1 or more TEAE. Overall, duloxetine-treated subjects (62.6%) reported TEAEs statistically significantly more frequently than placebo-treated subjects (51.9%; p=.014). Statistically significant treatment group differences in TEAEs (with subjects in the duloxetine treatment groups experiencing the highest percentage of events) occurred for the following AEs: nausea, somnolence, hyperhidrosis, yawning, abdominal discomfort, vision blurred, vomiting, and hypertension.

There was no statistically significant difference between treatment groups for the number and percent of subjects with suicide-related outcomes during treatment. During the study, the number of subjects reporting suicidal ideation was numerically higher for the placebo-treated subjects (29 [11.1%]) compared with the duloxetine-treated subjects (20 [8%]). Additionally, a statistically significantly higher incidence of treatment-emergent suicidal ideation relative to lifetime baseline was observed in the placebo group (13 [5%]) than in the duloxetine group (4 [1.6%]) (p=.046).

There were statistically significant (p<.05) mean differences from baseline to endpoint between duloxetine-treated subjects compared with placebo-treated subjects in 4 laboratory analytes (chloride, uric acid, mean cell volume, neutrophils).

One statistically significant difference between treatment groups was observed in the incidence of subjects with a treatment emergent abnormal laboratory value at any time during the double-blind treatment period: an elevated ALT was observed for 7.7% duloxetine subjects versus 2.6% placebo subjects (p=.033). No other statistically significant differences in categorical changes in lab values between treatment groups were observed during the double-blind treatment phase.

The duloxetine treatment group showed a statistically significant change (increase) from baseline to LOCF endpoint in pulse compared with the placebo-treatment group (p=.001). In addition, the placebo treatment group showed a statistically significant change (increase) from baseline to LOCF endpoint in weight compared with the duloxetine-treatment group (p<.001).

Similar results were seen in time course analyses of vital signs, where compared with the placebo treatment group, the duloxetine treatment group showed a statistically significant change (increase) in pulse at the Week-8 timepoint and in systolic pressure overall as well as at the Week 4 time point. For body weight, the duloxetine treatment group showed a decrease overall and at each timepoint, while the placebo treatment group showed an increase overall and at each timepoint; the differences between the treatment groups were statistically significant.

One duloxetine-treated subject and no placebo-treated subjects met the criteria for sustained hypertension, which was defined as either elevated sitting systolic blood pressure (≥140 mm Hg and an increase ≥10 mm Hg from baseline value) or elevated sitting diastolic blood pressure (≥90 mm Hg and an increase ≥10 mm Hg from baseline value) at 3 consecutive visits.

Conclusions:

This study demonstrated the efficacy of duloxetine 60 mg QD in the treatment of patients with MDD and at least moderate pain. Subjects who were treated with duloxetine had a statistically significantly greater reduction (improvement) in their BPI average pain rating compared with subjects treated with placebo over the 8-week double-blind treatment period. Additionally, subjects treated with duloxetine had statistically significantly greater improvement in their BPI average pain rating at each timepoint compared with subjects treated with placebo. Subjects who were treated with duloxetine had a statistically significantly greater improvement (reduction) in their depressive symptoms compared with subjects treated with placebo at the 8-week endpoint as well as at 2-week and 4-week timepoints, and over the 8-week double blind treatment phase (p<.001). Duloxetine was also superior to placebo on all gatekeeping measures and most other secondary outcome measures.

Overall, duloxetine was fairly well tolerated and safely administered. The safety and tolerability profile observed during this study was consistent with the known characteristics of duloxetine. This study provides evidence that duloxetine 60 mg QD is safe and effective for the treatment of DSM-IV-TR defined MDD and associated painful physical symptoms.