2. HMGF Synopsis

Clinical Study Report Synopsis: Study F1J-MC-HMGF

Title of Study: Duloxetine versus Placebo in the Treatment of Elderly Patients with Generalized Anxiety Disorder	
Number of Investigator(s): This multicenter/study included 47 principal investigators.	
Study Center(s): This study was conducted at 47 study centers in 9 countries.	
Publication(s) Based on the Study: None at this time.	
Length of Study: Date of first patient enrolled (assigned to therapy): 30 November 2010 Date of last patient visit entire study: 05 July 2012	**Phase of Development:** 4

Objectives: The primary objective of this study was to assess whether duloxetine 30 to 120 mg once daily (QD) is superior to placebo in the treatment of elderly patients (≥65 years old) with generalized anxiety disorder (GAD), as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition-Text Revised (DSM-IV-TR), during a 10-week, double-blind, acute therapy phase. "Superiority" was defined as statistically greater reduction on the mean change from baseline to Visit 6 in anxiety symptoms as measured by the Hamilton Anxiety Rating Scale (HAMA) total score. The Structured Interview Guide for the Hamilton Anxiety rating scale (SIGH-A) was the required method for collecting the HAMA data in this study.

If duloxetine was assessed to be statistically significantly superior to placebo, based on the primary analysis of the HAMA total score, then the following key secondary objective was tested for possible label inclusion using the Gatekeeper strategy:

- To evaluate the efficacy of duloxetine 30 to 120 mg QD compared with placebo in elderly patients (≥65 years old) during a 10-week, double-blind, acute therapy phase as measured by the mean improvement on the Sheehan Disability Scale (SDS) Global Functional Impairment score. The SDS work, social, and family items were analyzed, but not considered part of the gatekeeper strategy.

The additional secondary objectives of the study were:

- To assess the efficacy of duloxetine 30 to 120 mg QD compared with placebo in elderly patients (≥65 years old) during a 10-week, double-blind, acute therapy phase as measured by the following:
  - Rate of response, defined as at least a 50% reduction from baseline to endpoint on HAMA total score.
  - Rate of remission, defined as HAMA total score ≤7 (or ≤10) at endpoint.
  - Rate of improvement defined as Clinical Global Impressions of Improvement (CGI-Improvement) ≤2 at endpoint.
  - Rate of sustained improvement (overall), defined as at least a 30% improvement (reduction) on the HAMA total score from baseline to endpoint, at an earlier visit prior to the last visit of the study period, and at all visits in between.
  - Rate of sustained improvement (Week 2), defined as at least a 30% improvement on the HAMA total score from baseline to Week 2 and sustained through the last visit of the study period.
  - Time to first response (defined above), remission (defined above), sustained improvement (defined above), first functional remission (defined below), and first improvement (defined as CGI-Improvement ≤2)

- To evaluate the efficacy of duloxetine 30 to 120 mg QD compared with placebo in elderly patients (≥65 years old) during a 10-week, double-blind, acute therapy phase as measured by the mean improvement on the following:
    - Anxiety and Depression Subscales scores of the Hospital Anxiety Depression Scale (HADS).
    - Hamilton Anxiety Rating Scale Psychic Anxiety Factor Score (sum of Items 1 through 6, and 14); HAMA Somatic Anxiety Factor Score (sum of Items 7 through 13); HAMA individual items, specifically the anxious mood item (Item 1) and the tension item (Item 2).
    - Clinical Global Impressions of Improvement scale (CGI-Improvement).
    - Patient's Global Impressions of Improvement scale (PGI-Improvement).
    - Brief Pain Inventory-Modified Short Form (BPI-SF) pain severity items and interference scores.
- To compare the effects of duloxetine 30 to 120 mg QD with placebo in elderly patients (≥65 years old) during a 10-week, double-blind, acute therapy phase on patients' role functioning and quality of life using the following:
    - Sheehan Disability Scale individual work/school, social life, and family/home management individual impairment scores;
    - Sheehan Disability Scale functional remission rate, defined as a SDS Global Functional Impairment Score ≤5 (or ≤ 6) at endpoint; and
    - Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF) percent of maximum total score.
- To compare the safety and tolerability of duloxetine 30 to 120 mg QD with placebo in elderly patients (≥65 years old) during a 10-week, double-blind, acute therapy phase as measured by discontinuation rates, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), vital signs, the incidence of falling down using solicited assessment (FALLS), laboratory analyses, electrocardiograms (ECGs), and solicited questioning of suicide-related AEs (behavior and ideations), using the Columbia-Suicide Severity Rating Scale (C-SSRS).

An additional exploratory objective of the study was to validate the Geriatric Anxiety Inventory (GAI) by examining the mean change from baseline to Visit 6 and endpoint on the GAI total score in elderly patients treated with duloxetine compared with placebo during a 10-week, double-blind acute therapy phase.

Study Design: F1J-MC-HMGF (HMGF) was a multicenter, randomized, double-blind, placebo-controlled, Phase 4 study designed to assess the efficacy of duloxetine 30 to 120 mg QD in the acute treatment of elderly patients (≥65 years old) with GAD. Elderly patients who met criteria for GAD as defined by the DSM-IV-TR were eligible to participate in this study. Following a 3 to 30 day screening phase, eligible patients were randomly assigned at Visit 2 to receive treatment with duloxetine or placebo in a 1:1 ratio. A total of 291 patients (151 to duloxetine 30-120 mg QD and 140 to placebo) were randomly assigned to 10 weeks of double-blind treatment. Patients who discontinue treatment at the completion of Visit 6 or who require discontinuation of treatment at or after Visit 4 entered a 2-week, double-blind, discontinuation-taper phase (Study Period III). To achieve a relative balance across treatment groups with regard to patient age, treatment was randomly assigned by the stratum determined by patient's age (<75 or ≥75 years) at the randomization visit within each study site.

Number of Patients:

Planned: 144 duloxetine, 144 placebo
Randomized: 151 duloxetine 140 placebo
Treated (at least 1 dose): 151 duloxetine, 140 placebo
Completed: 115 duloxetine, 105 placebo

Diagnosis and Main Criteria for Inclusion: Male and female outpatients at least 65 years old presenting with GAD based on the DSM-IV-TR disease diagnostic criteria. The patient must suffer from a primary diagnosis of GAD and not from an adjustment disorder or anxiety disorder not otherwise specified (NOS). Symptoms of GAD should not be situational in nature. Patients with comorbid social phobia or specific phobia were allowed to participate in the study provided that GAD was the primary diagnosis.

Test Product Dose, and Mode of Administration:
Duloxetine 30 to 120 mg/day, given orally once a day.

Reference Therapy, Dose, and Mode of Administration: Placebo given once daily orally.

Duration of Treatment: 12 weeks
Treatment period: 10 weeks
Taper period: 2 weeks

Variables:
Efficacy: HAMA (using the SIGH-A), HADS, CGI-Improvement, PGI-Improvement, and BPI-SF.
Safety: SAEs, TEAEs, labs, ECGs, vitals, FALLS, and C-SSRS.
Health Outcomes: SDS and the Q-LES-Q-SF.

Statistical Evaluation Methods:

Efficacy: All analyses were conducted on an intent-to-treat (ITT) basis. Treatment effects were evaluated based on a 2-sided significance level of 0.05, and interaction effects at 0.05. No adjustments for multiple comparisons were made. The primary analysis compared treatment group mean changes from baseline in HAMA total score at the last visit in the acute therapy phase using a maximum likelihoodbased, mixed-effects repeated measures (MMRM) analysis. Secondary efficacy variables were analyzed using a repeated measures approach.

Change from baseline to endpoint for HAMA total score, secondary efficacy variables, and health outcomes/ quality of life variables were analyzed using an analysis of covariance (ANCOVA) model. Unless otherwise specified, when an analysis of variance (ANOVA) model was used to analyze a demographic, efficacy, or safety variable, the model contained the main effects of treatment and investigator. Similar logic was applied to an ANCOVA model, which in general refers to the ANOVA model with baseline included as a continuous covariate in addition to age group (<75, ≥ 75 years) as a categorical covariate. Type III sum-of-squares for the least squares mean (LSMean) was used for the statistical comparison using ANOVA or ANCOVA.

When computing total, factor, or subscale scores for selected efficacy and health outcome measures with missing items, an imputation method was used.

Rates of response, remission, sustained improvement, functional remission, and improvement were compared between treatments using the Cochran-Mantel-Haenszel (CMH) test controlling for investigator.

Time to first response, remission, sustained improvement, first functional remission, and first improvement were analyzed. Kaplan-Meier survival curves of time-to-event was calculated by treatment group. In the calculation, patients who did not have the event were considered as right-censored observations.
The comparison of the survival curves between treatment groups was conducted by a log-rank test as well as by a stratified log-rank test controlling for investigator.

Safety: Categorical safety variables from the C-SSRS, AEs, ECGs, sustained blood pressure elevation, and orthostatic blood pressure and pulse, and FALLS were analyzed using Fisher's exact test to compare treatment groups. Continuous safety variables such as laboratory, vital signs and weight, and ECG parameters were analyzed using an ANOVA model.

Health Outcomes: Change from baseline to each postbaseline visit in the double-blind acute therapy phase was analyzed for the global functional impairment score and the individual SDS items using the likelihood-based, mixed effects repeated measures analysis. Change from baseline to endpoint in Q-LES-Q SF percentage of maximum possible score was evaluated using the ANCOVA model described previously.

Summary:

The results of this multicenter, randomized, double-blind, placebo-controlled study indicate that duloxetine treatment (30 mg to 120 mg/day) is an effective and tolerated treatment for elderly patients (≥65 years old) with GAD. Efficacy of duloxetine was demonstrated across the primary outcome and the majority of disease-specific secondary measures, particularly for the primary symptoms of GAD.

Compared with placebo, duloxetine treatment significantly reduced anxiety illness severity across both psychic and somatic symptoms. The core features of GAD, anxious mood and tension, were found to improve significantly more with duloxetine treatment as early as Week 4 of treatment. During the first 2 weeks of treatment, all duloxetine patients received a 30-mg dose. After that 2-week period, dose increases were allowed based on investigator judgment to maximize efficacy, while maintaining individual tolerability. Therefore, statistically significant improvements for duloxetine at Week 4 were reflective of only 30- and 60-mg doses. Following the significant improvements at Week 4, the magnitude of overall symptom improvement with duloxetine treatment (30-, 60-, 90-, and 120-mg doses) continued to increase through the last study visit at Week 10.

Duloxetine-treated patients were significantly more likely to meet treatment responder and remission criteria, and to experience sustained improvement during acute therapy, than were placebo-treated patients. Patients on duloxetine reported significantly decreased impairment in performing major life roles, such as social life and family and home management. Significantly greater increases in levels of life enjoyment and satisfaction were also reported by patients treated with duloxetine.

Overall, the safety findings within this study were consistent with previous results from adult (≥18 years old) duloxetine studies in GAD and other indications. Although statistically significant mean changes were observed for blood pressure and heart rate in patients treated with duloxetine compared with placebo, the magnitude of these changes were not considered clinically relevant. With regard to TEAEs, the number of events that occurred with duloxetine at a rate of ≥5% and at least twice the rate of placebo was lower in this elderly GAD clinical trial than in previous elderly subgroup analyses from the pooled adult duloxetine studies in GAD (Davidson et al. 2008). The only TEAE reported statistically significantly more frequently for duloxetine compared to placebo was dry mouth, and there were no significant differences in the reported AEs leading to discontinuation between treatment groups.

Lastly, following database lock, it was discovered that a central laboratory programming error caused the omission of baseline (Visit 1) and endpoint (Visit 6/Discontinuation [DC]) glucose results from the individual patient laboratory reports sent to study sites. The error was corrected and a medical review of the full, corrected glucose dataset was conducted. This review included relevant clinical study data for each patient who had an abnormal glucose level at baseline or endpoint. The overall conclusion was that the reporting error did not appear to have had a significant impact on the interpretation and interpretability of the study's overall efficacy and safety results. All investigators were notified of the error and the actions taken. Investigators who had patients with abnormal glucose levels at study endpoint were also provided a clinical data profile for each of the patients from their site, and were asked to make a clinical decision about the need for any follow-up with individual patients.

Conclusions:

- This study found duloxetine to be an effective and tolerated treatment for elderly patients (≥65 years old) with GAD. These findings are based on patients taking the maximum duloxetine doses of 30 mg/day (32% of duloxetine-patients), 60 mg/day (34% of duloxetine-patients) and 90-120 mg/day (34% of duloxetine-patients) at any time during the 10-week acute treatment period of the study.
- Duloxetine (30 to 120 mg/day) was associated with a statistically greater improvement in overall anxiety symptoms, functional impairment, and enjoyment and satisfaction of life compared with placebo in elderly patients (≥65 years old).
- The safety results of this study were consistent with the known safety and tolerability profile for duloxetine and no new safety findings were identified.

References:

Davidson JR, Wittchen HU, Llorca PM, Erickson J, Detke M, Ball SG, Russell JM. Duloxetine treatment for relapse prevention in adults with generalized anxiety disorder: a double-blind placebo-controlled trial. *Eur Neuropsychopharmacol*. 2008;18(9):673-681.