2. HMCK Synopsis

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Clinical Study Report Synopsis: Study F1J-MC-HMCK

Title of Study: A Double-Blind, Efficacy and Safety Study of Duloxetine versus Placebo in the Treatment of Children and Adolescents with Major Depressive Disorder	
Number of Investigators: This multicenter study included 65 principal investigators.	
Study Centers: This study was conducted at 65 study centers in 9 countries in 4 world regions.	
Publications Based on the Study: None at this time.	
Length of Study: Date of first patient enrolled: 26 March 2009 Date of last patient completed: Study Period II: 24 March 2011 Date of last patient completed Study: 13 October 2011	**Phase of Development:** 3

Objectives:

The primary objective of this study was as follows: To assess the efficacy of duloxetine compared with placebo in the acute treatment of children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) who met criteria for major depressive disorder (MDD) without psychotic features, single or recurrent episode, as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision (DSM-IV-TR [APA 2000]). The primary objective was evaluated by assessing the mean change from baseline to endpoint (10 weeks) on the Children's Depression Rating Scale Revised (CDRS-R) total score between duloxetine and placebo.

The secondary objectives of the study were as follows:

- To test assay sensitivity by comparing fluoxetine with placebo treatment in children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) with MDD, during a 10-week, double-blind, acute treatment phase, as measured by the mean change from baseline to endpoint on CDRS-R total score.
- To evaluate the efficacy of treatment with duloxetine compared with placebo in the treatment of children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) with MDD, during a 10-week, double-blind, acute treatment phase, as measured by:
    - Mean change from baseline to endpoint on the CDRS-R subscales
    - Remission rates at endpoint using the CDRS-R total score
    - Mean change from baseline to endpoint on the Clinical Global Impression of Severity (CGI-S) scale
- To assess changes in depressive symptoms of children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) with MDD treated with duloxetine during a 6-month, double-blind extension phase using the above measures.

Secondary Objectives (continued)

- To evaluate the safety and tolerability of treatment with duloxetine compared with placebo in the treatment of children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) with MDD, during a 10-week, double-blind, acute treatment phase as measured by:
  - Treatment-emergent adverse events (TEAEs)
  - Vital signs
  - Rates and reasons for early discontinuation
  - Laboratory measurements and electrocardiograms (ECGs)
  - Suicide risk and suicide-related events (behavior and/or ideation) as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)
- To assess safety and tolerability of duloxetine in the treatment of children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) with MDD during a 6-month, double-blind extension phase using the above measures, as applicable.
- To characterize the pharmacokinetics (PK) of duloxetine at steady-state in the treatment of children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) with MDD. The characterization included estimation of duloxetine PK parameters, determination of inter-patient and intra-patient variability, and identification of potential patient factors (age, body weight, maturation, gender, and cytochrome P450 2D6 [CYP2D6] genotype status) that may influence duloxetine PK as measured by steady-state duloxetine plasma concentrations.
- To compare the steady-state duloxetine PK in the treatment of children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) with MDD with historical adult duloxetine PK using duloxetine steady-state concentration data and PK parameters.
- To investigate the relationship between duloxetine exposure and efficacy endpoints during a 10-week, double-blind, acute treatment phase in children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) with MDD using steady-state duloxetine plasma concentrations and CDRS-R total score.

Study Design: This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study in children and adolescents aged 7 through 17 years meeting DSM-IV-TR defined criteria for MDD. Safety and efficacy of orally delivered duloxetine hydrochloride was assessed across the dose range of 60 to 120 mg QD. A fully powered fluoxetine treatment arm (20-40 mg QD) was included to provide evidence of assay sensitivity. The study consisted of 4 periods: Period I was a 2-week screening period; Period II was a 10-week double-blind acute therapy period; Period III was a 6-month double-blind extension period; and Period IV was a 2-week tapering period. The total duration of this study was approximately 38 weeks.

Number of Patients:
Planned: 112 duloxetine, 112 fluoxetine, 112 placebo
Randomized to Study Period II: 117 duloxetine, 117 fluoxetine, 103 placebo
Treated in Study Period II: 117 duloxetine, 117 fluoxetine, 103 placebo
Completed Study Period II: 87 duloxetine, 91 fluoxetine, 87 placebo
Entered Study Period III: 83 DLX60120/DLX60120, 92 FLX2040/FLX2040, 86 PBO/DLX60120
Completed Study Period III: 56 DLX60120/DLX60120, 65 FLX2040/FLX2040, 69 PBO/DLX60120

Diagnosis and Main Criteria for Inclusion: Children and adolescents aged 7 to 17 years, inclusive, who met criteria for MDD without psychotic features, single or recurrent episode, as defined by the DSM-IV-TR and supported by the Mini International Psychiatric Interview for Children and Adolescents (MINI-KID).

Study Drug, Dose, and Mode of Administration:
Study Period II: Duloxetine flexible dosing (60, 90, or 120 mg), given orally once a day.
Study Period III: Duloxetine flexible dosing (60, 90, or 120 mg), given orally once a day.

Comparator, Dose, and Mode of Administration: For Study Period II, placebo (comparator), given orally once a day, fluoxetine (active control) flexible dosing (20 mg or 40 mg), given orally once a day. For Study Period III, fluoxetine flexible dosing (20 mg or 40 mg), given orally once a day.

Duration of Treatment:
Study Period II: 10 weeks
Study Period III: 26 weeks

Variables:

Primary Efficacy: The contrast between duloxetine and placebo at the last visit in Study Period II (Visit 8, Week 10), based on a mixed model repeated measures (MMRM) analysis on change from baseline in the CDRS-R total score.

Secondary Efficacy:

- Change from baseline to endpoint (Week 10) for CDRS-R Subscale, CDRS-R Item 13, and CGI-S
- Change from baseline to endpoint (Week 10) for CDRS-R total score (fluoxetine)
- Change from baseline at each postbaseline visit for CDRS-R total score (Study Periods II/III and III), CDRS-R Total Score (excluding age and age*visit covariates), CDRS-R Subscale and Item 13 scores, CGI-S
- Categorical variable for Remission Rate (CDRS-R) at endpoint, CDRS-R Remission Rate at last 2 nonmissing visits, 30% Response Rate (CDRS-R total score), 50% Response Rate (CDRS-R total score), Continuous Responder Analysis (CDRS-R total score), and CGI-S Response Rate
- Categorical Variable at each postbaseline Visit - Visitwise for Remission Rate, 30% Response Rate (CDRS-R total score), 50% Response Rate (CDRS-R total score), and CGI-S Response Rate
- Time to event for time to first remission (defined by the first visit that CDRS-R total score of $\leq$28), and time to first - 50% Response on CDRS total score

Safety:

- Percentages of patients that reported treatment-emergent adverse events (TEAEs), discontinuation-emergent adverse events (AEs), serious adverse events (SAEs), and discontinuations due to AEs
- Mean change in laboratory analytes, height, weight, vital signs, and ECG intervals from baseline to endpoint
- Categorical analyses of potentially clinically significant (PCS) changes in vital signs and ECG
- Proportion of patients with treatment-emergent abnormal laboratory values
- Columbia Suicide Severity Rating Scale (C-SSRS)

Statistical Evaluation Methods: Efficacy and safety analyses were done on an intent-to-treat (ITT) basis, unless otherwise specified. When mean change from baseline to endpoint was assessed, data was included in the analysis only if there was a baseline and a corresponding post-baseline measure. Baseline was defined as the last measurement taken at, or prior to, the visit where the study period began; endpoint was defined as the last nonmissing measurement for the study period of interest. All tests of hypotheses were considered statistically significant if the two sided p-value was <0.05. No adjustments for multiple comparisons were made.

A repeated measures analysis referred to a restricted maximum likelihood- (REML-) based, MMRM analysis using all the longitudinal observations at each postbaseline visit. Significance tests were based on least-squares means (LSMean) using a two-sided α=0.05.

Unless otherwise specified, when an analysis of variance (ANOVA) model was used to analyze a continuous efficacy variable, the model contained the main effects of treatment and investigator. Similar logic was applied to an analysis of covariance (ANCOVA) model, which, in general, referred to the ANOVA model with baseline values and age category (children [aged 7 through 11 years], adolescents [aged 12 through 17 years]) added as covariates. LSMean was used for the statistical comparison using ANOVA or ANCOVA. The last observation carried forward (LOCF) method was used for these analyses.

Statistical Evaluation Methods (continued): All investigative sites with fewer than 2 patients randomized to placebo, 2 patients randomized to duloxetine, and 2 patients randomized to fluoxetine (each patient had non-missing change CDRS-R total scores) were pooled together within each country (or 5 United States [US] regions if the country was US) and considered a single site for analyses. If this resulted in a site still having fewer than 2 patients randomized to placebo, 2 patients randomized to duloxetine, and 2 patients randomized to fluoxetine, these sites were pooled together with the next smallest site in that country (or 5 US regions if country was US), or if there were none, then the next smallest site in another country. Categorical comparisons between treatment groups were performed using Cochran-Mantel-Haenszel (CMH), controlling for pooled investigative site, and Fisher's exact tests, where appropriate, or Pearson's chi-squared test. In Study Period II, duloxetine was compared with placebo and fluoxetine was compared with placebo using statistical inference. In Study Period III, descriptive statistics were used to summarize the 3 treatment groups for Study Period III.

Efficacy: The primary efficacy analysis was the contrast between duloxetine and placebo at the last visit in Study Period II (Visit 8, Week 10) from a MMRM analysis on mean change from baseline in the CDRS-R total score. The model for this analysis included the fixed, categorical effects of treatment, investigator, visit, treatment-by-visit interaction, age category (children [aged 7 through 11years] and adolescents [aged 12 through 17 years), age category-by-visit interaction, as well as the continuous, fixed covariates of baseline CDRS-R total score and baseline CDRS-R total score-by-visit interaction. The ITT population was used to perform this analysis.

The secondary efficacy analyses was performed on the secondary variables mentioned above. Descriptive statistics were used to summarize these variables by treatment (fluoxetine and duloxetine) group during Study Period III. The treatment-by-investigator interaction was tested using a full ANCOVA model. When the interaction was statistically significant, the nature of the interaction was investigated and the appropriate statistical approaches were adapted based on the findings from the investigation.

Safety: Comparisons between treatment groups for all categorical safety measures were made using Fisher's exact test for Study Periods II and II/III. Descriptive statistics only were presented for the 3 treatment groups in Study Period III.

The incidence rates of TEAEs were analyzed for pairwise comparisons. Moreover, TEAEs were summarized by maximum severity and analyzed. SAEs and AEs reported as reasons for discontinuation were summarized by treatment group and compared between the treatment groups.

For laboratory values, a "treatment-emergent abnormal value" was defined as a change from normal at all visits prior to and including the baseline visit to abnormal at endpoint. A "treatment-emergent high value" was defined as a change from a value less than or equal to the high limit at all visits prior to and including the baseline visit to a value greater than the high limit at endpoint. A "treatment-emergent low value" was defined as a change from a value greater than or equal to the low limit at all visits prior to and including the baseline visit to a value less than the low limit at endpoint. The incidence rates of treatment-emergent abnormal, high, or low laboratory values at endpoint were assessed.

The incidence of patients meeting criteria for PCS changes in vital signs was compared between treatment groups. Patients with abnormal vital signs baseline assessments were excluded from the analysis of that measure.

The incidence of patients meeting criteria for PCS changes in ECG intervals and heart rate were compared between treatment groups.

Mean changes from baseline to endpoint in laboratory analytes were assessed using the ANOVA model. Rank-transformed data were used for the laboratory analysis.

Changes from baseline in vital signs, height, and weight were analyzed using an MMRM model for analysis similar to that used for the primary efficacy analysis. Raw values were used for analyses of vital signs and weight, unless normality assumptions appeared to be violated.

Statistical Evaluation Methods (continued):

Pharmacokinetic: Duloxetine plasma concentrations were merged with associated sampling time, dose, dosing time and demographic information to create the dataset for descriptive statistical and graphical analysis. The effect of dose, age, body weight, CYP2D6 phenotype, gender, ethnicity, and race on steady state duloxetine concentrations are illustrated graphically and summarized descriptively in the report.

Any concentrations reported as below the lower quantification limit of the assay (BQL) were treated as missing values for the descriptive analysis. Concentrations associated with longer than 96 hours (>5 half-lives of duloxetine) following the dose were excluded from the PK assessment. The patients were assigned a nonsmoking status when the cotinine test was negative.

Given the lack of dose dependent efficacy in this study, the exploratory exposure-response analyses were not conducted.

Summary:

This study was designed to evaluate the efficacy and safety of flexible dose duloxetine compared with placebo in children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) with MDD. This study was also designed to explore the PK characteristics of duloxetine. The study included a 6-month, flexible-dose extension period to collect additional longer-term exposure data and a 2-week tapering period to minimize discontinuation adverse effects. This was an international multicenter study with patients enrolled from the US (41.5%), Eastern Europe (33.5%), South Africa (19.9%), and Western Europe (5.0%). A total of 337 patients, aged 7 to 17 years, entered the study and met criteria for randomization. Approximately an equal number of males and females enrolled in this study; the median age of patients was 13.53 years and 81.4% of patients were White. Approximately 40 % of patients were children aged 7 to 11 years and 60% were adolescents aged 12 to 17 years. Among children, 53% were male and 47% were female. Among adolescents, 44% were male and 56% were female. Approximately 74% of duloxetine-treated patients completed the 10-week acute treatment period (Study Period II) compared with 78% for fluoxetine and 85% for placebo. Overall during Study Period II, a total of 3.9% of patients were discontinued due to an AE. There was no statistically significant difference between the duloxetine-treated group and the placebo-treated group with respect to the incidence of patients who discontinued due to an AE. However, significantly more duloxetine-treated patients discontinued due to adverse events during Study Period II compared with fluoxetine-treated patients.

Efficacy results from this study indicated that duloxetine was not significantly different from placebo in the treatment of children and adolescents with MDD. In addition, the active control (fluoxetine), with known efficacy in children and adolescents with MDD, was not statistically significantly different from placebo on the primary outcome measure in this study. In the primary efficacy analysis, although the duloxetine treatment arm showed improvement in the CDRS-R total score during the acute treatment period, it did not demonstrate a statistically significant improvement over placebo on the primary variable, the contrast between duloxetine and placebo at the last visit of Study Period II (Week 10) based on an MMRM analysis on the CDRS-R total score mean change. Mean CDRS-R improvements during acute treatment for the duloxetine treatment arm (24-point improvement) as well as the fluoxetine treatment arm (24-point improvement) were similar to mean improvements of approximately 22 points for fluoxetine in published studies of fluoxetine in the treatment of children and adolescents with MDD (Emslie et al. 1997; Emslie et al. 2002; March et al. 2004). In contrast, mean CDRS-R improvements during acute treatment for the placebo arm in this study (24-point improvement) was greater than mean improvements of 10 to 19 points for the placebo arms in published studies of fluoxetine in the treatment of children and adolescents with MDD (Emslie et al. 1997; Emslie et al. 2002; March et al. 2004) where statistically significant separation of fluoxetine from placebo was observed. Acute treatment remission rates at last observation in this study

(approximately 35% duloxetine and 30% fluoxetine) were also similar to those reported for fluoxetine in previously published studies (31% to 41%) in the treatment of children and adolescents with MDD (Emslie et al. 1997; Emslie et al. 2002).

The results of 2 separate sensitivity analyses on the primary measure: 1) a repeated measures analysis of the CDRS-R total score mean change from baseline that excluded age as a covariate; and 2) a repeated measures analysis to address the impact of missing data on the primary efficacy analysis, were consistent with the results of the primary analysis.

Secondary efficacy analyses of the 10-week acute treatment period generally showed no statistically significant differences between the active drugs (duloxetine and fluoxetine) or between the active drugs and placebo; however, there was 1 exception. In the subgroup analysis of mean change in the CDRS-R total score by race, the treatment by race interaction was statistically significant (p=.011) due to different responses to drug vs. placebo within each race subgroup. In Black or African American patients, the placebo group had greater improvement than either active drug group. In White patients, both drug groups had greater improvement than the placebo group. In the pooled race (including Asian, American Indian or Alaska Native, Multiple) group, duloxetine had greater improvement compared with placebo, and placebo had greater improvement compared with fluoxetine.

Efficacy results from the longer-term treatment periods suggested that improvement in MDD symptoms continued for all of the treatment groups based on the mean improvement on the CDRS-R total score and CGI-S score from Visits 9 to 16. For patients initially randomized to flexible dose duloxetine or fluoxetine for the 10-week acute treatment period and continued on flexibly dosed duloxetine or fluoxetine during the 6 month extension period, improvement in MDD symptoms was observed for both treatment groups based on the mean improvement on the CDRS-R total score and CGI-S score; however, there was no statistically significant difference between the DLX60120-treated group compared with the FLX2040-treated group at any time point during the 36-week study on the CDRS-R total score. There was a statistically significantly greater improvement observed for fluoxetine compared with duloxetine at 36-Weeks (study endpoint) on the CGI-Severity. In subgroup analyses of the CDRS-R total score, there were no statistically significant treatment-by-stratum interactions during Study Period II/III; however, there were statistically significant differences observed for gender and race subgroups between the DLX60120 and FLX2040 treatment groups during the 36-Week study. A statistically significantly greater improvement was observed for fluoxetine-treated male patients compared with duloxetine-treated male patients at LOCF endpoint during the 36-Week study. Also, a statistically significantly greater improvement was observed for fluoxetine-treated White patients compared with duloxetine-treated White patients at LOCF endpoint during the 36-Week study. There were no statistically significant differences between the duloxetine and fluoxetine treatment groups at any timepoint in the probability of achieving remission during the 36-week study. The probability of achieving remission at 36 weeks was 72% for duloxetine and 83% for fluoxetine.

Overall, with regard to efficacy, the study is considered to be inconclusive as neither the investigational drug (duloxetine) nor the active control (fluoxetine) demonstrated a statistically significant separation from placebo on the primary efficacy analysis of mean change from baseline to Week 10 on the CDRS-R total score.

A comprehensive report on the population PK of duloxetine in children and adolescents using data collected from this study along with data from Studies HMFN and HMCL will be analyzed using population modeling approaches. In this report, the findings related to the descriptive summary statistics of duloxetine steady-state concentrations in Study HMCK have been summarized. The steady-state duloxetine plasma concentrations increased with increasing

dose (60 to 120 mg) in both children and adolescents. Patient characteristics such as CYP2D6 metabolizer status, ethnicity, sex, age, and body weight did not appear to have an effect on steady-state duloxetine plasma concentrations.

Overall, safety findings were generally similar to those observed in the previous Phase 2, multicenter, open-label, single-arm study (Study HMFN) evaluating a range of duloxetine doses (20 to 120 mg QD) in children and adolescents (aged 7 through 17 years) diagnosed with MDD, as well as other duloxetine studies in adults. There were no deaths and no completed suicides in the study.

Consistent with study HMFN and PK profile of duloxetine in pediatric patients, the majority of duloxetine-treated patients had dose escalations to 90 and 120 mg QD to attempt to optimize efficacy. The last prescribed dose during acute treatment for 71% of duloxetine-treated patients was 90 or 120 mg QD, while 74% of fluoxetine-treated patients had a final dose of 40 mg QD. A total of 105 duloxetine- and 56 fluoxetine-treated patients had ≥6 months (180 days) of exposure to the drugs.

Treatment-emergent adverse events reported for duloxetine-treated children and adolescents with MDD in this study were generally similar to those reported in Study HMFN. The TEAE profile of duloxetine in this study is also consistent with that seen in duloxetine-treated adult patients with MDD (Brunton et al. 2010).

A total of 14 patients reported 20 SAEs. Of these 20 SAEs, 3 were suicide-related (1 intentional overdose which was considered a suicide attempt [fluoxetine] and 1 suicidal ideation [PBO/DLX60120]). The suicide attempt by intentional overdose occurred during the extension treatment phase approximately 3 months after the patient began treatment with fluoxetine. The suicidal ideation SAE occurred during the extension treatment phase approximately 3 months after the patient had been transitioned from placebo to duloxetine.

As assessed by the C-SSRS, suicidal ideation occurred in 14% to 15% of patients overall during acute treatment; however (compared to study baseline), the suicidal ideation was treatment-emergent in fewer patients (7% to 8%) during acute treatment. Treatment-emergent suicidal ideation was reported with similar frequency in all 3 drug arms: duloxetine (7%), fluoxetine (8%), and placebo (7%). These rates for suicidal ideation are consistent with the findings for antidepressant treatment arms reported in Hammad et al. 2006. During the long-term exposure period, suicidal ideation occurred in 9% to 16% of patients overall; and similarly (compared to the end of the acute treatment period), the suicidal ideation was treatment-emergent in 9% to 14% of patients overall.

During the study, no patients had an SAE related to laboratory results and no patients were discontinued due to abnormal laboratory values. One (1) patient in the FLX2040-treated group had a treatment-emergent ALT ≥3 times ULN during Study Period III, and the same patient had a treatment-emergent ALT ≥5 times during Study Period III; however, the elevated ALT returned to normal levels while the patient remained on fluoxetine. One (1) patient in the PBO/DLX60120 group (with abnormal ALT at study baseline) had a treatment-emergent ALT ≥3 times ULN at the last study visit during Study Period III, which returned to near normal levels as the patient tapered off of duloxetine per protocol at completion of the study.

During acute treatment, duloxetine-treated patients experienced mean increases in systolic and diastolic blood pressure of <2 mm Hg and mean increase in pulse of 3 bpm. Approximately 7% of duloxetine-, 6% of fluoxetine-, and 7% of placebo-treated patients experienced PCS elevations in systolic blood pressure, and 9% of duloxetine-, 8% of fluoxetine-, and 17% of placebo-treated patients experienced PCS elevations in diastolic blood pressure during acute treatment. Most of these elevations in blood pressure were transient and returned to non-PCS levels

while the patients continued in the study and remained on study drug. Of the 3 (3.0%) duloxetine-treated patients who experienced PCS elevations of systolic blood pressure at endpoint, the maximum systolic value was 146 mm Hg. Of the 5 (4.9%) duloxetine-treated patients who experienced PCS elevations of diastolic blood pressure at endpoint, the maximum diastolic value was 90 mm Hg. Two (2) patients (placebo) experienced sustained elevation in diastolic blood pressure and 2 patients (duloxetine and placebo) experienced sustained elevation in systolic blood pressure.

During the long-term exposure period (Study Period III), duloxetine-treated patients experienced mean increases in systolic and diastolic blood pressure of <2 mm Hg, and mean increases in pulse of up to 3.5 bpm. Approximately 13% of DLX60120/DLX60120-, 13% of FLX2040-, and 10% of PBO/DLX60120-treated patients experienced PCS elevations in systolic blood pressure, and 17% of DLX60120/DLX60120-, 12% of FLX2040-, and 5% of PBO/DLX60120-treated patients experienced potentially clinically significant elevations in diastolic blood pressure at anytime during the long-term exposure period. Most of these elevations in blood pressure were transient and returned to non-PCS levels while the patients continued in the study and remained on study drug.

During Study Period II/III, of the patients initially randomized to duloxetine, there were 7 patients who had potentially clinically significant elevations at endpoint in diastolic blood pressure (maximum value of 101 mm Hg), and 8 patients who had PCS elevations in systolic blood pressure at endpoint during the long-term exposure period (maximum value of 150 mm Hg). Three (3) patients (3.0%) initially randomized to duloxetine experienced sustained elevation in systolic blood pressure and 4 patients (3.9%) initially randomized to duloxetine experienced sustained elevation in diastolic blood pressures during the long-term exposure period. These results are in contrast to the results from Study HMFN (36-week, open-label study) where >40% of patients experienced PCS blood pressures at endpoint and 14% experienced sustained elevation in blood pressure.

Safety outcomes for the 5 duloxetine-treated patients identified as CYP2D6 PMs do not suggest an increased safety risk. No duloxetine-treated PM experienced an SAE, discontinued due to an AE, had abnormal ALT ≥3 times ULN, had an abnormal ECG, or had PCS vital signs or weight observations.

A separate report will discuss observations regarding growth and development using pooled data from this and other studies of duloxetine in pediatric patients.

Overall, safety findings from this study were consistent with the known safety and tolerability profiles for duloxetine.

Conclusions: Overall, with regard to efficacy, the study is considered to be inconclusive as neither the investigational drug (duloxetine) nor the active control (fluoxetine) demonstrated a statistically significant separation from placebo on the primary efficacy analysis of mean change from baseline to Week 10 on the CDRS-R total score.

Overall, safety findings from this study were consistent with the known safety and tolerability profile for duloxetine.