Summary ID# 7106

Clinical Study Summary: F1J-MC-HMDW

A Comparison of Duloxetine Hydrochloride, Venlafaxine-Extended Release, and Placebo in the Treatment of Generalized Anxiety Disorder

Date summary approved by Lilly: 14 February 2008

Brief Summary of Results

Study F1J-MC-HMDW was a multicenter, randomized, double-blind, placebo, and active comparator-controlled Phase 3 study. The primary objective of this study was to assess whether duloxetine hydrochloride 60 to 120 mg once daily (QD) was superior to placebo in the treatment of generalized anxiety disorder (GAD), as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), during a 10-week, double-blind, acute therapy phase. Superiority was defined as statistically greater reduction in the mean change from baseline to endpoint in anxiety symptoms as measured by the Hamilton Anxiety Rating Scale (HAMA) Total score (Hamilton 1959). The majority of patients were Caucasian (67.47%) and female (57.14%). The mean age was 42.76 years. Results of the study are as follows:

- Primary Objective: Duloxetine 60 to 120 mg ($p \leq .001$) showed statistically significant improvement in symptoms of anxiety as measured by the HAMA Total score compared with placebo.
- Gatekeeper Secondary Objective: Compared with placebo, duloxetine 60 to 120 mg-treated patients ($p=.002$) experienced a significantly greater mean improvement on the Sheehan Disability Scale (SDS) Global Functional Impairment score.

- Noninferiority Secondary Objective: Data from 2 studies with a similar design (Study F1J-MC-HMDU [HMDU; CT#7107] and Study F1J-MC-HMDW [HMDW]) were combined for a noninferiority analysis of the mean change from baseline to endpoint in the HAMA Total score. Duloxetine 60 to 120 mg demonstrated noninferiority to venlafaxine 75 to 225 mg for a priori defined per-protocol set of patients.

Combined data from studies F1J-MC-HMDU and F1J-MC-HMDW

Additional secondary objectives

- Compared with placebo, venlafaxine-extended release 75 to 225 mg and duloxetine 60 to 120 mg, both demonstrated statistically significantly ($p \leq .001$) faster time to sustained improvement in Kaplan-Meier plot of sustained improvement (onset of action, Study HMDU and Study HMDW was combined) using a stratified log-rank test.

Safety and tolerability results

- Two hundred thirty-six (73.8%) patients from duloxetine 60 to 120 mg QD, 255 (76.6%) patients from venlafaxine 75 to 225 mg-treated group and 219 (66.2%) patients from placebo group reported >1 TEAE.
- Patients with ≥5% TEAE reported in duloxetine 60 to 120 mg QD-treated patients included: nausea (26.9%), headache (14.4%), dizziness (11.6%), dry mouth (12.5%), constipation (12.8%), diarrhea (11.3%), somnolence (10%), fatigue (8.1%), insomnia (6.9%), decreased appetite (6.9%), hyperhidrosis (6.3%) and yawning (5%).
- Patients with ≥5% TEAE reported in venlafaxine 75 to 225 mg-treated included: nausea (20.1%), headache (17.1%), dizziness (12.9%), dry mouth (13.2%), constipation (10.5%), somnolence (9%), fatigue (9%), insomnia (8.1%), diarrhea (6%), and decreased appetite (5.1%).
- Treatment-emergent events with a statistically significant difference in duloxetine 60 to 120 mg-treated patients compared with venlafaxine 75 to 225 mg-treated patients included: nausea (p=.044), diarrhea (p=.018), yawning (p=.048), nasopharyngitis (p=.047), and blurred vision (p=.023).

- Compared with placebo, a statistically significantly greater number of patients treated with venlafaxine 75 to 225 mg experienced abnormal inorganic phosphorus (0% vs 1.7% patients, p=.025), high potassium (0% vs 2.4% patients, p=.008), and cholesterol (1.4% vs 6.1 patients, p=.004). Compared with placebo, a statistically significantly greater number of patients treated with duloxetine 60 to 120 mg experienced abnormal uric acid (0% vs 1.5% patients, p=.035), high potassium (0 % vs 1.9% patients, p=.019), high alkaline phosphatase (1.1% vs 4.7% patients, p=.011), high aspartate transaminase (AST/SGOT) (3.7% vs 8.3% patients, p=.029), cholesterol (1.4% vs 4.4% patients, p=.039), and low uric acid (0% vs 1.4% patients, p=.035).
- When comparing the duloxetine 60 to 120 mg and venlafaxine 75 to 225 mg-treatment groups, there were no treatment-emergent chemistry laboratory changes that demonstrated statistically significant differences. Compared with placebo, a statistically significantly greater number of venlafaxine 75 to 225 mg-treated patients experienced high hemoglobin (0% vs 1.6% patients, p=.037). Compared with duloxetine 60 to 120 mg-treated patients, a statistically significantly greater number of patients treated with placebo experienced abnormal (1.3% vs 5% patients, p=.022) and low neutrophils (1.3% vs 5% patients, p=.022).
- There were no statistically significant differences between duloxetine 60 to 120 mg and venlafaxine 75 to 225 mg for treatment-emergent chemistry and hematology laboratories, vital signs, and weight. Patients treated with duloxetine 60 to 120 mg QD experienced a statistically significant (p=.037) mean increase in pulse rate compared with placebo-treated patients. There were no statistically significant differences between placebo and venlafaxine 75 to 225 mg for pulse rate. Patients treated with duloxetine 60 to 120mg and venlafaxine 75 to 225 mg both experienced a statistically significant (p=.007, p=.005, respectively) mean decrease in weight compared with placebo.

- A total of 38 (11.9%) patients from duloxetine 60 to 120 mg; 51 (15.3%) patients from venlafaxine 75 to 225 mg, and 35 (10.6%) patients from placebo experienced ≥1 DEAE. Overall, there were no statistically significant differences between treatment groups for patients with ≥1 discontinuation-emergent adverse events (DEAEs). There were no events reported for patients with ≥5% DEAE. Events with a statistically significant in duloxetine 60 to 120 mg-treated patient included: dizziness (p=.16) and diarrhea (p=.012, compared with placebo) and diarrhea (p=.012, compared with venlafaxine 75 to 225 mg). Statistically a significant event in venlafaxine 75 to 225 mg-treated included dizziness (p=.016, compared with placebo). Event with a statistically significant in placebo-treated patients included upper respiratory tract infection (p=.046, compared with duloxetine 60 to 120 mg).

Additional secondary objectives: F1J-MC-HMDW

- Duloxetine 20 mg (p=.007) showed statistically significant improvement in symptoms of anxiety as measured by the HAMA Total score compared with placebo.
- Duloxetine 60 to 120 mg (65%) demonstrated statistically significantly (p≤.001) higher response rates at endpoint compared with placebo (42%).
- Patients treated with duloxetine 60 to 120 mg showed statistically significant improvement compared with patients treated with placebo as measured by the Hospital Anxiety Depression (HADS) subscale score (p≤.001), HAMA Psychic Anxiety Factor score (p≤.001), HAMA Somatic Anxiety Factor score (p=.028), HAMA anxious mood item (p≤.001), HAMA tension item (p≤.001), Clinical Global Impressions of Improvement (CGI-Improvement) Scale (p≤.001) and Patient's Global Impressions of Improvement (PGI-Improvement) Scale (p≤.001).
- In the completers analysis SDS duloxetine 60 to 120 mg-treatment showed statistically significant improvement compared with placebo in the SDS Global score (p≤.001), SDS Item 1 (p=.011), SDS Item 2 (p≤.001), and SDS Item 3 (p=.002).
- Duloxetine 60 to 120 mg did not show statistically significant improvement compared with placebo in Q-LES-Q-SF Total score (p=.083) and percent of maximum possible score (p=.091). Duloxetine 60 to 120 mg did not show statistically significant improvement compared with placebo in EQ-5D Index score (p=.117) and EQ-5D VAS Health score (p=.507)

- No statistically significant change was observed among all duloxetine 60 to 120 mg and venlafaxine 75 to 225 mg patients in frequency of study drug dose escalation during the acute therapy phase (p=.618).

Safety and tolerability results from F1J-MC-HMDW

- Out of 170 patients, 102 (60%) patients from placebo-treated group, out of 158 patients, 100 (63.3%) from duloxetine 60 to 120 mg-treated group reported at least 1 treatment-emergent adverse event (TEAE). Overall, there were no statistically significant differences between treatment groups in the proportion of patients reporting at least one TEAE.
- There was statistically significant difference between patients treated with duloxetine 60 to 120 mg and placebo for the following TEAEs: nausea (p=.004), fatigue (p=.031), hyperhidrosis (p=.003), somnolence (p=.009), dry mouth (p≤.001), constipation (p=.020), erectile dysfunction (p=.031), decreased libido (p=.012), decreased appetite (p=.012), delayed ejaculation (p=.025), and blurred vision (p=.025).
- No deaths occurred in the study.
- A total of 6 serious adverse events (SAEs) were reported for 2 placebo-treated patients (agitation, ideas of reference, insomnia, panic attack, and paranoia) and 1 venlafaxine 75 to 225 mg treated patient (traumatic brain injury). There were no SAEs reported in the duloxetine 60 to 120 mg-treatment groups. No statistically significant differences between treatment groups were observed.
- Patients treated with duloxetine 60 to 120 mg experienced a statistically significant mean decrease in uric acid (p≤.001) and chloride (p=.017) and statistically significant mean increase in mean cell hemoglobin (p=.030) and mean platelet count (p=.031) compared with placebo.
- Overall, there were no statistically significant differences between treatment groups for patients with ≥1 DEAEs. Dizziness was reported statistically significantly more often by duloxetine 60 to 120 mg (p=.029), and venlafaxine 75 to 225 mg-treated patients (p=.016) than by placebo-treated patients. There were no events for duloxetine 60 to 120 mg, venlafaxine 75 to 225 mg, or placebo that were observed in >10% of the patients during the taper phase.
- Duloxetine 60 to 120 mg-treated patients experienced a statistically significant mean increase in pulse rate (p=.01) compared with placebo-treated patients. There were no statistically significant difference reported between either duloxetine 60 to 120 mg or venlafaxine 75 to 225 mg compared to placebo for weight, systolic and diastolic blood pressures.

Title of Study: A Comparison of Duloxetine Hydrochloride, Venlafaxine-Extended Release, and Placebo in the Treatment of Generalized Anxiety Disorder	
Investigator(s): This multicenter study included 35 principal investigators.	
Study Center(s): This study was conducted at 35 study centers in 8 countries.	
Length of Study: Date first patient enrolled: 12 April 2005 Date last patient completed: 24 January 2007	**Phase of Development:** 3

Objectives: The primary objective of this study was to assess whether duloxetine (DLX) 60 to 120 mg once daily (QD) was superior to placebo in the treatment of generalized anxiety disorder (GAD) during a 10-week, double-blind, acute therapy phase. Superiority was defined as statistically greater reduction in the mean change from baseline to endpoint in anxiety symptoms as measured by the Hamilton Anxiety Rating Scale (HAMA) Total score (Hamilton 1959).

The gatekeeper objective for the study was to evaluate the efficacy of duloxetine 60 to 120 mg QD compared with placebo during a 10-week, double-blind, acute therapy phase as measured by the mean improvement in the Sheehan Disability Scale (SDS) Global Functional Impairment score (Sheehan 1983).

The noninferiority objective for this study was to compare the efficacy of duloxetine 60 to 120 mg QD with venlafaxine (VEN)-extended release 75 to 225 mg QD, on the per-protocol set of patients during 10 weeks of therapy in treating GAD as measured by the HAMA Total score. Data from 2 studies with a similar design (Study F1J-MC-HMDU [HMDU] and Study F1J-MC-HMDW [HMDW]) were combined for a noninferiority analysis of the mean change from baseline to endpoint in the HAMA Total score.

Additional secondary objectives are as follows:

- To assess the efficacy of duloxetine 60 to 120 mg QD compared with placebo during a 10-week, double-blind, acute therapy phase as measured by response rates, mean improvement on the secondary efficacy measures, and quality of life
- To compare the frequency of titration of duloxetine 60 to 120 mg QD with venlafaxine-extended release 75 to 225 mg QD
- To compare the safety and tolerability of duloxetine 60 to 120 mg QD with placebo during a 10-week, double-blind acute therapy phase
- To evaluate the safety and tolerability of duloxetine 60 to 120 mg QD and venlafaxine-extended release 75 to 225 mg QD during a 10-week, double-blind acute therapy phase (data from 2 studies with a similar design [Study HMDU and Study HMDW] was to be combined)
- To evaluate and compare the effects of discontinuation of duloxetine 60 to 120 mg QD, venlafaxine-extended release 75 to 225 mg QD, and placebo.
- To compare the time to onset of action of duloxetine 60 to 120 mg QD with venlafaxine-extended release 75 to 225 mg QD (data from 2 studies was combined)
- To evaluate the efficacy of duloxetine 20 mg QD compared with placebo during a 10-week, double-blind, acute therapy phase

Study Design: Patients meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association [APA] 2000) criteria for GAD were studied in this double-blind, randomized, placebo- and comparator-controlled, Phase 3 study.
Eligible patients received duloxetine hydrochloride 60 to 120 mg QD, duloxetine hydrochloride 20 mg QD, venlafaxine-extended release 75 to 225 mg QD, or placebo for approximately 10 weeks (Figures HMDW.1 and HMDW.2).

Number of Patients:
Planned: 560 (80 DLX 20 mg QD, 160 DLX 60 to 120 mg QD, 160 VEN 75 to 225 mg, and 160 placebo)
Randomized: 581 (84 DLX 20 mg QD, 158 DLX 60 to 120 mg QD, 169 VEN 75 to 225 mg, and 170 placebo)
Completed: 396 (63 DLX 20 mg QD, 109 DLX 60 to 120 mg QD, 122 VEN 75 to 225 mg, and 102 placebo)
Per-Protocol Population (HMDW and HMDU Combined): 768 (239 DLX 60 to 120 mg QD, 262 mg VEN 75 to 225 mg QD, and 267 placebo)

Diagnosis and Main Criteria for Inclusion: Patients enrolled in this study met the DSM-IV-TR criteria for GAD. Patients had a disease severity of at least moderate intensity as defined by a Hospital Anxiety Depression Scale (HADS) Anxiety subscale score of >10 and a Covi-Anxiety score (CAS) score $\geq$9. No item in the Raskin Depression Scale (RDS) was >3. The CAS score was greater than the RDS score. In addition, patients had a Clinical Global Impressions of Severity (CGI-Severity) score >4 at Visit 1 and Visit 2.

Test Product Dose, and Mode of Administration: Duloxetine 20 mg, duloxetine 60 to 120 mg, or venlafaxine 75 to 225 mg given QD orally.

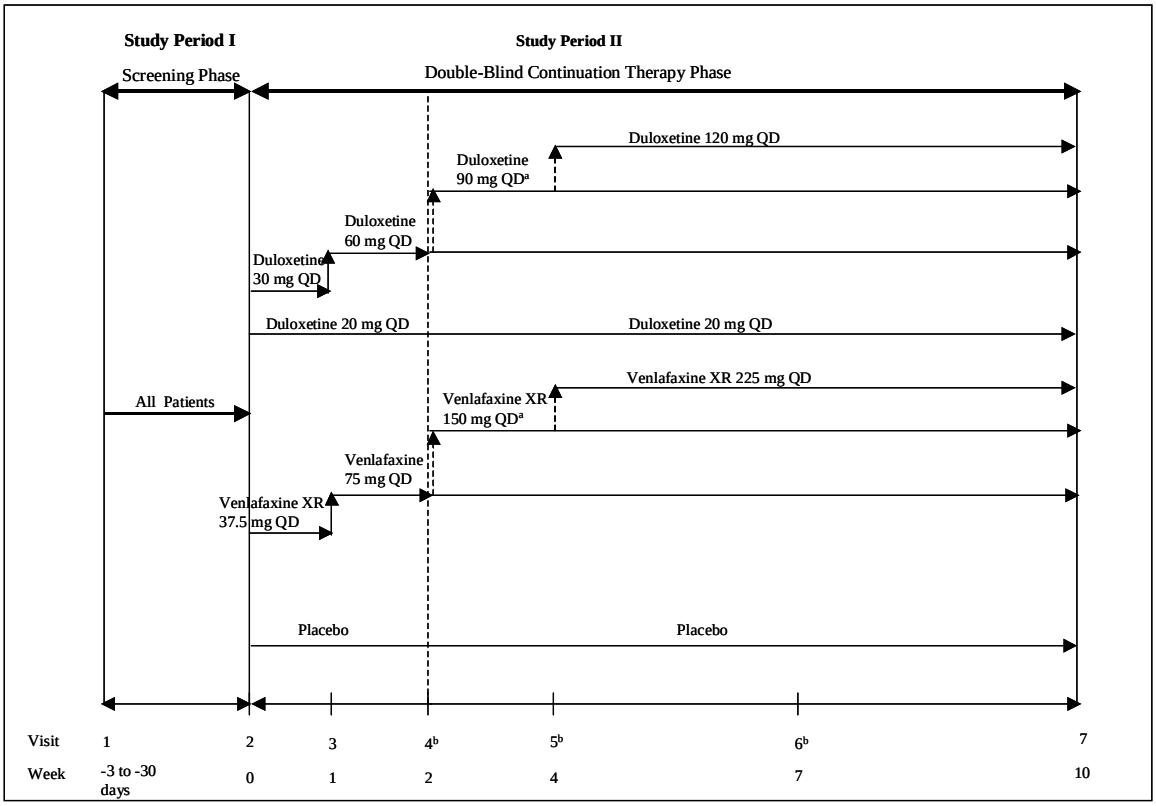
Duration of Treatment: Ten-week acute therapy followed by 2 weeks of drug tapering.

Variables:
Efficacy: HAMA Total score, HADS, HAMA Factors and Individual Items (subscales), Clinical Global Impressions of Improvement (CGI-Improvement) Scale, Patient's Global Impressions of Improvement (PGI-Improvement) Scale.
Safety: Adverse events (AEs), laboratory tests, and vital sign measurements.
Health Outcomes: SDS, Quality-of-Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF), Euro-Qol Questionnaire – 5 Dimension (EQ-5D).

Evaluation Methods:
Statistical: All analyses planned for Study HMDW data only were conducted on an intent-to-treat (ITT) set of patients, except for analysis of quality-of-life measures and the assessment of the noninferiority of duloxetine 60 to 120 mg to venlafaxine 75 to 225 mg. Analysis was conducted on completers set of patients for quality-of-life measures. As directed by ICH Guidance, noninferiority analysis was conducted on a priori defined per-protocol set of patients from combined studies F1J-MC-HMDU and F1J-MC-HMDW. Mean change from baseline to endpoint analysis was assessed for all patients with a baseline and postbaseline measurement. Treatment effects were evaluated based on a two-sided significance level of 0.05, and interaction effects at 0.05. No adjustments for multiple comparisons were made. Continuous measures were analyzed by either an analysis of variance (ANOVA) model or an analysis of covariance (ANCOVA) model. The ANOVA model contains main effects of treatment and investigator; the ANCOVA model refers to the ANOVA model with baseline values added as a covariate. Type III sum-of squares was used for the statistical comparison of treatment least-squares mean (LS Mean) change from baseline. Cochran-Mantel-Haenszel test controlling for investigator was used for categorical efficacy variables, and Fisher's exact test was used to assess categorical safety variables. Noninferiority analysis of combined data from Study HMDW and Study HMDU used an ANCOVA model with main effects of treatment and study and baseline as a covariate. Unless otherwise specified, in all the analyses for the acute therapy phase, "baseline" refers to the last nonmissing observation at or before randomization visit (Visit 2), and "endpoint" refers to the last nonmissing observation in the acute therapy phase (at or before Visit 7).

Study Design

Figures HMDW.1 and HMDW.2 illustrate the study design.

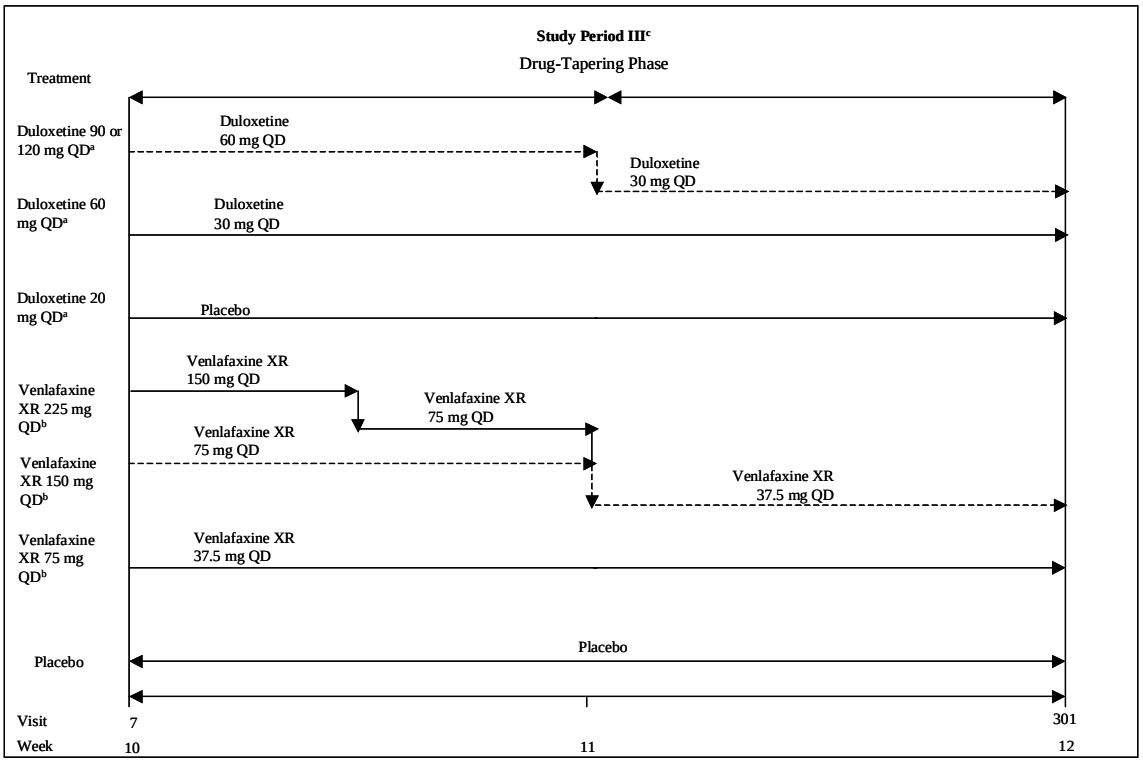


Abbreviations: mg = milligram, QD = once daily, venlafaxine XR = venlafaxine-extended release.

[a] Patients could increase to the allowed maximum dose of drug only after taking the intermediate dose for at least one-visit interval. Flexible dosing was allowed at Visit 4 through Visit 6.

[b] Titration occurred if Clinical Global Impressions of Improvement (CGI-Improvement) score was 3 or higher and patient tolerated a dose increase.

Figure HMDW.1. F1J-MC-HMDW study design, Study periods I-II, screening phase, and acute therapy phase.



Abbreviations: mg = milligram, QD = once daily, venlafaxine XR = venlafaxine-extended release.

[a] Duloxetine 90 or 120 mg QD-treated patients received 60 mg QD for 1 week followed by 30 mg QD for 1 week. Duloxetine 60 mg QD-treated patients received 30 mg QD for 2 weeks. Duloxetine 20 mg QD-treated patients received placebo for 2 weeks.

[b] Venlafaxine-extended release 225 mg QD-treated patients received 150 mg QD for 4 days and 75 mg QD for the remainder of the week, followed by 37.5 mg QD for 1 week. Venlafaxine-extended release 150 mg QD-treated patients received 75 mg QD for 1 week followed by 37.5 mg QD for 1 week. Venlafaxine-extended release 75 mg QD-treated patients received 37.5 mg QD for 2 weeks.

[c] Patients who completed the study through Visit 7 then entered the drug-tapering phase. Patients also had the option to enter the drug-tapering phase any time after Visit 4 and prior to Visit 7.

Figure HMDW.2. F1J-MC-HMDW study design, Study period III, and drug-tapering phase.

Results:

Patient Demographics

The majority of patients were Caucasian (67.47%) and female (57.14%). The mean age was 42.76 years (Table HMDW.1). No statistically significant differences among treatment groups were observed in any of the patient demographic variables.

Table HMDW.1. Demographics and Baseline Characteristics
All Randomized Patients
Acute Therapy Phase – Study F1J-MC-HMDW

Variable	Placebo (N = 170)	DLX20 (N = 84)	DLX60-120 (N = 158)	VEN75-225 (N = 169)	Total (N = 581)	p-value
Age- yrs, mean (SD)	42.57 (12.11)	44.75 (13.45)	42.58 (12.58)	42.13 (13.32)	42.76 (12.79)	.473**
Gender, n (%)						.137*
Female	108 (63.53)	41 (48.81)	90 (56.96)	93 (55.03)	332 (57.14)	
Male	62 (36.47)	43 (51.19)	68 (43.04)	76 (44.97)	249 (42.86)	
Race, n (%)						.986***
Caucasian	115 (67.65)	58 (69.05)	106 (67.09)	113 (66.86)	392 (67.47)	
Hispanic	35 (20.59)	17 (20.24)	37 (23.42)	39 (23.08)	128 (22.03)	
East Asian	18 (90)	09 (100)	10 (66.67)	16 (94.12)	61 (10.50)	
African	02 (10)	0	2 (13.33)	1 (5.88)	5 (8.20)	
West Asian	0	0	2 (13.33)	0	2 (3.28)	
Native American	0	0	1 (6.67)	0	1 (1.64)	
Patients with ≥1 significant historical diagnosis, n (%)	11 (6.5)	10 (11.9)	17 (10.8)	19 (11.2)	57 (9.8%)	.341*
Age at first diagnosis GAD, yrs, mean (SD)	37.66 (13.45)	40.94 (13.62)	38.31 (14.00)	38.78 (12.61)	38.64 (13.40)	.321**
Duration of GAD, yrs, mean (SD)	5.15 (9.82)	4.11 (8.51)	4.44 (8.40)	3.64 (5.60)	4.37 (8.19)	.394**
Patients with ≥1 benzodiazepine, n (%)	39 (22.94)	24 (28.57)	42 (26.58)	37 (21.89)	142 (24.44)	.573*
Patients with ≥1 previous therapy drug, n (%)	54 (31.76)	32 (38.10)	52 (32.91)	51 (30.18)	189 (32.53)	.643*
Patients with ≥1 concomitant drug therapy, n (%)	92 (54.12)	48 (57.14)	87 (55.06)	82 (48.52)	309 (53.18)	.519*

Abbreviations: DLX20 = duloxetine 20 mg, DLX60-120 = duloxetine 60 to 120 mg, GAD = generalized anxiety disorder; N = number of randomized patients, n = number of patients with a baseline and at least one nonmissing postbaseline data, SD = standard deviation, VEN75-225 = venlafaxine-extended release 75 to 225 mg, yrs = years.

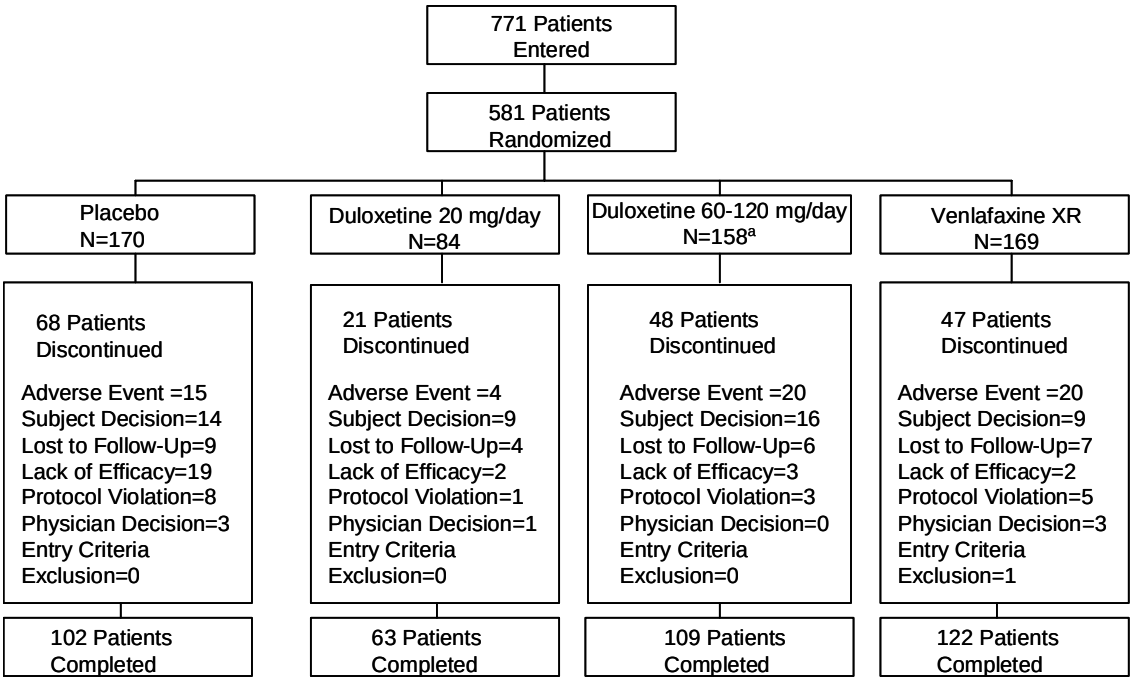
*Frequencies are analyzed using Fisher's exact test.

**Means are analyzed using type III sums of squares analysis of variance (ANOVA): Model=Treatment.

***Chi-square test was used to compare Caucasian, Hispanic, and other (other race group includes East Asian, African, West Asian, and Native American).

Patient Disposition

Figure HMDW.3 summarizes patient disposition during the acute therapy phase of the study.



[a] There was one duloxetine 60-120 mg/day-treated patient whose reason for discontinuation was unknown.

Figure HMDW.3. Patient disposition for Study F1J-MC-HMDW.

Table HMDW.2 shows reasons for discontinuation for all randomly assigned patients in the acute therapy phase for each treatment group. There was not a statistically significant difference among the treatment groups in percentage of patients discontinuing the study due to adverse events: duloxetine 60 to 120 mg-treated patients (12.66%) and venlafaxine 75 to 225 mg-treated patients (11.83%) and placebo-treated patients (8.82%). Statistically significant higher percentage of patients treated with duloxetine 20 mg once daily (QD) (75%, p=.02) and venlafaxine 75 to 225 mg (71.19%, p=.02) completed the acute therapy phase compared with placebo-treated patients (60.0%). Statistically significantly more placebo-treated patients (11.18%, p≤.001) discontinued the study due to lack of efficacy compared with patients treated with duloxetine 20 mg (2.38%, p=.015), duloxetine 60 to 120 mg (1.90%, p≤.001), and venlafaxine 75 to 225 mg (1.18%, p≤.001).

Table HMDW.2. Reasons for Study Discontinuation
All Randomized Patients
Acute Therapy Phase – Study F1J-MC-HMDW

Primary Reason for Discontinuation	Treatment	N	n	Percent	Overall p-Value*	Pairwise p-Values* vs 2)	vs 3)	vs 4)
DC due to ANY reason	1) PLACEBO	170	68	40.00	.041	.025	.083	.022
	2) DLX20	84	21	25.00				
	3) DLX60120	158	48	30.38				
	4) VEN75225	169	47	27.81				
Completed (Visit 7)	1) PLACEBO	170	102	60.00	.043	.025	.106	.022
	2) DLX20	84	63	75.00				
	3) DLX60120	158	109	68.99				
	4) VEN75225	169	122	72.19				
Adverse Event	1) PLACEBO	170	15	8.82	.190	.316	.287	.378
	2) DLX20	84	4	4.76				
	3) DLX60120	158	20	12.66				
	4) VEN75225	169	20	11.83				
Subject Decision	1) PLACEBO	170	14	8.24	.317	.497	.571	.388
	2) DLX20	84	9	10.71				
	3) DLX60120	158	16	10.13				
	4) VEN75225	169	9	5.33				
Lost to follow up	1) PLACEBO	170	9	5.29	.932	1.00	.602	.799
	2) DLX20	84	4	4.76				
	3) DLX60120	158	6	3.80				
	4) VEN75225	169	7	4.14				
Lack of Efficacy	1) PLACEBO	170	19	11.18	<.001	.015	<.001	<.001
	2) DLX20	84	2	2.38				
	3) DLX60120	158	3	1.90				
	4) VEN75225	169	2	1.18				

(Continued)

Table HMDW.2. Reasons for Study Discontinuation
All Randomized Patients
Acute Therapy Phase – Study F1J-MC-HMDW (Concluded)

Primary Reason for Discontinuation	Treatment	N	n	Percent	Overall p-Value*	Pairwise p-Values* vs 2)	vs 3)	vs 4)
Protocol Violation	1) PLACEBO	170	8	4.71	.424	.279	.222	.573
	2) DLX20	84	1	1.19				
	3) DLX60120	158	3	1.90				
	4) VEN75225	169	5	2.96				
Physician Decision	1) PLACEBO	170	3	1.76	.321	1.00	.249	1.00
	2) DLX20	84	1	1.19				
	3) DLX60120	158	0	0.00				
	4) VEN75225	169	3	1.78				
Entry Criteria Exclusion	1) PLACEBO	170	0	0.00	.707			.499
	2) DLX20	84	0	0.00				
	3) DLX60120	158	0	0.00				
	4) VEN75225	169	1	0.59				

Abbreviations: DC = discontinuations, DLX20 = duloxetine 20 mg, DLX60120 = duloxetine 75 to 225 mg, N = number of patients with a baseline and at least one nonmissing postbaseline data, n = number of patients who discontinued, VEN75225 = venlafaxine-extended release 75 to 225 mg.

Hamilton Anxiety Rating Scale

Table HMDW.3 shows results from the mean change analysis of the primary efficacy measure, Hamilton Anxiety Rating Scale (HAMA) Total score. Duloxetine 20 mg, duloxetine 60 to 120 mg (primary objective), and venlafaxine 75 to 225 mg showed statistically significant greater reduction in the mean change from baseline to endpoint compared with placebo in anxiety symptoms as measured by HAMA Total score.

Table HMDW.3. Hamilton Anxiety Rating Scale Total Score Mean Change from Baseline to Endpoint All Randomized Patients Acute Therapy Phase – Study F1J-MC-HMDW

Treatment Group	N	Baseline Mean (SD)	LS Mean (SE) Change	p-Value* Vs Placebo
Placebo	163	27.33 (7.33)	-11.6 (0.69)	
DLX 20 mg	83	27.65 (7.99)	-14.7 (0.96)	.007
DLX 60-120 mg	151	27.74 (7.32)	-15.3 (0.72)	≤.001
VEN 75-125 mg	158	27.36 (7.57)	-15.5 (0.71)	≤.001

Abbreviations: DLX = duloxetine, LS Mean = least-squares mean, N = number of patients with a baseline and at least one nonmissing postbaseline data, SD = standard deviation, SE = standard error, VEN = venlafaxine.

*Type III sums of squares from ANCOVA: model = treatment, investigator, and baseline.

Sheehan Disability Scale Global Functioning Score

Table HMDW.4 summarizes mean change from baseline to endpoint on the Sheehan Disability Scale (SDS) in the acute therapy phase. Compared with placebo, duloxetine 60 to 120 mg (p=.002, gatekeeper objective), duloxetine 20 mg (p=.027), and venlafaxine 75 to 225 mg-treated patients (p≤.001) experienced a statistically significantly greater mean improvement on the SDS Global Functional Impairment score.

Table HMDW.4. Sheehan Disability Scale Mean Change from Baseline to Endpoint All Randomized Patients Acute Therapy Phase – Study F1J-MC-HMDW

Treatment Group	N	Baseline Mean (SD)	LS Mean (SE) Change	p-value*Vs Placebo
Placebo	150	18.00 (6.64)	-6.19 (0.61)	
DLX 20 mg	77	17.21 (6.15)	-8.45 (0.84)	.027
DLX 60-120 mg	142	17.80 (6.32)	-8.86 (0.63)	.002
VEN 75-225 mg	149	18.15 (5.98)	-9.09 (0.61)	≤.001

Abbreviations: DLX 60-120 = duloxetine 60 to 120 mg, N = number of patients with a baseline and at least one nonmissing postbaseline data, SD = standard deviation, SE = standard error, LS Mean = least-squares mean, VEN = venlafaxine.

*Type III sums of squares from ANCOVA: model = treatment, investigator, and baseline.

Noninferiority Objective

Mean change analysis of per-protocol set of patients from combined data from Studies HMDU and HMDW

The noninferiority analysis was performed using the per-protocol population from combined data from Study HMDU and HMDW. A per-protocol set was defined by patients who completed Visit 5 (4 weeks of study treatment), provided baseline and postbaseline HAMA Total scores (postbaseline score will be nonmissing value at Week 4, Week 7, or Week 10) and had no significant protocol violations.

In order for noninferiority to be established the consensus panel consists of non-Lilly experts recommended that the following criteria be met:

- Duloxetine 60 to 120 mg and venlafaxine 75 to 225 mg both had to be statistically significantly better than placebo on change in HAMA Total score from baseline to endpoint.
- Duloxetine 60 to 120 mg and venlafaxine 75 to 225 mg had to score greater than placebo on mean improvement in HAMA Total score by ≥2 HAMA Total score points.
- Response rate for duloxetine 60 to 120 mg and venlafaxine 75 to 225 mg had to be ≥10 percentage points better than placebo.
- Response rate for duloxetine 60 to 120 mg could not be more than 5 percentage points lower than venlafaxine 75 to 225 mg.
- The lower bound of the one-sided 97.5% CI for the difference between duloxetine and venlafaxine 75 to 225 mg in mean change in HAMA Total score had to be above the noninferiority margin -1.5.

Duloxetine 60 to 120 mg demonstrated noninferiority to venlafaxine 75 to 225 mg for the per-protocol population by meeting the criteria established by the consensus panel:

- Duloxetine 60 to 120 mg and venlafaxine 75 to 225 mg both showed statistically significantly greater improvement in change in HAMA Total score from baseline to endpoint compared with placebo ($p \leq .001$, $p \leq .001$). This was true for per-protocol sets of patients and the intent-to-treat (ITT) as summarized in Tables HMDW.5 and HMDW.6, respectively.

- Both duloxetine 60 to 120 mg and venlafaxine 75 to 225 mg had greater mean improvement than placebo by at least 2 HAMA Total score points. The mean change from baseline to endpoint for treatment groups in the per-protocol population were as follows: -11.60 placebo, -15.42 duloxetine 60 to 120 mg, and -15.22 venlafaxine 75 to 225 mg. The mean change from baseline to endpoint for treatment groups in the ITT population were as follows: -10.36 placebo; -13.58 duloxetine 60 to 120 mg, and -14.00 venlafaxine 75 to 225 mg.
- The ITT response rates for duloxetine 60 to 120 mg QD (56%) and venlafaxine 75 to 225 mg (58%) were greater than or equal to 10 percentage points better than placebo (40%). Table HMDW.7 shows the response rates for the ITT group of patients.
- ITT response rates for duloxetine 60 to 120 mg were not more than 5 percentage points lower than venlafaxine 75 to 225 mg.
- For the per-protocol set of patients, the lower bound of the one-sided 97.5% confidence interval for the difference between duloxetine and venlafaxine 75 to 225 mg in change in HAMA was above the noninferiority margin -1.5 [duloxetine 60 to 120 minus venlafaxine 75 to 225 mg (-1.28, 1.67)].

Table HMDW.5. Hamilton Anxiety Rating Scale Total Score Mean Change from Baseline to Endpoint Per-Protocol Patient Population Acute Therapy Phase Combined Data from Studies: F1J-MC-HMDU and F1J-MC-HMDW

Treatment Group	N	Baseline Mean (SD)	LS Mean (SE) Change	p-Value*	
				vs Placebo	Pair-wise
Placebo	267	26.28 (6.87)	-11.60 (0.51)		
DLX 60-120 mg	239	27.09 (6.79)	-15.42 (0.54)	≤.001	.794
VEN 75-225 mg	262	26.20 (6.55)	-15.22 (0.52)	≤.001	

Abbreviations: DLX = duloxetine, LS Mean = least-squares mean, N = number of patients with a baseline and at least one nonmissing postbaseline data at or after Week 4, SD = standard deviation, SE = standard error, VEN = venlafaxine-extended release.

*Type III Sums of Squares from ANCOVA: Model = baseline, treatment, and study.

Table HMDW.6. Hamilton Anxiety Rating Scale Total Score Mean Change from Baseline to Endpoint Intent-to-Treat Patient Population Acute Therapy Phase Combined Data from Studies: F1J-MC-HMDU and F1J-MC-HMDW

Treatment Group	N	Baseline Mean (SD)	LS Mean (SE) Change	p-value*	
				vs Placebo	Pair-wise
Placebo	321	26.17 (6.73)	-10.36 (0.50)		
DLX 60-120 mg	300	27.09 (6.61)	-13.58 (0.51)	≤.001	.562
VEN 75-225 mg	317	26.20 (6.71)	-14.00 (0.50)	≤.001	

Abbreviations: DLX = duloxetine, LS Mean = least-squares mean, N = number of patients with a baseline and at least one nonmissing postbaseline data at or after Week 4, SD = standard deviation, SE = standard error, VEN = venlafaxine-extended release.

*Type III Sums of Squares from ANCOVA: Model = baseline, treatment, and study.

Table HMDW.7. Response Rate at Endpoint for All Randomized Patients Study F1J-MC-HMDU and Study F1J-MC-HMDW Acute Therapy Phase

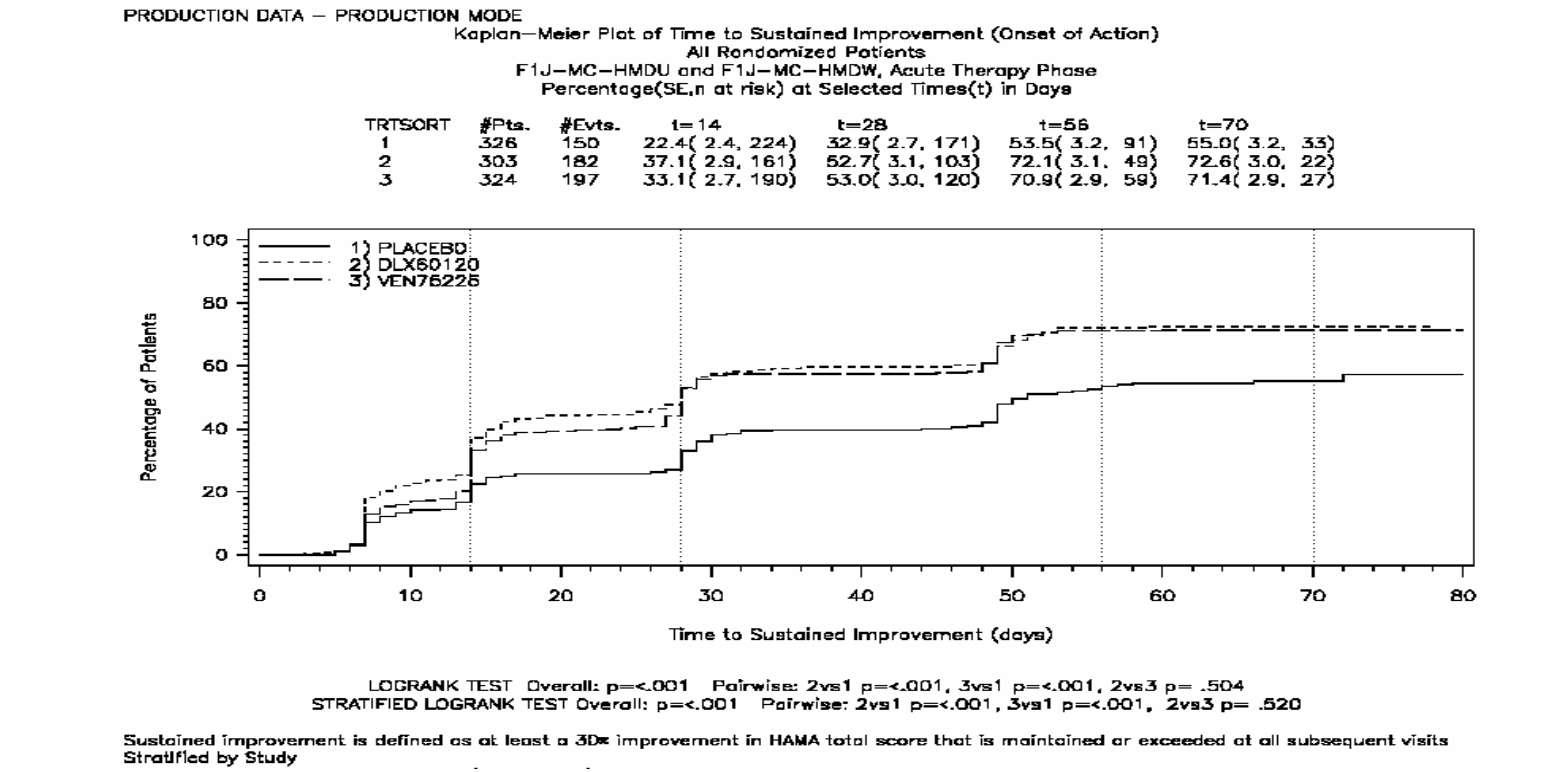
Therapy	N	Responders n (%)
1) PLACEBO	321	127 (40%)
2) DLX60120	300	168 (56%)
3) VEN75225	317	183 (58%)

Abbreviations: N = number of patients with a baseline and postbaseline measurement, n = responders, DLX60120 = duloxetine 60 to 120 mg, VEN75225 = venlafaxine-extended release 75 to 225 mg.

Response is defined as a 50% or greater reduction from baseline in Hamilton Anxiety Rating Scale score.

Additional Secondary Objectives: Combined data from Studies HMDU and HMDW

Figure HMDW.4 shows the Kaplan-Meier plot of time to sustained improvement (onset of action, combined data from Study HMDU and Study HMDW). Compared with placebo, duloxetine 60 to 120 mg and venlafaxine 75 to 225 mg demonstrated statistically significantly ($p \leq .001$, for both comparisons) faster time to sustained improvement using a stratified log-rank test. There was no statistically significant difference in time to sustained improvement (onset of action) between duloxetine 60 to 120 mg and venlafaxine 75 to 225 mg (p-value >.5).



Abbreviations: DLX = duloxetine, pts = patients, SE =standard error, VEN = venlafaxine-extended release.

Figure HMDW.4. Kaplan-Meier plot of sustained improvement (onset of action) for all randomized patients in the acute therapy phase (Study F1J-MC-HMDU and Study F1J-MC-HMDW).

Safety and Tolerability Results from Combined Data from Studies F1J-MC-HMDU and F1J-MC-HMDW

Serious Adverse Events

A total of 15 SAEs were reported by 8 randomly assigned patients (3, 0.9% placebo; 2, 0.6% duloxetine 60 to 120 mg; and 3, 0.9% venlafaxine 75 to 225 mg) in the combined data from Study HMDU and Study HMDW for all randomized patients in the acute therapy phase. There were no statistical significances between treatment groups as summarized in Table HMDW.8.

Table HMDW.8. Serious Adverse Events by Decreasing Frequency
All Randomized Patients Acute Therapy Phase
Combined Data from Study F1J-MC-HMDU and Study F1J-MC-HMDW

Event	1) PLACEBO (N=331) n(%)	2) DLX60120 (N=320) n(%)	3) VEN75225 (N=333) n(%)	Total (N=984) n(%)	p-Value* Overall	1vs2	1vs3	2vs3
PATIENTS WITH >=1 SERIOUS ADVERSE EVENT	3(0.9%)	2(0.6%)	3(0.9%)	8(0.8%)	.897	.675	.994	.672
Abdominal pain upper	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.367	.319		.314
Agitation	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.382	.335	.319	
Alcoholism	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.367	.319		.314
Angina pectoris	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.374		.322	.320
Cardiac failure congestive	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.363	.316	.313	
Depression	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.367	.319		.314
Epistaxis	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.374		.322	.320
Ideas of reference	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.382	.335	.319	
Insomnia	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.382	.335	.319	
Panic attack	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.382	.335	.319	
Paranoia	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.382	.335	.319	
Renal cell carcinoma stage unspecified	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.367	.319		.314
Self mutilation	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.367	.319		.314
Traumatic brain injury	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.379		.316	.334
Vomiting	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.367	.319		.314

Abbreviations: DLX60120 = duloxetine 60 to 120 mg, N = number of randomized patients, n = number of patients with a serious adverse event, VEN 75225 = venlafaxine-extended release 75 to 225 mg.

*Frequencies are analyzed using a Cochran-Mantel-Haenszel test stratified by study.

Discontinuation-Emergent Adverse Events

Table HMDW.9 summarizes the combined data from Study HMDU and Study HMDW for discontinuation-emergent adverse events (DEAEs)-preferred term by decreasing frequency for all patients entering the drug-tapering phase. A total of 124, 12.6% patients (35, 10.6% placebo; 38, 11.9% duloxetine 60 to 120 mg; and 51, 15.3% venlafaxine 75 to 225 mg) experienced a DEAE.

Events with a statistically significantly higher incidence in duloxetine 60 to 120 mg-treated patient included: dizziness and diarrhea (compared with placebo) and diarrhea (compared with venlafaxine 75 to 225 mg). Events with a statistically significantly higher incidence in venlafaxine 75 to 225 mg-treated included: dizziness (compared with placebo). Events with a statistically significantly higher incidence in placebo-treated patients included: upper respiratory tract infection (compared with duloxetine 60 to 120 mg).

Table HMDW.9. Discontinuation-Emergent Adverse Events
All Patients Entering Drug-Tapering Phase Combined Data from Study F1J-MC-HMDU and Study F1J-MC-HMDW

Event	1)PLACEBO (N=331) n(%)	2)DLX60120 (N=320) n(%)	3)VEN75225 (N=333) n(%)	Total (N=984) n(%)	p-Value* Overall	1vs2	1vs3	2vs3
Patients with >=1 Discontinuation-Emergent Event	35(10.6%)	38(11.9%)	51(15.3%)	124(12.6%)	.165	.592	.070	.199
Dizziness	1(0.3%)	8(2.5%)	14(4.2%)	23(2.3%)	.004	.016	<.001	.233
Headache	3(0.9%)	5(1.6%)	5(1.5%)	13(1.3%)	.728	.448	.490	.963
Nausea	2(0.6%)	5(1.6%)	5(1.5%)	12(1.2%)	.467	.251	.261	.963
Irritability	1(0.3%)	2(0.6%)	4(1.2%)	7(0.7%)	.377	.520	.178	.454
Anxiety	2(0.6%)	2(0.6%)	2(0.6%)	6(0.6%)	.998	.941	1.000	.957
Diarrhoea	0(0.0%)	6(1.9%)	0(0.0%)	6(0.6%)	.002	.012		.012
Upper respiratory tract infection	4(1.2%)	0(0.0%)	1(0.3%)	5(0.5%)	.073	.046	.173	.320
Agitation	1(0.3%)	0(0.0%)	3(0.9%)	4(0.4%)	.186	.335	.312	.093
Insomnia	1(0.3%)	2(0.6%)	1(0.3%)	4(0.4%)	.757	.536	.996	.545
Abdominal pain	2(0.6%)	1(0.3%)	0(0.0%)	3(0.3%)	.372	.591	.156	.301
Abnormal dreams	0(0.0%)	3(0.9%)	0(0.0%)	3(0.3%)	.046	.080		.078
Back pain	0(0.0%)	1(0.3%)	2(0.6%)	3(0.3%)	.374	.300	.161	.581
Disturbance in attention	1(0.3%)	1(0.3%)	1(0.3%)	3(0.3%)	.999	.981	.997	.978
Myalgia	1(0.3%)	1(0.3%)	1(0.3%)	3(0.3%)	1.000	.997	.996	.978
Panic attack	1(0.3%)	1(0.3%)	1(0.3%)	3(0.3%)	.998	.959	.997	.962
Sinusitis	2(0.6%)	0(0.0%)	1(0.3%)	3(0.3%)	.372	.164	.557	.320
Abdominal pain upper	0(0.0%)	2(0.6%)	0(0.0%)	2(0.2%)	.126	.150		.149
Aspartate Amino transferase increased	0(0.0%)	0(0.0%)	2(0.6%)	2(0.2%)	.143		.155	.171
Asthenia	0(0.0%)	1(0.3%)	1(0.3%)	2(0.2%)	.593	.300	.316	.962
Asthma	0(0.0%)	0(0.0%)	2(0.6%)	2(0.2%)	.143		.155	.171
Blood glucose increased	1(0.3%)	0(0.0%)	1(0.3%)	2(0.2%)	.617	.335	.996	.320
Chest discomfort	0(0.0%)	1(0.3%)	1(0.3%)	2(0.2%)	.593	.300	.316	.962
Fatigue	0(0.0%)	0(0.0%)	2(0.6%)	2(0.2%)	.143		.155	.171
Flatulence	0(0.0%)	2(0.6%)	0(0.0%)	2(0.2%)	.126	.150		.149
Flushing	1(0.3%)	1(0.3%)	0(0.0%)	2(0.2%)	.596	.959	.319	.301
Hyperhidrosis	1(0.3%)	1(0.3%)	0(0.0%)	2(0.2%)	.596	.959	.319	.301
Hypertonia	0(0.0%)	1(0.3%)	1(0.3%)	2(0.2%)	.610	.319	.322	.993
Influenza like illness	0(0.0%)	2(0.6%)	0(0.0%)	2(0.2%)	.126	.150		.149
Initial insomnia	1(0.3%)	0(0.0%)	1(0.3%)	2(0.2%)	.617	.316	.996	.334
Nasopharyngitis	0(0.0%)	2(0.6%)	0(0.0%)	2(0.2%)	.134	.158		.154
Neck pain	0(0.0%)	0(0.0%)	2(0.6%)	2(0.2%)	.142		.159	.166

(Continued)

Table HMDW.9. Discontinuation-Emergent Adverse Events
All Patients Entering Drug-Tapering Phase Combined Data from Study F1J-MC-HMDU and Study F1J-MC-HMDW

Event	1) PLACEBO (N=331) n(%)	2) DLX60120 (N=320) n(%)	3) VEN75225 (N=333) n(%)	Total (N=984) n(%)	p-Value* Overall	1vs2	1vs3	2vs3
Pneumonia	1(0.3%)	0(0.0%)	1(0.3%)	2(0.2%)	.617	.316	.996	.334
Pruritus	0(0.0%)	0(0.0%)	2(0.6%)	2(0.2%)	.139		.161	.159
Pyrexia	0(0.0%)	1(0.3%)	1(0.3%)	2(0.2%)	.610	.319	.322	.993
Sinus headache	0(0.0%)	1(0.3%)	1(0.3%)	2(0.2%)	.610	.319	.322	.993
Stomach discomfort	1(0.3%)	1(0.3%)	0(0.0%)	2(0.2%)	.599	.981	.313	.301
Syncope	0(0.0%)	0(0.0%)	2(0.6%)	2(0.2%)	.142		.159	.166
Tension headache	0(0.0%)	2(0.6%)	0(0.0%)	2(0.2%)	.134	.158		.154
Tinnitus	2(0.6%)	0(0.0%)	0(0.0%)	2(0.2%)	.131	.155	.153	
Vertigo	0(0.0%)	1(0.3%)	1(0.3%)	2(0.2%)	.602	.300	.322	.978
Vomiting	0(0.0%)	1(0.3%)	1(0.3%)	2(0.2%)	.593	.300	.316	.962
Acne	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.374		.322	.320
Alanine aminotransferase increased	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.379		.316	.334
Arthralgia	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.374		.322	.320
Blepharitis	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.382	.335	.319	
Blood AP increased	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.379		.316	.334
Blood CP increased	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.379		.316	.334
Cough	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.374		.322	.320
Cystitis	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.363	.316	.313	
Dissociation	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.342	.300		.301
Dysmenorrhoea	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.382	.335	.319	
Dyspepsia	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.379		.316	.334
Dysphoria	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.379		.316	.334
Dyspnoea	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.367	.319		.314
Dysuria	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.382	.335	.319	
Ear pain	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.374		.322	.320
Enterocolitis infectious	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.374		.322	.320
Eye pain	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.382	.335	.319	
Eye pruritus	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.374		.322	.320
Fungal infection	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.367	.319		.314
GGT increased	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.379		.316	.334
Gastritis	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.342	.300		.301
Hand fracture	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.367	.319		.314
Heart rate increased	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.374		.322	.320
Herpes zoster	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.367	.319		.314

(Continued)

Table HMDW.9. Discontinuation-Emergent Adverse Events All Patients Entering Drug-Tapering Phase Combined data from Study F1J-MC-HMDU and Study F1J-MC-HMDW (Concluded)

Event	1)PLACEBO (N=331) n(%)	2)DLX60120 (N=320) n(%)	3)VEN75225 (N=333) n(%)	Total (N=984) n(%)	p-Value* Overall	1vs2	1vs3	2vs3
Hyperacusis	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.374		.322	.320
Influenza	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.363	.316	.313	
Intestinal ulcer	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.367	.319		.314
Joint stiffness	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.367	.319		.314
Microcytic anaemia	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.379		.316	.334
Migraine	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.379		.316	.334
Muscle contracture	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.382	.335	.319	
Muscle spasms	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.363	.316	.313	
Nephrolithiasis	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.363	.316	.313	
Neuropathy peripheral	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.374		.322	.320
Oedema peripheral	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.363	.316	.313	
Orthostatic hypotension	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.379		.316	.334
Pain in extremity	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.382	.335	.319	
Paraesthesia	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.382	.335	.319	
Periorbital haematoma	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.379		.316	.334
Pharyngitis streptococcal	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.374		.322	.320
Pharyngolaryngeal pain	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.374		.322	.320
Photophobia	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.374		.322	.320
Post procedural pain	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.367	.319		.314
Respiratory tract congestion	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.374		.322	.320
Rhinitis	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.382	.335	.319	
Sleep disorder	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.342	.300		.301
Sluggishness	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.367	.319		.314
Swelling face	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.367	.319		.314
Tearfulness	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.382	.335	.319	
Therapeutic response unexpected	0(0.0%)	0(0.0%)	1(0.3%)	1(0.1%)	.379		.316	.334
Tremor	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.342	.300		.301
tract infection	0(0.0%)	1(0.3%)	0(0.0%)	1(0.1%)	.342	.300		.301
Vaginitis bacterial	1(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	.382	.335	.319	

Abbreviations: AP = alkaline phosphatase, CP = creatinine phosphokinase, DLX60120 = duloxetine 60 to 120 mg, GGT = gamma-glutamyl transferase, N = number of patients entering the drug-tapering phase, N = sample size, n = number of patients with discontinuation-emergent adverse event, VEN 75 to 225 = venlafaxine-extended release 75 to 225 mg.

*Frequencies are analyzed using a Cochran-Mantel-Haenszel test stratified by study.

Treatment-Emergent Adverse Events

Table HMDW.10 summarizes the combined data from study HMDU and study HMDW of treatment-emergent adverse event (TEAE) that were reported statistically significantly more by duloxetine 60 to 120 mg or venlafaxine 75 to 225 mg-treated patients than by placebo-treated patients or were reported by ≥5% of patients treated with placebo, duloxetine 60 to 120 mg, or venlafaxine 75 to 225 mg.

Events with a statistically significantly higher incidence in duloxetine 60 to 120 mg QD-treated patients compared with venlafaxine 75 to 225 mg-treated patients included: nausea, diarrhea, constipation, somnolence, yawning, nasopharyngitis, and blurred vision.

Events with a statistically significantly higher incidence in venlafaxine75 to 225 mg-treated patients compared with duloxetine 60 to 120 mg-treated patients included: headache, dizziness, dry mouth, fatigue, and insomnia.

Statistically significantly more duloxetine 60 to 120 mg QD and venlafaxine 75 to 225 mg-treated patients reported >1 TEAE compared with placebo-treated patients.

Events with a statistically significantly higher incidence in placebo-treated patients included: headache (in comparisons with duloxetine 60 to 120 mg QD and venlafaxine 75 to 225 mg) and nasopharyngitis (in comparisons with venlafaxine 75 to 225 mg). Events with a statistically significantly higher incidence in duloxetine 60 to 120 mg QD-treated patients included: nausea, dry mouth, constipation, fatigue, diarrhea, somnolence, decreased appetite, hyperhidrosis, yawning, blurred vision (in comparison with placebo), nausea, diarrhea, yawning, nasopharyngitis, and blurred vision (in comparison with venlafaxine75 to 225 mg).

Events with a statistically significantly higher incidence in venlafaxine75 to 225 mg-treated included: nausea, dizziness, constipation, dry mouth, somnolence, fatigue, insomnia, decreased appetite, hyperhidrosis, and yawning (in comparison with placebo).

Table HMDW.10. Treatment-Emergent Adverse Events in Statistically Significant and ≥5%
All Randomized Patients
Acute Therapy Phase: Combined Data from Study F1J-MC-HMDU and Study F1J-MC-HMDW

TEAE	Placebo (1`) (N = 331) n (%)	DLX 60-120 mg (2) (N = 320) n (%)	VEN 75-225 mg (3) (N = 158) n (%)	Pair-wise Comparison p-Value*			
				Overall	1 vs 2	1 vs 3	2 vs 3
Patient with ≥1 TEAE	219 (66.2%)	236 (73.8)	255 (76.6)	.008	.040	.003	.350
Nausea	39 (11.8%)	86 (26.9)	67 (20.1)	≤.001	≤.001	.003	.044
Headache	69 (20.8%)	46 (14.4)	57 (17.1)	.089	.030	.216	.332
Dizziness	27 (8.2%)	37 (11.6)	43 (12.9)	.130	.147	.047	.597
Dry mouth	15 (4.2%)	40 (12.5)	44 (13.2)	≤.001	≤.001	≤.001	.771
Constipation	14 (4.2%)	41 (12.8)	35 (10.5)	≤.001	≤.001	.002	.371
Diarrhea	22 (6.6%)	36 (11.3)	20 (6)	.029	.043	.726	.018
Somnolence	9 (2.7%)	32 (10)	30 (9)	≤.001	≤.001	≤.001	.692
Fatigue	11 (3.3%)	26 (8.1)	30 (9)	.008	.008	.002	.678
Insomnia	13 (3.9%)	22 (6.9)	27 (8.1)	.075	.093	.024	.543
Nasopharyngitis	14 (4.2%)	13 (4.1)	5 (1.5)	.086	.893	.033	.047
Yawning	0	16 (5)	7 (2.1)	≤.001	≤.001	.008	.048
Blurred vision	4 (1.2%)	13 (4.1)	4 (1.2)	.016	.024	.982	.023
Decreased appetite	4 (1.2%)	22 (6.9%)	17 (5.1%)	.002	≤.001	.004	.361
Hyperhidrosis	2 (0.6%)	20 (6.3%)	13 (3.9%)	≤.001	≤.001	.004	.162

Abbreviations: DLX = duloxetine, N = number of randomized patients, n = number of patients with treatment-emergent adverse event, TEAE = treatment-emergent adverse event, VEN = venlafaxine-extended release.

*Frequencies are analyzed using a Cochran-Mantel-Haenszel test stratified by study.

Laboratory Values

Tables HMDW.11 and HMDW.12 summarize treatment-emergent chemistry and hematology laboratory analytes. Comparing duloxetine 60 to 120 mg and venlafaxine 75 to 225 mg, there were no treatment-emergent chemistry and hematology labs that were statistically significantly different.

Compared with placebo: a statistically significantly greater number of venlafaxine 75 to 225 mg-treated patients experienced abnormal inorganic phosphorus; a statistically significantly greater number of venlafaxine 75 to 225 mg-treated patients experienced high potassium and cholesterol.

Compared with placebo: a statistically significantly greater number of duloxetine 60 to 120 mg-treated patients experienced abnormal uric acid; a statistically significantly greater number of duloxetine 60 to 120 mg-treated patients experienced high potassium, alkaline phosphate, AST/SGOT, and cholesterol; a statistically significantly greater number of duloxetine 60 to 120 mg-treated patients experienced low uric acid. In comparisons between duloxetine 60 to 120 mg and venlafaxine75 to 225 mg, there were no treatment-emergent chemistry labs that demonstrated statistically significant differences.

Compared with placebo: a statistically significantly greater number of venlafaxine 75 to 225 mg-treated patients experienced high hemoglobin; a statistically significantly greater number of duloxetine 60 to 120 mg-treated patients experienced abnormal and low neutrophils. In comparisons between duloxetine 60 to 120 mg and venlafaxine75 to 225 mg, there were no treatment-emergent hematology labs that demonstrated statistically significant differences.

Table HMDW.11. Laboratory Values – Chemistry Analytes Treatment-Emergent Abnormal Labs at Any Time
All Randomized Patients
Acute Therapy Phase: Combined Data from Study F1J-MC-HMDU and Study F1J-MC-HMDW

Laboratory Analytes	Directions	Therapy	N	n (%)	p-Value*		
					Overall	vs 2	vs 3
Albumin (gram/liter)	Abnormal	Placebo	151	2 (1.3)	.404	.179	.590
		DLX 60-120 mg	136	0			.331
		VEN 75-225 mg	144	1 (0.7)			
	High	Placebo	149	4 (2.7)	.674	.482	.455
		DLX 60-120 mg	135	2 (1.5)			.971
		VEN 75-225 mg	140	2 (1.4)			
	Low	Placebo	151	2 (1.3)	.404	.179	.590
		DLX 60-120 mg	136	0			.331
		VEN 75-225 mg	144	1 (0.7)			
Alkaline phosphatase (units/liter)	High	Placebo	279	3 (1.1)	.043	.011	.077
		DLX 60-120 mg	253	12 (4.7)			.367
		VEN 75-225 mg	281	9 (3.2)			
ALT/SGPT (units/liter)	Abnormal	Placebo	290	1 (0.3)	.802	.952	.573
		DLX 60-120 mg	266	1 (0.4)			.610
		VEN 75-225 mg	290	2 (0.7)			
	High	Placebo	267	25 (9.4)	.351	.698	.145
		DLX 60-120 mg	227	19 (8.4)			.318
		VEN 75-225 mg	254	15 (5.9)			
	Low	Placebo	290	1 (0.3)	.802	.952	.573
		DLX 60-120 mg	266	1 (0.4)			.610
		VEN 75-225 mg	290	2 (0.7)			
AST/SGOT (units/liter)	Abnormal	Placebo	285	0	.370		.307
		DLX 60-120 mg	264	0			.331
		VEN 75-225 mg	288	1 (0.3)			
	High	Placebo	269	10 (3.7)	.087	.029	.277
		DLX 60-120 mg	241	20 (8.3)			.265
		VEN 75-225 mg	263	15 (5.7)			
	Low	Placebo	285	0	.370		.307
		DLX 60-120 mg	264	0			.331
		VEN 75-225 mg	288	1 (0.3)			
Bicarbonate (millimole/liter)	Abnormal	Placebo	287	4 (1.4)	.609	.453	.385
		DLX 60-120 mg	264	2 (0.8)			.919
		VEN 75-225 mg	287	2 (0.7)			

(Continued)

Table HMDW.11. Laboratory Values – Chemistry Analytes
Treatment-Emergent Abnormal Labs at Any Time
All Randomized Patients
Acute Therapy Phase: Combined Data from Study F1J-MC-HMDU and Study F1J-MC-HMDW (Continued)

Laboratory Analytes	Directions	Therapy	N	n (%)	p-Value*		
					Overall	vs 2	vs 3
Bicarbonate (millimole/liter)	High	Placebo	289	3 (1.0)	.184	.351	.329
		DLX 60-120 mg	266	1 (0.4)			.076
		VEN 75-225 mg	288	6 (2.1)			
	Low	Placebo	287	4 (1.4)	.609	.4531	.385
		DLX 60-120 mg	264	2 (0.8)			.919
		VEN 75-225 mg	287	2 (0.7)			
Chloride (millimole/liter)	Abnormal	Placebo	291	0	.333	.299	
		DLX 60-120 mg	266	1 (0.4)			.289
		VEN 75-225 mg	291	0			
	High	Placebo	291	2 (0.7)	.149	.177	.158
		DLX 60-120 mg	265	0			
		VEN 75-225 mg	289	0			
	Low	Placebo	291	0	.333	.299	
		DLX 60-120 mg	266	1 (0.4)			.289
		VEN 75-225 mg	291	0			
Calcium (millimole/liter)	High	Placebo	283	5 (1.8)	.314	.640	.271
		DLX 60-120 mg	258	6 (2.3)			.121
		VEN 75-225 mg	282	2 (0.7)			
Cholesterol (millimole/liter)	Abnormal	Placebo	266	18 (6.8)	.253	.614	.243
		DLX 60-120 mg	239	19 (7.9)			.101
		VEN 75-225 mg	270	12 (4.4)			
	High	Placebo	279	4 (1.4)	.017	.039	.004
		DLX 60-120 mg	250	11 (4.4)			.386
		VEN 75-225 mg	279	17 (6.1)			
	Low	Placebo	266	18 (6.8)	.253	.614	.243
		DLX 60-120 mg	239	19 (7.9)			.101
		VEN 75-225 mg	270	12 (4.4)			
Total Bilirubin (millimole/liter)	Abnormal	Placebo	282	7 (2.5)	.199	.861	.114
		DLX 60-120 mg	257	7 (2.7)			.178
		VEN 75-225 mg	280	14 (5)			
	High	Placebo	282	4 (1.4)	.928	.897	.716
		DLX 60-120 mg	258	4 (1.6)			.807
		VEN 75-225 mg	275	5 (1.8)			
	Low	Placebo	282	7 (2.5)	.199	.861	.114
		DLX 60-120 mg	257	7 (2.7)			.178
		VEN 75-225 mg	280	14 (5)			

(Continued)

**Table HMDW.11. Laboratory Values: Chemistry Analytes
Treatment-Emergent Abnormal Labs at Any Time
All Randomized Patients
Acute Therapy Phase: Combined Data from Study F1J-MC-HMDU and Study F1J-MC-HMDW (Continued)**

Laboratory Analytes	Directions	Therapy	N	n (%)	p- Value		
					Overall	vs 2	vs 3
Creatinine (micromole/liter)	Abnormal	Placebo	291	0	.372		.308
		DLX 60-120 mg	267	0			.333
		VEN 75-225 mg	291	1 (0.3)			
	High	Placebo	287	3 (1.0)	.648	.622	.675
		DLX 60-120 mg	264	4 (1.5)			.345
		VEN 75-225 mg	288	2 (0.7)			
	Low	Placebo	291	0	.372		.308
		DLX 60-120 mg	267	0			.333
		VEN 75-225 mg	291	1 (0.3)			
GGT (GGPT/SGGT/YGGT) (units/liter)	Abnormal	Placebo	290	2 (0.7)	.380	.617	.164
		DLX 60-120 mg	266	1 (0.4)			.291
		VEN 75-225 mg	290	0			
	High	Placebo	269	7 (2.6)	.423	.218	.717
		DLX 60-120 mg	239	11 (4.6)			.367
		VEN 75-225 mg	264	8 (3)			
	Low	Placebo	290	2 (0.7)	.380	.617	.164
		DLX 60-120 mg	266	1 (0.4)			.291
		VEN 75-225 mg	290	0			
Fasting glucose (millimole/liter)	Abnormal	Placebo	122	4 (3.3)	.086	.053	.188
		DLX 60-120 mg	113	0			.328
		VEN 75-225 mg	118	1 (0.8)			
	High	Placebo	116	4 (3.4)	.305	.474	.391
		DLX 60-120 mg	111	6 (5.4)			.124
		VEN 75-225 mg	119	2 (1.7)			
	Low	Placebo	122	4 (3.3)	.086	.053	.188
		DLX 60-120 mg	113	0			.328
		VEN 75-225 mg	118	1 (0.8)			
HDL Cholesterol-dextran precipitate (millimole/liter)	Abnormal	Placebo	113	2 (1.8)	.774	.570	.958
		DLX 60-120 mg	102	3 (2.9)			.531
		VEN 75-225 mg	119	2 (1.7)			
	High	Placebo	110	5 (4.5)	.854	.964	.637
		DLX 60-120 mg	107	5 (4.7)			.606
		VEN 75-225 mg	120	4 (3.3)			
	Low	Placebo	113	2 (1.8)	.774	.570	.958
		DLX 60-120 mg	102	3 (2.9)			.531
		VEN 75-225 mg	119	2 (1.7)			

(Continued)

Table HMDW.11. Laboratory Values: Chemistry Analytes
Treatment-Emergent Abnormal Labs at Any Time
All Randomized Patients
Acute Therapy Phase: Combined Data from Study F1J-MC-HMDU and Study F1J-MC-HMDW (Continued)

Laboratory Analytes	Directions	Therapy	N	n (%)	p-Value		
					Overall	vs 2	vs 3
Random glucose (millimole/liter)	Abnormal	Placebo	154	0	.322	.119	.306
		DLX 60-120 mg	139	2 (1.4)			.621
		VEN 75-225 mg	145	1 (0.7)			
	Low	Placebo	154	0	.322	.119	.306
		DLX 60-120 mg	139	2 (1.4)			.621
		VEN 75-225 mg	145	1 (0.7)			
Potassium (millimole/liter)	Abnormal	Placebo	290	0	.335	.292	
		DLX 60-120 mg	265	1 (0.4)			.300
		VEN 75-225 mg	290	0			
	High	Placebo	289	0	.037	.019	.008
		DLX 60-120 mg	263	5 (1.9)			.682
		VEN 75-225 mg	288	7 (2.4)			
	Low	Placebo	290	0	.335	.292	
		DLX 60-120 mg	265	1 (0.4)			.300
		VEN 75-225 mg	290	0			
Hemoglobin A1C (actual count)	High	Placebo	110	0	.039	.076	
		DLX 60-120 mg	106	3 (2.8)			.068
		VEN 75-225 mg	117	0			
Inorganic phosphorus (millimole/liter)	Abnormal	Placebo	288	0	.070	.138	.025
		DLX 60-120 mg	266	2 (0.8)			.300
		VEN 75-225 mg	291	5 (1.7)			
	High	Placebo	290	1 (0.3)	.580	.958	.307
		DLX 60-120 mg	266	1 (0.4)			.289
		VEN 75-225 mg	291	0			
	Low	Placebo	288	0	.070	.138	.025
		DLX 60-120 mg	266	2 (0.8)			.300
		VEN 75-225 mg	291	5 (1.7)			
Uric acid (micromole/liter	Abnormal	Placebo	290	0	.054	.035	.307
		DLX 60-120 mg	264	4 (1.5)			.150
		VEN 75-225 mg	290	1 (0.3)			
	High	Placebo	281	9 (3.2)	.627	.400	.473
		DLX 60-120 mg	247	5 (2.0)			.899
		VEN 75-225 mg	274	6 (2.2)			
	Low	Placebo	290	0	.054	.035	.307
		DLX 60-120 mg	264	4 (1.5)			.150
		VEN 75-225 mg	290	1 (0.3)			
Creatine phosphokinase (units/liter)	High	Placebo	259	31 (12.0)	.712	.442	.891
		DLX 60-120 mg	230	33 (14.3)			.527
		VEN 75-225 mg	250	31 (12.4)			

(Continued)

Table HMDW.11. Laboratory Values Chemistry Analytes Treatment-Emergent Abnormal Labs at Any Time
All Randomized Patients
Acute Therapy Phase: Combined Data from Study F1J-MC-HMDU and Study F1J-MC-HMDW (Concluded)

Laboratory Analytes	Directions	Therapy	N	n (%)	p*-Value		
					Overall	vs 2	vs 3
Sodium (millimole/liter)	Abnormal	Placebo	291	1 (0.3)	.591	.948	.307
		DLX 60-120 mg	265	1 (0.4)			.302
		VEN 75-225 mg	290	0			
	High	Placebo	287	2 (0.7)	.860	.617	.996
		DLX 60-120 mg	260	1 (0.4)			.625
		VEN 75-225 mg	281	2 (0.7)			
	Low	Placebo	291	1 (0.3)	.591	.948	.307
		DLX 60-120 mg	265	1 (0.4)			.302
		VEN 75-225 mg	290	0			
Total protein (gram/liter)	Abnormal	Placebo	291	0	.592	.301	.308
		DLX 60-120 mg	267	1 (0.4)			.951
		VEN 75-225 mg	291	1 (0.3)			
	High	Placebo	289	6 (2.1)	.051	.078	.054
		DLX 60-120 mg	258	1 (0.4)			.923
		VEN 75-225 mg	285	1 (0.4)			
	Low	Placebo	291	0	.592	.301	.308
		DLX 60-120 mg	267	1 (0.4)			.951
		VEN 75-225 mg	291	1 (0.3)			
Fasting triglycerides (milligram/deciliter)	Abnormal	Placebo	111	2 (1.8)	.205	.637	.136
		DLX 60-120 mg	109	3 (2.8)			.065
		VEN 75-225 mg	123	0			
	High	Placebo	111	7 (6.3)	.271	.633	.124
		DLX 60-120 mg	100	8 (8)			.305
		VEN 75-225 mg	114	14 (12.3)			
	Low	Placebo	111	2 (1.8)	.205	.637	.136
		DLX 60-120 mg	109	3 (2.8)			.065
		VEN 75-225 mg	123	0			

Table HMDW.11. Laboratory Values Chemistry Analytes Treatment-Emergent Abnormal Labs at Any Time
All Randomized Patients
Acute Therapy Phase: Combined Data from Study F1J-MC-HMDU and Study F1J-MC-HMDW (Concluded)

Urea nitrogen (millimole/liter)	Abnormal	Placebo	291	1 (0.3)	.396	.343	.329
		DLX 60-120 mg	267	0			
		VEN 75-225 mg	290	0			
	High	Placebo	288	1 (0.3)	.198	.074	.101
		DLX 60-120 mg	264	5 (1.9)			.897
		VEN 75-225 mg	288	5 (1.7)			
	Low	Placebo	291	1 (0.3)	.396	.343	.329
		DLX 60-120 mg	267	0			
		VEN 75-225 mg	290	0			

Abbreviations: ALT/SGPT = alanine transaminase, AST/SGOT = aspartate transaminase, DLX = duloxetine, GGT = gamma glutamyl transferase, HDL cholesterol = high-density lipoprotein, N = number of patients with baseline and postbaseline measurements who were normal respective to the specified direction at baseline, n = number of patients with an abnormal postbaseline measurement, VEN = venlafaxine-extended release, 1 = placebo, 2 = DLX 60-120 mg, 3 = VEN 75-225 mg.

*Frequencies are analyzed using Cochran-Mantel-Haenzsel test controlling for study.

Table HMDW.12. Laboratory Values – Hematology Analytes Treatment-Emergent Abnormal Labs at Any Time Covance Reference Ranges in All Randomized Patients
Acute Therapy Phase: Combined Data from Study F1J-MC-HMDU and Study F1J-MC-HMDW

Laboratory Analytes	Directions	Therapy	N	n (%)	p-value		
					Overall	vs 2	vs 3
Basophils (billion/liter)	High	Placebo	246	1 (0.4)	.385	.327	.331
		DLX 60-120 mg	237	0			
		VEN 75-225 mg	247	0			
Eosinophils (billion/liter)	High	Placebo	247	3 (1.2)	.051	.089	.079
		DLX 60-120 mg	237	0			
		VEN 75-225 mg	246	0			
Erythrocyte count (trillion/liter)	Abnormal	Placebo	238	4 (1.7)	.244	.416	.388
		DLX 60-120 mg	236	2 (0.8)			.102
		VEN 75-225 mg	241	7 (2.9)			
	High	Placebo	247	1 (0.4)	.365	.328	.303
		DLX 60-120 mg	237	0			
		VEN 75-225 mg	246	0			
	Low	Placebo	238	4 (1.7)	.244	.416	.388
		DLX 60-120 mg	236	2 (0.8)			.102
		VEN 75-225 mg	241	7 (2.9)			
Hematocrit (actual count)	Abnormal	Placebo	242	2 (0.8)	.138	.163	.155
		DLX 60-120 mg	235	0			
		VEN 75-225 mg	244	0			
	High	Placebo	239	4 (1.7)	.754	.456	.723
		DLX 60-120 mg	225	2 (0.9)			.680
		VEN 75-225 mg	237	3 (1.3)			
	Low	Placebo	242	2 (0.8)	.138	.163	.155
		DLX 60-120 mg	235	0			
		VEN 75-225 mg	244	0			
Hemoglobin (millimole/liter)	Abnormal	Placebo	239	1 (0.4)	.344	.176	.576
		DLX 60-120 mg	233	4 (1.7)			.371
		VEN 75-225 mg	237	2 (0.8)			
	High	Placebo	247	0	.114	.147	.037
		DLX 60-120 mg	237	2 (0.8)			.392
		VEN 75-225 mg	246	4(1.6)			
	Low	Placebo	239	1 (0.4)	.344	.176	.576
		DLX 60-120 mg	233	4 (1.7)			.371
		VEN 75-225 mg	237	2 (0.8)			
Hemoglobin A1C (actual count)	High	Placebo	236	1 (0.4)	.229	.087	.272
		DLX 60-120 mg	223	5 (2.2)			.453
		VEN 75-225 mg	232	3 (1.3)			

(Continued)

Table HMDW.12. Laboratory Values – Hematology Analytes Treatment-Emergent Abnormal Labs
All Randomized Patients
Acute Therapy Phase: Combined Data from Study F1J-MC-HMDU and Study F1J-MC-HMDW

Laboratory Analytes	Directions	Therapy	N	n (%)	p-value		
					Overall	vs 2	vs 3
Leukocyte count (billion/liter)	Abnormal	Placebo	246	8 (3.3)	.316	.144	.383
		DLX 60-120 mg	236	3 (1.3)			.541
		VEN 75-225 mg	244	5 (2.0)			
	High	Placebo	242	3 (1.2)	.739	.443	.717
		DLX 60-120 mg	230	5 (2.2)			.700
		VEN 75-225 mg	243	4 (1.6)			
	Low	Placebo	246	8 (3.3)	.316	.144	.383
		DLX 60-120 mg	236	3 (1.3)			.541
		VEN 75-225 mg	244	5 (2.0)			
Lymphocytes (billion/liter)	Abnormal	Placebo	247	5 (2.0)	.206	.280	.098
		DLX 60-120 mg	236	2 (0.8)			.551
		VEN 75-225 mg	245	1 (0.4)			
	High	Placebo	244	0	.132		
		DLX 60-120 mg	237	2 (0.8)		.148	
		VEN 75-225 mg	245	0			.162
	Low	Placebo	247	5 (2.0)	.206	.280	.098
		DLX 60-120 mg	236	2 (0.8)			.551
		VEN 75-225 mg	245	1 (0.4)			
Mean cell hemoglobin (femtomole)	Abnormal	Placebo	238	3 (1.3)	.198	.991	.078
		DLX 60-120 mg	231	3 (1.3)			.069
		VEN 75-225 mg	238	0			
	High	Placebo	243	1 (0.4)	.775	.986	.559
		DLX 60-120 mg	237	1 (0.4)			.548
		VEN 75-225 mg	246	2 (0.8)			
	Low	Placebo	238	3 (1.3)	.198	.991	.078
		DLX 60-120 mg	231	3 (1.3)			.069
		VEN 75-225 mg	238	0			
MCV (femtoliter)	Abnormal	Placebo	235	2 (0.9)	.124	.156	.141
		DLX 60-120 mg	232	0			
		VEN 75-225 mg	239	0			
	High	Placebo	231	7 (3.0)	.962	.844	.975
		DLX 60-120 mg	222	6 (2.7)			.801
		VEN 75-225 mg	228	7 (3.1)			
	Low	Placebo	235	2 (0.9)	.124	.156	.141
		DLX 60-120 mg	232	0			
		VEN 75-225 mg	239	0			

(Continued)

Table HMDW.12. Laboratory Values – Hematology Analytes Treatment-Emergent Abnormal Labs at Any Time
All Randomized Patients
Acute Therapy Phase: Combined Data from Study F1J-MC-HMDU and Study F1J-MC-HMDW (Concluded)

Laboratory Analytes	Directions	Therapy	N	n (%)	p-Value		
					Overall	vs 2	vs 3
MCHC (millimole/liter)	Abnormal	Placebo	226	2 (0.9)	.255	.095	.245
		DLX 60-120 mg	224	7 (3.1)			.586
		VEN 75-225 mg	232	5 (2.2)			
	Low	Placebo	226	2 (0.9)	.255	.095	.245
		DLX 60-120 mg	224	7 (3.1)			.586
		VEN 75-225 mg	232	5 (2.2)			
Monocytes (billion/liter)	Abnormal	Placebo	247	0	.338	.305	
		DLX 60-120 mg	236	1 (0.4)			.291
		VEN 75-225 mg	246	0			
	High	Placebo	247	0	.400		.333
		DLX 60-120 mg	236	0			344
		VEN 75-225 mg	246	1 (0.4)			.
	Low	Placebo	247	0	.338	.305	
		DLX 60-120 mg	236	1 (0.4)			.291
		VEN 75-225 mg	246	0			
Segmented neutrophil (billion/liter)	Abnormal	Placebo	239	12 (5.0)	.077	.022	.440
		DLX 60-120 mg	231	3 (1.3)			.110
		VEN 75-225 mg	242	9 (3.7)			
	High	Placebo	242	9 (3.7)	.340	.188	.281
		DLX 60-120 mg	230	4 (1.7)			.781
		VEN 75-225 mg	241	5 (2.1)			
	Low	Placebo	239	12 (5.0)	.077	.022	.401
		DLX 60-120 mg	231	3 (1.3)			.110
		VEN 75-225 mg	242	9 (3.7)			
Platelet count (billion/liter)	Abnormal	Placebo	241	0	.339	.306	
		DLX 60-120 mg	230	1 (0.4)			.290
		VEN 75-225 mg	240	0			
	High	Placebo	237	3 (1.3)	.565	.285	.470
		DLX 60-120 mg	227	6 (2.6)			.722
		VEN 75-225 mg	235	5 (2.1)			
	Low	Placebo	241	0	.339	.306	
		DLX 60-120 mg	230	1 (0.4)			.290
		VEN 75-225 mg	240	0			

Abbreviation: DLX = duloxetine, MCV = mean cell volume, N = number of patients with baseline and postbaseline measurements who were normal respective to the specified direction at baseline, MCHC = mean cell hemoglobin concentration, n = number of patients with an abnormal postbaseline measurement, VEN = venlafaxine-extended release, 1 = placebo, 2 = DLX 60-120 mg, 3 = VEN 75-225 mg.

*Frequencies are analyzed using Cochran-Mantel-Haenzsel test controlling for study.

Vital Signs and Weight

Table HMDW.13 summarizes mean change from baseline to endpoint of vital signs and weight from combined acute therapy phase data from Study HMDU and Study HMDW in the. No statistically significant differences between duloxetine 60 to 120 mg and venlafaxine 75 to 225 mg for vital signs or weight were reported.

Duloxetine 60 to 120 mg QD-treated patients experienced a statistically significant mean increase in pulse rate compared with placebo. There were no statistically significant differences between placebo and venlafaxine75 to 225 mg for pulse rate. Both duloxetine 60 to 120 mg- and venlafaxine75 to 225 mg-treated patients experienced a statistically significant mean decrease in weight compared with placebo.

Table HMDW.13. Vital Signs and Weight Mean Change from Baseline to Endpoint All Randomized Patients Acute Therapy Phase: Combined Data from Study F1J-MC-HMDU and Study F1J-MC-HMDW

Treatment Group	N	Baseline Mean (SD)	LS Mean (SE) Change	Pair wise comparison		
				1 vs 2	1 vs 3	2 vs 3
Pulse Rate (beats per minute)						
Placebo	322	71.67 (9.71)	0.84 (0.53)	.037	.121	.582
DLX 60-120 mg	298	71.55 (9.26)	2.43 (0.55)			
VEN 75-225 mg	314	72.03 (9.25)	2.01 (0.54)			
Sitting Systolic Blood Pressure (millimeter of mercury)						
Placebo	322	119.57 (14.43)	-0.97 (0.63)	.411	.489	.890
DLX 60-120 mg	298	120.66 (14.90)	-0.22 (0.66)			
VEN 75-225 mg	314	119 (13.19)	-0.35 (0.64)			
Sitting Diastolic Blood Pressure (millimeter of mercury)						
Placebo	322	76.20 (8.86)	-0.33 (0.50)	.552	.156	.424
DLX 60-120 mg	298	76.55 (9.35)	0.09 (0.52)			
VEN 75-225 mg	314	76.21 (9.32)	0.67 (0.50)			
Weight (kilogram)						
Placebo	270	76.43 (18.98)	0.14 (0.15)	.007	.005	.964
DLX 60-120 mg	258	77.05 (18.90)	-0.45 (0.16)			
VEN 75-225 mg	281	76.77 (17.98)	-0.46 (0.15)			

Abbreviations: DLX = duloxetine, N = number of patients with a baseline and at least one nonmissing postbaseline data, VEN = venlafaxine-extended release. 1 = placebo, 2 = DLX 60-120 mg, 3 = VEN 75-225 mg.

Type III Sums of Squares from ANOVA: Model = Treatment and Study.

Additional Secondary Objectives: Study F1J-MC-HMDW results

Response was defined as at least a 50% reduction from baseline to endpoint on HAMA Total score. Duloxetine 20 mg (60%), 60 to 120 mg (65%), and venlafaxine 75 to 225 mg (61%) demonstrated statistically significantly ($p \leq .001$) higher response rates at endpoint compared with placebo (42%). Table HMDW.14 summarize the analysis of mean change from baseline to endpoint for additional secondary objectives.

Duloxetine 20 mg, duloxetine 60 to 120 mg, and venlafaxine75 to 225 mg treated patients showed statistically significant improvement compared with placebo on the HAMA Psychic Anxiety Factor score ($p=.002$, $p \leq .001$ and $p \leq .001$, respectively), HAMA Somatic Anxiety Factor score ($p=.066$, $p=.028$, and $p=.002$ respectively), Clinical Global Impressions of Improvement (CGI-Improvement) Scale ($p \leq .001$ for all three treatment groups) and Patient's Global Impressions of Improvement (PGI-Improvement) Scale ($p \leq .001$ for all three treatment group).

Table HMDW.14. Additional Secondary Objectives (All Randomized Patients) Acute Therapy Phase Study – Study F1J-MC-HMDW

Treatment Group	N	Mean Baseline (SD)	LS Mean (SE) Change	p-value*vs Placebo
Hospital Anxiety Depression Scale Anxiety Subscale Score				
Placebo	157	14.87 (3.46)	-4.86 (0.37)	
DLX 20 mg	81	14.62 (3.43)	-7.02 (0.51)	≤.001
DLX 60-120 mg	147	14.92 (3.62)	-7.70 (0.38)	≤.001
VEN 75-225 mg	152	14.57 (3.17)	-6.89 (0.38)	≤.001
Hospital Anxiety Depression Scale Depression Subscale Score				
Placebo	157	7.74 (3.94)	-1.85 (0.27)	
DLX 20 mg	81	7.33 (3.87)	-3.34 (0.37)	≤.001
DLX 60-120 mg	147	7.87 (4.18)	-3.50 (0.28)	≤.001
VEN 75-225 mg	152	8.11 (4.19)	-3.57 (0.27)	≤.001
Hospital Anxiety Depression Scale Psychic Anxiety Factor Score				
Placebo	163	15.14 (3.76)	-6.03 (0.40)	
DLX 20 mg	83	15.11 (3.95)	-8.13 (0.56)	.002
DLX 60-120 mg	151	15.34 (3.32)	-8.71 (0.42)	≤.001
VEN 75-225 mg	158	15.30 (3.53)	-8.58 (0.41)	≤.001
Hamilton Anxiety Rating Scale, Somatic Anxiety Factor Score				
Placebo	163	12.19 (4.78)	-5.52 (0.34)	.
DLX 20 mg	83	12.54 (4.84)	-6.57 (0.47)	.066
DLX 60-120 mg	151	12.39 (5.11)	-6.57 (0.35)	.028
VEN 75-225 mg	158	12.06 (5.01)	-6.96 (0.35)	.002
Hamilton Anxiety Rating Scale, Item 1: Anxious Mood				
Placebo	163	2.91 (0.68)	-1.04 (0.08)	
DLX 20 mg	83	2.90 (0.69)	-1.57 (0.11)	≤.001
DLX 60-120 mg	151	2.94 (0.58)	-1.60 (0.09)	≤.001
VEN 75-225 mg	158	2.87 (0.75)	-1.54 (0.08)	≤.001
Hamilton Anxiety Rating Scale, Item 2: Tension				
Placebo	163	2.60 (0.81)	-1.05 (0.08)	
DLX 20 mg	83	2.63 (0.73)	-1.41 (0.11)	.008
DLX 60-120 mg	151	2.74 (0.66)	-1.53 (0.08)	≤.001
VEN 75-225 mg	158	2.74 (0.73)	-1.47 (0.08)	≤.001
Clinical Global Improvement: Improvement Score				
Placebo	163	NA	2.97 (0.10)	
DLX 20 mg	83	NA	2.35 (0.14)	≤.001
DLX 60-120 mg	152	NA	2.30 (0.10)	≤.001
VEN 75-225 mg	158	NA	2.28 (0.10)	≤.001
Patient Global Impression: Improvement Score				
Placebo	164	NA	3.13 (0.11)	
DLX 20 mg	83	NA	2.55 (0.15)	.001
DLX 60-120 mg	152	NA	2.41 (0.11)	≤.001
VEN 75-225 mg	158	NA	2.51 (0.11)	≤.001

Abbreviations: DLX = duloxetine, LS = least-squares mean, N = number of patients with a baseline and at least one nonmissing postbaseline data, SD = standard deviation, SE = standard error, VEN = venlafaxine-extended release.

*Type III Sums of Squares from ANCOVA: Model = baseline, treatment, and investigator.

Table HMDW.15 summarizes the completers' analysis of mean change from baseline to endpoint of the Analysis of Quality-of-Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF), EuroQol Questionnaire-5-Dimension ([EQ-5D] Index score), EQ-5D Visual Analog Scale (VAS) Health score, and Sheehan Disability Scale.

In the completers analysis SDS duloxetine 20 mg, duloxetine 60 to 120 mg-treatment and venalfaxine 75 to 225 mg treatment showed statistically significant improvement compared with placebo in the SDS Global score (p=.025, p≤.001 and p=.004 respectively), SDS Item 1 (p=.038, p=.011 and p=.013 respectively), SDS Item 2 (p=.030, p≤.001, and p=.004 respectively) and SDS Item 3 (p=.015, p=.002, and p=.007 respectively).

Duloxetine 20 mg and venalfaxine 75 to 225 mg treatment showed statistically significant improvement compared with placebo in Q-LES-Q-SF Total score (p=.017 and p=.011) and percent of maximum possible score (p=.018 and p=.012).

Duloxetine 60 to 120 mg did not show statistically significant improvement compared with placebo in Q-LES-Q-SF Total score (p=.083) and percent of maximum possible score (p=.091).

Duloxetine 20 mg, duloxetine 60 to 120 mg, and venalfaxine 75 to 225 mg did not show statistically significant (p=.299, p=.117, and p=.077) improvement compared with placebo in EQ-5D Index score. Duloxetine 20 mg, duloxetine 60 to 120 mg, and venalfaxine 75 to 225 mg did not show statistically significant (p=.634, p=.114 and p=.507) improvement compared with placebo in EQ-5D VAS Health score.

Table HMDW.15. Quality-of-Life Enjoyment and Satisfaction Questionnaire – Short Form Total Score
Mean Change from Baseline to Endpoint
Completers Analysis
Acute Therapy Phase – Study F1J-MC-HMDW

Treatment Group	N	Baseline Mean (SD)	LS Mean (SE) Change	Pair wise Comparison p-value*
SDS Global Score				
Placebo	112	18.81 (6.34)	-7.85 (0.66)	
DLX 20 mg	66	17.33 (6.11)	-10.2 (0.84)	.025
DLX 60-120 mg	116	18.48 (6.09)	-11.0 (0.65)	≤.001
VEN 75-225 mg	126	18.27 (6.11)	-10.4 (0.62)	.004
SDS Item 1: Work School				
Placebo	98	6.18 (2.18)	-2.62 (0.25)	
DLX 20 mg	54	5.85 (2.45)	-3.45 (0.32)	.038
DLX 60-120 mg	102	6.01 (2.45)	-3.46 (0.24)	.011
VEN 75-225 mg	114	6.01 (2.66)	-3.43 (0.23)	.013
SDS Item 2: Social Life				
Placebo	112	6.54 (2.57)	-2.67 (0.24)	
DLX 20 mg	66	5.85 (2.13)	-3.51 (0.31)	.030
DLX 60-120 mg	116	6.22 (2.32)	-3.96 (0.24)	≤.001
VEN 75-225 mg	126	6.26 (2.29)	-3.62 (0.23)	.004
SDS Item 3: Family Life Home Responsibilities				
Placebo	112	6.18 (2.43)	-2.60 (0.23)	
DLX 20 mg	66	5.65 (2.49)	-3.50 (0.29)	.015
DLX 60-120 mg	116	6.19 (2.30)	-3.60 (0.23)	.002
VEN 75-225 mg	126	5.98 (2.14)	-3.44 (0.22)	.007
Q-LES-Q-SF-Total Score				
Placebo	111	36.41 (8.40)	10.09 (0.97)	
DLX 20 mg	65	38.56 (8.07)	13.77 (1.23)	.017
DLX 60-120 mg	116	36.72 (9.36)	12.36 (0.94)	.083
VEN 75-225 mg	126	37.41 (8.75)	13.37 (0.90)	.011
Q-LES-Q-SF-Percentage of Maximum Possible Score				
Placebo	111	40.04 (15.06)	18.07 (1.73)	.
DLX 20 mg	65	43.88 (14.47)	24.56 (2.19)	.018
DLX 60-120 mg	116	40.63 (16.75)	22.02 (1.68)	.091
VEN 75-225 mg	126	41.83 (15.67)	23.89 (1.61)	.012
EQ-5D Index Score				
Placebo	110	0.49 (0.33)	0.25 (0.02)	
DLX 20 mg	66	0.54 (0.30)	0.29 (0.03)	.299
DLX 60-120 mg	114	0.47 (0.33)	0.30 (0.02)	.117
VEN 75-225 mg	126	0.52 (0.30)	0.30 (0.02)	.077

(Continued)

Table HMDW.15. Quality-of-Life Enjoyment and Satisfaction Questionnaire – Short Form Total Score
Mean Change from Baseline to Endpoint
Completers Analysis
Acute Therapy Phase – Study F1J-MC-HMDW (concluded)

Treatment Group	N	Baseline Mean (SD)	LS Mean (SE) Change	Pair wise comparison p-value*
EQ-5D VAS Health State Score				
Placebo	110	50.58 (20.44)	17.37 (4.82)	
DLX 20 mg	66	54.74 (20.56)	20.99 (6.03)	.634
DLX 60-120 mg	114	50.81 (20.84)	27.74 (4.72)	.114
VEN 75-225 mg	126	60.00 (86.74)	21.65 (4.49)	.507

Abbreviations: DLX = duloxetine, EQ-5D = EuroQol Questionnaire-5-Dimension, LS Mean = least-squares mean, N = number of patients with a baseline and at least one nonmissing postbaseline data, SD = standard deviation, SE = standard error, Q-LES-Q-SF = Quality-of-Life Enjoyment and Satisfaction Questionnaire – Short Form, SDS = Sheehan Disability Scale, VAS = Visual Analog Scale, VEN = venlafaxine-extended release 75 to 225 mg.
*Type III Sums of Squares from ANCOVA: Model = baseline, treatment, and investigator.

Table HMDW.16 summarize study drug dose escalation for all duloxetine and venlafaxine 75 to 225 mg patients during the acute therapy phase. There was no statistically significant difference between duloxetine 60 to 120 mg and venlafaxine 75 to 225 mg in the number of patients who experienced dose escalation in the acute phase.

Table HMDW.16. Dose Escalation
Duloxetine and Venlafaxine-Treatment Groups
Acute Therapy Phase – Study F1J-MC-HMDW

Escalation	DLX 60-120 mg (N = 133) n (%)	VEN 75-225 mg (N = 146) n (%)	p-Value*
No Escalation[a]	23 (17.3)	28 (19.2)	.618
1-Escalation[b]	39 (29.3)	49 (33.6)	
2-Escalation[c]	71 (53.4)	69 (47.3)	

Abbreviations: DLX = duloxetine, N = number of randomized patients, n = number of patients, VEN = venlafaxine-extended release.
[a] No escalation = duloxetine 60 mg QD or venlafaxine 75 mg QD at all visits in acute therapy phase.
[b] 1-Escalation = duloxetine 90 mg QD or venlafaxine 150 mg QD for at least one visit in acute therapy phase.
[c] 2-Escalation = duloxetine 120 mg QD or venlafaxine 225 mg QD for at least one visit in acute therapy phase.
*Frequencies are analyzed using Fisher's exact test.

Duloxetine 20 mg showed statistically significant (p.007) mean improvement (LS mean change, standard error: -(14.7, 0.96) in the HAMA total score.

Safety and tolerability results from F1J-MC-HMDW

Discontinuation Emergent-Adverse Events

Table HMDW.17 summarizes discontinuation-emergent adverse events (DEAEs) in order of decreasing frequency. Overall, there were no statistically significant differences between treatment groups. Dizziness was reported statistically significantly more often by duloxetine 20 mg, duloxetine 60 to 120 mg, and venlafaxine 75 to 225 mg -treated patients than by placebo-treated patients. There were no events for duloxetine 20 mg, duloxetine 60 to 120 mg, venlafaxine 75 to 225 mg, or placebo that were observed in >10% of the patients during the taper phase.

Table HMDW.17. Discontinuation-Emergent Adverse Events
Drug-Tapering Phase Study F1J-MC-HMDW

Event	1) PLACEBO (N=108) n (%)	2) DLX20 (N=64) n (%)	3) DLX60120 (N=111) n (%)	4) VEN75225 (N=125) n (%)	Total (N=408) n (%)	p-Value* Overall	1 vs. 2	1 vs. 3	1 vs. 4
Patients with >=1 Discontinuation-Emergent Event	19(17.6%)	14(21.9%)	20(18.0%)	23(18.4%)	76(18.6%)	.906	.550	1.00	1.00
Dizziness	0(0.0%)	3(4.7%)	6(5.4%)	7(5.6%)	16(3.9%)	.040	.050	.029	.016
Irritability	1(0.9%)	0(0.0%)	2(1.8%)	3(2.4%)	6(1.5%)	.766	1.00	1.00	.626
Anxiety	2(1.9%)	0(0.0%)	2(1.8%)	1(0.8%)	5(1.2%)	.712	.530	1.00	.598
Headache	1(0.9%)	1(1.6%)	3(2.7%)	0(0.0%)	5(1.2%)	.222	1.00	.622	.464
Nausea	0(0.0%)	2(3.1%)	1(0.9%)	2(1.6%)	5(1.2%)	.329	.137	1.00	.501
Agitation	1(0.9%)	0(0.0%)	0(0.0%)	3(2.4%)	4(1.0%)	.296	1.00	.493	.626
Diarrhoea	0(0.0%)	1(1.6%)	3(2.7%)	0(0.0%)	4(1.0%)	.077	.372	.247	
Fatigue	0(0.0%)	1(1.6%)	0(0.0%)	2(1.6%)	3(0.7%)	.243	.372		.501
Insomnia	1(0.9%)	1(1.6%)	1(0.9%)	0(0.0%)	3(0.7%)	.560	1.00	1.00	.464
Panic attack	1(0.9%)	0(0.0%)	1(0.9%)	1(0.8%)	3(0.7%)	1.00	1.00	1.00	1.00
Tremor	0(0.0%)	2(3.1%)	1(0.9%)	0(0.0%)	3(0.7%)	.081	.137	1.00	
Abdominal pain	1(0.9%)	0(0.0%)	1(0.9%)	0(0.0%)	2(0.5%)	.670	1.00	1.00	.464
Aspartate aminotransferase increased	0(0.0%)	0(0.0%)	0(0.0%)	2(1.6%)	2(0.5%)	.430			.501
Asthenia	0(0.0%)	0(0.0%)	1(0.9%)	1(0.8%)	2(0.5%)	1.00		1.00	1.00
Asthma	0(0.0%)	0(0.0%)	0(0.0%)	2(1.6%)	2(0.5%)	.430			.501
Chest discomfort	0(0.0%)	0(0.0%)	1(0.9%)	1(0.8%)	2(0.5%)	1.00		1.00	1.00
Disturbance in attention	1(0.9%)	0(0.0%)	0(0.0%)	1(0.8%)	2(0.5%)	.833	1.00	.493	1.00
Flushing	1(0.9%)	0(0.0%)	1(0.9%)	0(0.0%)	2(0.5%)	.670	1.00	1.00	.464
Hyperhidrosis	1(0.9%)	0(0.0%)	1(0.9%)	0(0.0%)	2(0.5%)	.670	1.00	1.00	.464
Muscle contracture	1(0.9%)	1(1.6%)	0(0.0%)	0(0.0%)	2(0.5%)	.251	1.00	.493	.464
Syncope	0(0.0%)	1(1.6%)	0(0.0%)	1(0.8%)	2(0.5%)	.526	.372		1.00
Vomiting	0(0.0%)	0(0.0%)	1(0.9%)	1(0.8%)	2(0.5%)	1.00		1.00	1.00
Abdominal pain upper	0(0.0%)	0(0.0%)	1(0.9%)	0(0.0%)	1(0.2%)	.694		1.00	
Abnormal dreams	0(0.0%)	0(0.0%)	1(0.9%)	0(0.0%)	1(0.2%)	.694		1.00	
Aggression	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	1(0.2%)	.157	.372		
Alanine aminotransferase increased	0(0.0%)	0(0.0%)	0(0.0%)	1(0.8%)	1(0.2%)	1.00			1.00
Back pain	0(0.0%)	0(0.0%)	1(0.9%)	0(0.0%)	1(0.2%)	.694		1.00	
Blepharitis	1(0.9%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.2%)	.422	1.00	.493	.464
Blood alkaline phosphatase increased	0(0.0%)	0(0.0%)	0(0.0%)	1(0.8%)	1(0.2%)	1.00			1.00

(Continued)

Table HMDW.17. Discontinuation-Emergent Adverse Events
Drug-Tapering Phase Study F1J-MC-HMDW

Event	1) PLACEBO (N=108) n (%)	2) DLX20 (N=64) n (%)	3) DLX60120 (N=111) n (%)	4) VEN75225 (N=125) n (%)	Total (N=408) n (%)	p-Value* Overall	1 vs. 2	1 vs. 3	1 vs. 4
Blood creatine phosphokinase increased	0(0.0%)	0(0.0%)	0(0.0%)	1(0.8%)	1(0.2%)	1.00			1.00
Blood glucose increased	1(0.9%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.2%)	.422	1.00	.493	.464
Cough	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	1(0.2%)	.157	.372		
Dissociation	0(0.0%)	0(0.0%)	1(0.9%)	0(0.0%)	1(0.2%)	.694		1.00	
Dysmenorrhoea	1(0.9%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.2%)	.422	1.00	.493	.464
Dyspepsia	0(0.0%)	0(0.0%)	0(0.0%)	1(0.8%)	1(0.2%)	1.00			1.00
Dysphoria	0(0.0%)	0(0.0%)	0(0.0%)	1(0.8%)	1(0.2%)	1.00			1.00
Dysuria	1(0.9%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.2%)	.422	1.00	.493	.464
Eye pain	1(0.9%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.2%)	.422	1.00	.493	.464
Flatulence	0(0.0%)	0(0.0%)	1(0.9%)	0(0.0%)	1(0.2%)	.694		1.00	
Gamma-glutamyltransferase increased	0(0.0%)	0(0.0%)	0(0.0%)	1(0.8%)	1(0.2%)	1.00			1.00
Gastritis	0(0.0%)	0(0.0%)	1(0.9%)	0(0.0%)	1(0.2%)	.694		1.00	
Increased appetite	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	1(0.2%)	.157	.372		
Influenza like illness	0(0.0%)	0(0.0%)	1(0.9%)	0(0.0%)	1(0.2%)	.694		1.00	
Initial insomnia	0(0.0%)	0(0.0%)	0(0.0%)	1(0.8%)	1(0.2%)	1.00			1.00
Lethargy	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	1(0.2%)	.157	.372		
Microcytic anaemia	0(0.0%)	0(0.0%)	0(0.0%)	1(0.8%)	1(0.2%)	1.00			1.00
Migraine	0(0.0%)	0(0.0%)	0(0.0%)	1(0.8%)	1(0.2%)	1.00			1.00
Myalgia	0(0.0%)	0(0.0%)	0(0.0%)	1(0.8%)	1(0.2%)	1.00			1.00
Nasopharyngitis	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	1(0.2%)	.157	.372		
Neck pain	0(0.0%)	0(0.0%)	0(0.0%)	1(0.8%)	1(0.2%)	1.00			1.00
Orthostatic hypotension	0(0.0%)	0(0.0%)	0(0.0%)	1(0.8%)	1(0.2%)	1.00			1.00
Pain in extremity	1(0.9%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.2%)	.422	1.00	.493	.464
Paraesthesia	1(0.9%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.2%)	.422	1.00	.493	.464
Periorbital haematoma	0(0.0%)	0(0.0%)	0(0.0%)	1(0.8%)	1(0.2%)	1.00			1.00
Pneumonia	0(0.0%)	0(0.0%)	0(0.0%)	1(0.8%)	1(0.2%)	1.00			1.00
Poor quality sleep	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	1(0.2%)	.157	.372		
Pruritus	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	1(0.2%)	.157	.372		
Rhinitis	1(0.9%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.2%)	.422	1.00	.493	.464
Sinusitis	1(0.9%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.2%)	.422	1.00	.493	.464
Sleep disorder	0(0.0%)	0(0.0%)	1(0.9%)	0(0.0%)	1(0.2%)	.694		1.00	
Somnolence	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	1(0.2%)	.157	.372		

(Continued)

Table HMDW.17. Discontinuation-Emergent Adverse Events
Drug-Tapering Phase Study F1J-MC-HMDW (Concluded)

Event	1) PLACEBO (N=108) n (%)	2) DLX20 (N=64) n (%)	3) DLX60120 (N=111) n (%)	4) VEN75225 (N=125) n (%)	Total (N=408) n (%)	p-Value* Overall	1 vs. 2	1 vs. 3	1 vs. 4
Stomach discomfort	0(0.0%)	0(0.0%)	1(0.9%)	0(0.0%)	1(0.2%)	.694		1.00	
Tearfulness	1(0.9%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.2%)	.422	1.00	.493	.464
Therapeutic response unexpected	0(0.0%)	0(0.0%)	0(0.0%)	1(0.8%)	1(0.2%)	1.00			1.00
Torticollis	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	1(0.2%)	.157	.372		
Upper respiratory tract infection	1(0.9%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.2%)	.422	1.00	.493	.464
Urinary tract infection	0(0.0%)	0(0.0%)	1(0.9%)	0(0.0%)	1(0.2%)	.694		1.00	
Vaginitis bacterial	1(0.9%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.2%)	.422	1.00	.493	.464
Vertigo	0(0.0%)	0(0.0%)	1(0.9%)	0(0.0%)	1(0.2%)	.694		1.00	

Abbreviations: DLX20 = duloxetine 20 mg, DLX60120 = duloxetine 60-120 mg, N = number of patients entering drug-tapering phase, n = number of patients with treatment-emergent adverse event, VEN = venlafaxine-extended release.

*Frequencies are analyzed using a Fisher's exact test.

Treatment-Emergent Adverse Events

Table HMDW.18 contains statistically significant and ≥5% of patients with treatment-emergent adverse events (TEAE). There were no statistically significant differences between placebo treated vs duloxetine 60 to 120 mg-treated patients, duloxetine 20 mg-treated and venlafaxine 75 to 225 mg-treated patients vs placebo in the proportion of patients reporting at least 1 TEAE.

There were statistically significant differences between patients treated with duloxetine 60 to 120 mg and placebo for the following TEAEs: nausea, headache, fatigue, hyperhidrosis, somnolence, dry mouth, constipation, erectile dysfunction, decreased libido, decreased appetite, delayed ejaculation, and blurred vision.

There were statistically significant differences between patients treated with venlafaxine 75 to 225 mg and placebo for the following TEAEs: dry mouth, hyperhidrosis, decreased libido, and influenza.

Statistically significant difference in rates of TEAEs between duloxetine 20 mg and placebo (with patients in the duloxetine 20 mg treatment group experiencing the higher percentage of events) occurred for the following AEs: nausea and blurred vision.

Table HMDW.18. Treatment-Emergent Adverse Events in Statistically Significant and ≥5% of the Patients

Preferred Term	Placebo (1) N = 170 n (%)	DLX 20 mg (2) N = 84 n (%)	DLX 60-120 mg (3) N = 158 n (%)	VEN 75-225 mg (4) N = 169 n (%)	Pair-wise Comparison p-value*		
					1 vs 2	1 vs 3	1 vs 4
Patient with ≥1 TEAE	102 (60)	56 (66.7)	100 (63.3)	115 (68)	.337	.571	.141
Nausea	17 (10)	16 (19.0)	35 (22.2)	29 (17.2)	.049	.004	.058
Headache	32 (18.8)	12 (14.3)	24 (15.2)	24 (14.2)	.481	.463	.306
Dizziness	12 (7.1)	7 (8.3)	19 (12.0)	20 (11.8)	.801	.135	.142
Dry mouth	5 (2.9)	6 (7.1)	21 (13.3)	15 (8.9)	.186	≤.001	.022
Constipation	7 (4.1)	6 (7.1)	18 (11.4)	13 (7.7)	.366	.020	.175
Fatigue	5 (2.9)	6 (7.1)	14 (8.9)	11 (6.5)	.186	.031	.133
Insomnia	10 (5.9)	4 (4.8)	10 (6.3)	12 (7.1)	1.00	1.00	.667
Diarrhea	8 (4.7)	5 (6.0)	14 (8.9)	8 (4.7)	.764	.184	1.00
Hyperhidrosis	2 (1.2)	4 (4.8)	13 (8.2)	9 (5.3)	.095	.003	.035
Somnolence	3 (1.8)	3 (3.6)	13 (8.2)	8 (4.7)	.400	.009	.139
Vomiting	6 (3.5)	2 (2.4)	8 (5.1)	8 (4.7)	1.00	.589	.599
Erectile dysfunction	1 (0.6)	1 (1.2)	7 (4.4)	4 (2.4)	.553	.031	.215
Decreased libido	0	0	6 (3.8)	7 (4.1)	NA	.012	.007
Decreased appetite	0	2 (2.4)	6 (3.8)	3 (1.8)	.108	.012	.123
Delayed ejaculation	0	1 (1.2)	5 (3.2)	4 (2.4)	.331	.025	.061
Blurred vision	0	3 (3.6)	5 (3.2)	1 (0.6)	.035	.025	.499
Influenza	8 (4.7)	2 (2.4)	2 (1.3)	1 (0.6)	.504	.106	.037

Abbreviations: DLX = duloxetine, N = number of randomized patients, n = number of patients with treatment-emergent adverse event, NA = not applicable, TEAE = treatment-emergent adverse event, VEN = venlafaxine-extended release.

*Frequencies are analyzed using a Fisher's exact test.

Deaths

No deaths were reported in this study.

Other Serious Adverse Events

Table HMDW.19 presents serious adverse events (SAEs) that occurred during the acute therapy phase. A total of 6 SAEs were reported for 2 placebo-treated patients and 1 venlafaxine 75 to 225 mg-treated patient. There were no SAEs reported in the duloxetine 60 to 120 mg-treatment and duloxetine 20 mg-treated group. No statistically significant differences among treatment groups were observed.

Table HMDW.19. Serious Adverse Events by Decreasing Frequency
All Randomized Patients
Acute Therapy Phase – Study F1J-MC-HMDW

Preferred Term	Placebo (N = 170) n (%) 1	DLX 20 mg (N =84) n (%) 2	DLX 60-120 mg (N = 158) n (%) 3	VEN 75-225 mg (N = 169) n (%) 4	Pair-wise Comparison p-value*		
					1 vs 2	1 vs 3	1 vs 4
Patient with ≥1 SAE	2 (1.2)	0	0	1	1.00	.499	1.00
Agitation	1 (0.6)	0	0	0	1.00	1.00	1.00
Ideas of reference	1 (0.6)	0	0	0	1.00	1.00	1.00
Insomnia	1 (0.6)	0	0	0	1.00	1.00	1.00
Panic attack	1 (0.6)	0	0	0	1.00	1.00	1.00
Paranoia	1 (0.6)	0	0	0	1.00	1.00	1.00
Traumatic brain injury	0	0	0	1 (0.6)			.499

Abbreviations: DLX = duloxetine, N = number of randomized patients, n = number of patients with a serious adverse event, SAE = serious adverse event, VEN = venlafaxine-extended release.
*Frequencies are analyzed using a Fisher's exact test.

Laboratory Values – Acute Therapy Phase for Study F1J-MC-HMDW

Analysis of Chemistry Analytes

Table HMDW.20 summarizes the analysis of statistically significant mean change from baseline to endpoint for chemistry analytes during the acute therapy phase.

Duloxetine 20 mg-treated patients experienced a statistically significant, mean decrease in alanine transaminase/serum glutamic pyruvic transaminase (ALT/SGPT: p=.026), gamma glutamyl transaminase (GGT: p=.012), and uric acid (p=.017) compared with placebo.

Patients treated with duloxetine 60 to 120 mg experienced a statistically significant mean decrease in uric acid (p≤.001) and chloride (p=.017) compared with placebo.

There was a statistically significant mean increase in mean cell hemoglobin (p=.030) and mean platelet count (p=.031) for duloxetine 60 to 120 mg-treated patients compared with placebo-treated patients.

Venlafaxine 75 to 225 mg-treated patients experienced a statistically significant, mean increase in alkaline phosphatase (ALKPH: p≤.001) and GGT (p=.046) and statistically significant, mean decrease in direct bilirubin (p=.002), total bilirubin (p=.004), chloride (p=.032), inorganic phosphorus (p≤.001), and uric acid (p≤.001) compared with placebo.

Table HMDW.20. Summary of Laboratory Values with Statistically Significant Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase – Study F1J-MC-HMDW

Laboratory Tests (units)	N	Baseline Mean (SD)	Change to Endpoint Mean (SD)	p-value* vs Placebo
Chloride (milli mole/liter)				
Placebo	140	103.964 (2.514)	0.093 (2.332)	
DLX 20 mg	72	104.028 (2.373)	-0.431 (2.232)	.462
DLX 60-120 mg	130	104.038 (2.085)	0.762 (2.299)	.017
VEN 75-225 mg	136	104.154 (2.237)	-0.632 (2.587)	.032
Uric Acid (micromole/liter)				
Placebo	140	303.236 (85.315)	2.807 (48.854)	
DLX 20 mg	72	333.042 (86.992)	-11.347 (45.383)	.017
DLX 60-120 mg	130	313.927 (91.357)	-18.265 (43.198)	≤.001
VEN 75-225 mg	136	323.816 (91.311)	-25.162 (57.358)	≤.001
Mean Cell Hemoglobin (femtoliter)				
Placebo	125	1.843 (0.121)	-0.002 (0.077)	.
DLX 20 mg	67	1.832 (0.126)	0.007 (0.070)	.039
DLX 60-120 mg	121	1.835 (0.120)	0.016 (0.091)	030
VEN 75-225 mg	119	1.858 (0.110)	0.005 (0.064)	.141
Platelet Count (billion/liter)				
Placebo	124	281.452 (68.088)	-6.153 (38.686)	.
DLX 20 mg	67	251.045 (52.126)	2.672 (36.743)	.343
DLX 60 mg-120 mg	118	269.602 (62.474)	9.449 (41.425)	031
VEN 75-225 mg	115	262.678 (55.497)	4.730 (50.781)	.344
Alkaline Phosphatase (units/liter)				
Placebo	140	72.343 (24.061)	-1.114 (12.539)	
DLX 20 mg	72	74.917 (25.247)	1.083 (9.802)	.090
DLX 60 mg-120 mg	130	75.385 (22.453)	2.308 (12.827)	.069
VEN 75-225 mg	136	72.574 (21.078)	4.265 (12.570)	≤.001
Direct Bilirubin (micromole/liter)				
Placebo	137	2.029 (0.9701)	-0.095 (0.785)	
DLX 20 mg	71	2.155 (1.104)	-0.113 (0.949)	.938
DLX 60 mg-120 mg	128	2.109 (0.872)	-0.148 (0.764)	.429
VEN 75-225 mg	131	2.313 (1.222)	-0.412 (1.066)	.002
Total Bilirubin (micromole/liter)				
Placebo	141	8.762 (4.997)	-0.191 (3.680)	
DLX 20 mg	72	9.153 (4.674)	-0.396 (3.246)	.974
DLX 60 mg-120 mg	130	9.162 (4.123)	-0.308(3.107)	.646
VEN 75-225 mg	135	9.993 (5.564)	-1.581(5.025)	.004
Gamma Glutamyl Transferase (units/liter)				
Placebo	140	27.286 (26.666)	-1.429 (15.748)	
DLX 20 mg	72	37.875 (36.457)	-4.375 (22.860)	.012
DLX 60 mg-120 mg	130	30.338 (26.291)	-0.246 (22.326)	.652
VEN 75-225 mg	136	30.824 (37.698)	0.632 (17.235)	.046

(Continued)

**Table HMDW.20. Summary of Laboratory Values with Statistically Significant Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase – Study F1J-MC-HMDW (Concluded)**

Laboratory Tests (units)	N	Baseline Mean (SD)	Change to Endpoint Mean (SD)	p-value* vs Placebo
Inorganic Phosphorus (millimole/liter)				
Placebo	139	1.137 (0.165)	0.037 (0.160)	
DLX 20 mg	72	1.106 (0.180)	0.031 (0.215)	.703
DLX 60-120 mg	130	1.154 (0.176)	0.013 (0.184)	.516
VEN 75-225 mg	136	1.153 (0.155)	-0.031 (0.193)	≤.001
Alanine Transaminase/Serum Glutamic Pyruvic Transaminase (units/liter)				
Placebo	141	21.972 (11.954)	0.596 (13.384)	
DLX 20 mg	72	29.417 (27.547)	-1.819 (8.702)	.026
DLX 60 mg-120 mg	130	25.262 (16.248)	3.031 (21.543)	.870
VEN 75-225 mg	135	24.415 (15.119)	-1.333 (10.978)	.060

Abbreviations: DLX = duloxetine, N = number of patients with a baseline and at least one nonmissing postbaseline data, SD = standard deviation, VEN = venlafaxine-extended release 75 to 225 mg.
*Type III sums of squares from an analysis of variance (ANOVA) on the ranks: Model-Treatment and Investigator.

Vital Signs: Acute Therapy Phase for Study F1J-MC-HMDW

Patients treated with duloxetine 60 to 120 mg experienced a statistically significant (p=.01) mean increase in pulse rate compared with placebo-treated patients (change of 3.59 beats per minute with SE = 0.79 vs change of 0.86 beats per minute with SE = 0.76 beats per minute, respectively).

There were no other statistically significant difference observed between duloxetine 20 mg, duloxetine 60 to 120 mg, and venlafaxine 75 to 225 mg vs placebo treatment groups for systolic blood pressure, diastolic blood pressure, and weight.

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