

Summary ID# 5075

Clinical Study Summary: Study F1J-MC-HMBR

Duloxetine Hydrochloride 60 mg or 120 mg Once Daily Compared with Placebo in Patients with Generalized Anxiety Disorder

Date summary approved by Lilly: 06 April 2007

Brief Summary of Results

This was a multicenter, randomized, double-blind, placebo-controlled Phase 3 study with a single-blind placebo lead-in phase and a double-blind acute therapy phase. The primary objective of this study was to assess whether duloxetine 120 mg once daily (QD) was superior to placebo in the treatment of generalized anxiety disorder (GAD).

- The results of this study demonstrate that both duloxetine 120 mg once daily (QD) and duloxetine 60 mg QD were statistically significantly superior to placebo ($p \leq .001$) in improving symptoms of anxiety in the treatment of generalized anxiety disorder (GAD) as measured by the Hamilton Anxiety Rating Scale (HAMA) total score.
- Duloxetine-treated patients, both 60 mg QD and 120 mg QD, demonstrated statistically significant greater improvements on all but one of the secondary efficacy measures, including: HAMA psychic anxiety factor score, HAMA anxious mood item 1, HAMA tension item 2, HAMA response rates, HAMA somatic anxiety scores, and the Hospital Anxiety and Depression Scale (HADS) anxiety subscale score, as well as secondary global measures of wellness outcome, including the Clinical Global Impressions of Improvement (CGI-Improvement) and the Patient's Global Impressions of Improvement (PGI-Improvement), and the Visual Analog Scale (VAS) for pain items. There were no statistically significant differences for either duloxetine treatment groups compared with placebo for the Symptom Questionnaire-Somatic Subscale total score (SQ-SS).

- Duloxetine 120 mg QD also demonstrated statistical superiority compared with placebo in the gatekeeper analysis; mean change from baseline to endpoint on the Sheehan Disability Scale (SDS) Global Functional Impairment score ($p \leq .001$). The effect of duloxetine treatment (both treatment groups) on functional impairment also demonstrated superiority compared with placebo on the SDS items, Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF), and the EuroQol Questionnaire – 5 Day (EQ-5D) (p-values ranged from $\leq .001$ to $.007$).
- No patient deaths occurred during the acute-therapy phase and one placebo-treated patient reported a serious adverse event (SAE). The discontinuation rate due to an adverse event (AE) was statistically significantly greater with both duloxetine-treatment groups compared with placebo-treatment groups. Duloxetine-treated patients, 60 mg QD and 120 mg QD, reported treatment-emergent adverse events (TEAEs) statistically significantly more frequently than placebo-treated patients ($p = .009$ and $p < .001$, respectively). The TEAEs associated with duloxetine were generally mild to moderate in severity.
- No patient deaths occurred during drug-tapering phase and one placebo-treated patient reported an SAE. Three patients discontinued due to an AE during the drug-taper phase. There was no statistical significance among treatment groups associated with the study drug stopping method (taper compared with abrupt) during the drug-tapering phase.
- Although there were some statistically significant changes in analyte concentrations, vital signs, and electrocardiograms (ECGs) between both duloxetine treatment groups compared with placebo, none of these mean changes were of sufficient magnitude to have clinical relevance.
- In the drug-taper phase, statistically significantly more duloxetine-treated patients (both 60 mg and 120 mg in both the taper and abrupt groups) reported discontinuation-emergent adverse events (DEAEs) compared with placebo ($p = .004$ -.024). Among duloxetine treatment groups (both duloxetine 60 mg QD patients who tapered and abruptly discontinued and duloxetine 120 mg QD treated patients who tapered and abruptly) there were no statistically significant differences. No statistically significant differences between treatment groups were observed for chemistry or hematology analytes or vital signs during the drug-taper phase.

Title of Study: Duloxetine Hydrochloride 60 mg or 120 mg Once Daily Compared with Placebo in Patients with Generalized Anxiety Disorder	
Investigator(s): This multicenter study included 41 principal investigators.	
Study Center(s): This study was conducted at 41 study centers in 7 countries.	
Length of Study: 15 months Date of first patient enrolled: 06 July 2004 Date of last patient completed: 29 September 2005	Phase of Development: 3
<p>Objectives: To assess whether duloxetine 120 mg QD was superior to placebo in the treatment of GAD, during a 9-week, double-blind, acute therapy phase. Superiority was defined as statistically greater reduction on the mean change from baseline to endpoint in anxiety symptoms as measured by the HAMA total score.</p> <p>Secondary Objectives included:</p> <ul style="list-style-type: none"> To evaluate the efficacy of duloxetine 120 mg QD compared with placebo on the improvement on the SDS Global Functional Impairment score (gatekeeper objective). To assess whether duloxetine 60 mg QD was superior to placebo in the treatment of GAD as measured by the mean change from baseline to endpoint in the primary efficacy measure, the HAMA total score. To assess the efficacy of duloxetine (60 mg QD and 120 mg QD) compared with placebo as measured by response rates, defined as at least a 50% reduction from baseline to endpoint on HAMA total score. To evaluate the efficacy of duloxetine (60 mg QD and 120 mg QD) compared with placebo on the improvement of the following measures: <ul style="list-style-type: none"> HADS HAMA Psychic Factor Score and the Somatic Factor Score CGI-Improvement PGI-Improvement The Visual Analog Scale (VAS) Symptom Questionnaire-Somatic Subscale total score (SQ-SS) To compare the effects of duloxetine (60 mg QD and 120 mg QD) with the effects of placebo on patients' quality of life using the SDS impairment scores, the Q-LES-Q-SF, and the EQ-5D. To evaluate safety and tolerability of duloxetine (60 mg QD and 120 mg QD) compared with placebo using information on discontinuation rates, TEAEs, vital signs, laboratory analyses, and ECGs. To evaluate the effects of discontinuation of duloxetine treatment as compared with placebo, and to compare the method of stepwise reducing the dosage with that of stopping the drug abruptly in a 2-week, double-blind taper phase. Information collected for evaluation included discontinuation rate, discontinuation-emergent events, vital signs, and weight. 	
<p>Study Design: This was a multicenter, randomized, double-blind, placebo-controlled Phase 3 outpatient study with a single-blind placebo lead-in phase and a double-blind acute therapy phase. Following the 3- to 30-day screening period and a 5- to 9-day single-blind placebo lead-in period, eligible patients were randomly assigned at Visit 3 to receive treatment with duloxetine 60 mg QD, duloxetine 120 mg QD, or placebo in a 1:1:1 ratio. Patients completing the double-blind treatment phase (Visit 8) were eligible for the 2-week, double-blind drug-tapering phase. The study design, illustrated in Figure HMBR.1, consisted of four study periods.</p>	

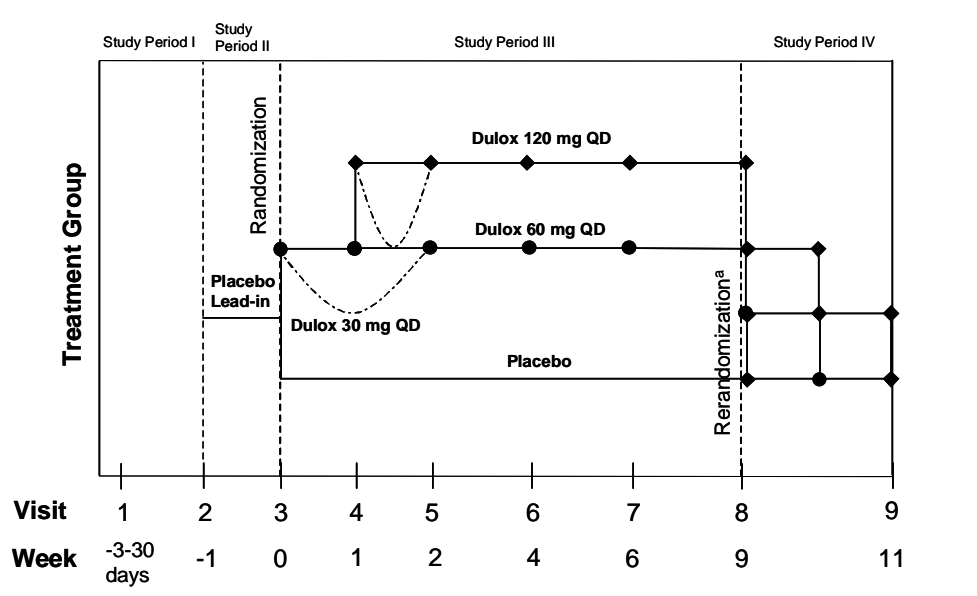
<p>Number of Patients:</p> <p>Planned: 480 patients (160 per treatment group in the double-blind treatment phase)</p> <p>Randomized/Entered: 168 duloxetine 60 mg QD, 170 duloxetine 120 mg QD, 175 placebo</p> <p>Completed: 135 duloxetine 60 mg QD, 124 duloxetine 120 mg QD, 130 placebo</p>
<p>Diagnosis and Main Criteria for Inclusion: Male or female outpatients at least 18 years of age presenting with GAD as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. Patients must have had a disease severity of at least moderate intensity as defined by a HADS anxiety subscale score of ≥ 10 and a Covi Anxiety Scale (CAS) score ≥ 9. No item in the Raskin Depression Scale (RDS) was >3 and the CAS score was greater than the RDS score. In addition, patients had a CGI-Severity score ≥ 4 at Visit 1 and Visit 2. Female patients could not be breastfeeding, must have tested negative for pregnancy at the time of enrollment, and either used an approved method of contraception during the study or were not of childbearing potential.</p>
<p>Study Drug, Dose, and Mode of Administration:</p> <p>Duloxetine 60 mg/day, given orally as 2 duloxetine 30-mg capsules plus 2 placebo capsules</p> <p>Duloxetine 120 mg/day, given orally as 4 duloxetine 30-mg capsules</p>
<p>Reference Therapy, Dose, and Mode of Administration:</p> <p>Placebo, given orally once a day as 4 capsules</p>
<p>Duration of Treatment:</p> <p>Duloxetine 60 mg Frequency: 9 weeks</p> <p>Duloxetine 120 mg Frequency: 9 weeks (duloxetine 60 mg/day plus placebo during Week 1, then duloxetine 120 mg/day during Weeks 2-9)</p> <p>Placebo Frequency: 9 weeks (plus 5-9 days in the placebo lead-in phase)</p>
<p>Variables:</p> <p><u>Efficacy:</u> The following efficacy measures were collected</p> <ul style="list-style-type: none"> • HAMA • HADS • HAMA Factors and Individual Items • CGI-Improvement Scale • PGI-Improvement Scale • VAS for Pain • SQ-SS <p><u>Safety:</u> TEAEs/SAEs; concomitant therapies; laboratory data including chemistry, hematology, and urinalysis panels; vital signs including blood pressure, pulse rate, weight, and height; and ECGs.</p> <p><u>Health Outcomes:</u> SDS, Q-LES-Q-SF, and EQ-5D</p>

Evaluation Methods:

Statistical:

The primary efficacy analysis was the comparison of duloxetine 120 mg QD with placebo in mean change from baseline to endpoint in the HAMA total score for the double-blind acute therapy phase. The treatment group differences were evaluated using analysis of covariance (ANCOVA). For the secondary gatekeeper objective of this study (SDS Global Functional Impairment score) treatment group differences were evaluated using the ANCOVA model. Other secondary efficacy variables were analyzed by the ANCOVA model (HADS Anxiety Subscale and Depression Subscale scores, HAMA Psychic Anxiety Factor Score and Somatic Anxiety Factor Score, VAS, and SQ-SS), analysis of variance (ANOVA) model (endpoint and all postbaseline data for CGI-Improvement and PGI-Improvement), or the Cochran-Mantel-Haenszel test (Response Rate). Health outcome measures (SDS, Q-LES-Q-SF, and EG-5D) were also analyzed by the ANCOVA model. Mean changes from baseline to endpoint in laboratory analytes, vital signs, weight, and ECG parameters were assessed using the ANOVA model. Treatment group differences in the incidence rates of serious adverse events were evaluated using Fisher’s exact test. The Fisher’s exact test was used for adverse events reported as reasons for discontinuation, the incidence rates of TEAEs, treatment-emergent abnormal laboratory values, and abnormal ECGs.

Unless otherwise specified, when an 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 ANCOVA model, which, in general, refers to the ANOVA model with baseline values added as a covariate. Type III sum-of-squares for the least-squares means (LSMean) was used for the statistical comparison using ANOVA or ANCOVA. Unless otherwise specified, pairwise comparisons were always performed when evaluating efficacy measures. Treatment effects were evaluated based on a two-sided significance level of 0.05, and interaction effects at 0.05



Abbreviations: Dulox = duloxetine, QD = once daily.

^a One-half of the patients in the duloxetine 60 mg QD and duloxetine 120 mg QD treatment groups started on placebo immediately following Visit 8, whereas the other half of the patients in these treatment groups tapered off duloxetine.

Figure HMBR.1. Study design.

Results:**Patient Demographics**

Table HMBR.1 summarizes patient demographics for all patients randomly assigned to treatment. The majority of patients were Caucasian and female. The mean age was 43.8 years. No statistically significant differences among treatment groups were observed in any of the patient demographic variables. In relation to psychiatric history, the mean age of patients at first diagnosis was 38.69 years.

**Table HMBR.1. Patient Demographics
All Randomly Assigned Patients
Acute Therapy Phase**

VARIABLE	PLACEBO (N=175)	DLX60QD (N=168)	DLX120QD (N=170)	TOTAL (N=513)	p-Value
Gender					
No. Patients	175	168	170	513	.269*
Female	117 (66.86)	108 (64.29)	123 (72.35)	348 (67.84)	
Male	58 (33.14)	60 (35.71)	47 (27.65)	165 (32.16)	
Age (yrs)					
No. Patients	175	168	170	513	.718**
Mean	44.12	43.11	44.10	43.78	
Median	43.92	43.43	43.87	43.79	
Standard Dev.	13.42	12.92	12.64	12.98	
Minimum	18.01	19.33	18.35	18.01	
Maximum	83.47	76.89	70.75	83.47	
Race					
No. Patients	175	168	170	513	.239*
Caucasian	173 (98.86)	163 (97.02)	169 (99.41)	505 (98.44)	
African	1 (0.57)	1 (0.60)	1 (0.59)	3 (0.58)	
Hispanic	1 (0.57)	0	0	1 (0.19)	
East Asian	0	2 (1.19)	0	2 (0.39)	
West Asian	0	2 (1.19)	0	2 (0.39)	

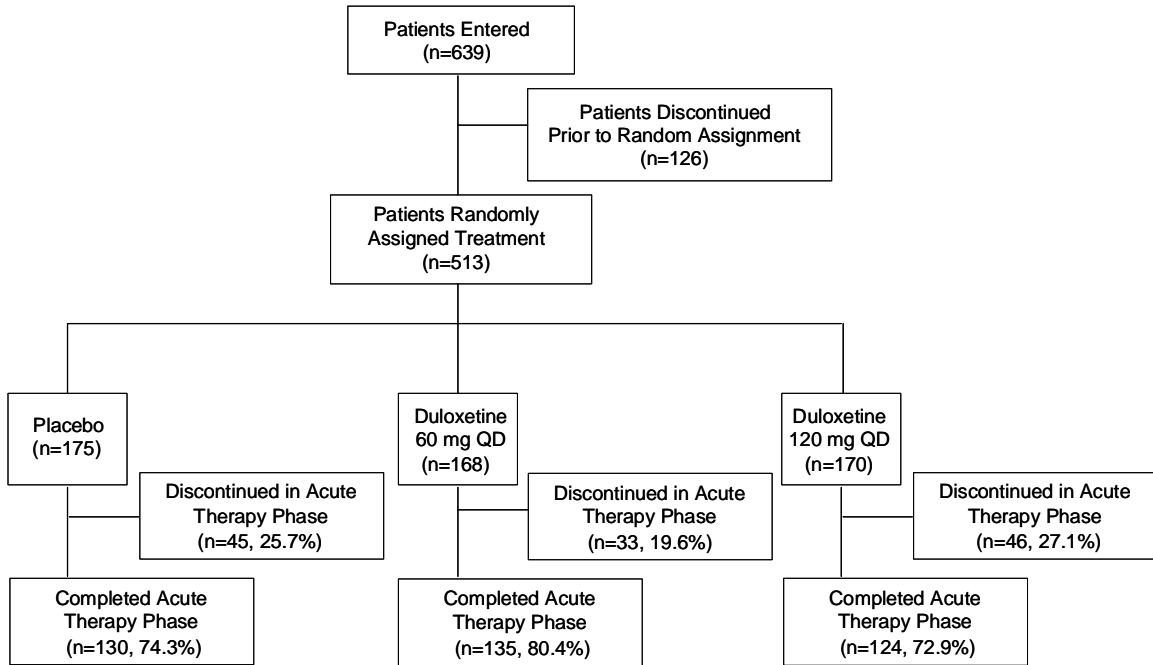
Abbreviations: DLX = duloxetine; N = number of patients; No. = number; and yrs = years.

* Frequencies are analyzed using Fisher's Exact test

** Means are analyzed using a Type III sums of squares analysis of variance (ANOVA): Model=treatment

Patient Disposition

Figure HMBR.2 summarizes patient disposition. Of the 639 patients that entered the study, a total of 513 patients were randomized to study drug and 389 completed the double-blind acute treatment phase (130 placebo-treated patients, 135 duloxetine 60 mg QD patients, and 124 duloxetine 120 mg QD patients).



Abbreviations: n = number of patients; QD = once daily.

Figure HMBR.2. Patient disposition.

Table HMBR.2 shows reasons for study discontinuation of all randomly assigned patients in the acute therapy phase for each treatment group. A statistically significantly higher percentage of duloxetine-treated patients (both 60 mg QD and 120 mg QD) compared with placebo-treated patients discontinued from the study due to AE ($p < .001$ for both), while a statistically significantly higher percentage of placebo-treated patients discontinued due to lack of efficacy ($p < .001$ and $p = .002$, respectively); there was no statistically significant difference found between duloxetine-treatment groups. More patients discontinued due to AE and lack of efficacy than for other reasons.

**Table HMBR.2. Reasons for Study Discontinuation
All Randomly Assigned Patients
Acute Therapy Phase**

Primary Reason for Discontinuation	1) PLACEBO	2) DLX60QD	3) DLX120QD	Total	p-Values*			
	(N=175) n (%)	(N=168) n (%)	(N=170) n (%)	(N=513) n (%)	Overall	1 vs. 2	1 vs. 3	2 vs. 3
DC due to ANY reason	45 (25.7)	33 (19.6)	46 (27.1)	124 (24.2)	.235	.199	.808	.123
Adverse Event	4 (2.3)	19 (11.3)	26 (15.3)	49 (9.6)	<.001	<.001	<.001	.337
Lack of Efficacy	23 (13.1)	3 (1.8)	6 (3.5)	32 (6.2)	<.001	<.001	.002	.502
Subject Decision	9 (5.1)	4 (2.4)	7 (4.1)	20 (3.9)	.430	.259	.799	.542
Lost to follow up	4 (2.3)	4 (2.4)	3 (1.8)	11 (2.1)	.932	1.00	1.00	.722
Protocol Violation	3 (1.7)	2 (1.2)	1 (0.6)	6 (1.2)	.789	1.00	.623	.622
Physician Decision	2 (1.1)	1 (0.6)	2 (1.2)	5 (1.0)	1.00	1.00	1.00	1.00
Entry Criteria Exclusion	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	.659		.493	1.00
Patients Continuing	130 (74.3)	135 (80.4)	124 (72.9)	389 (75.8)	.235	.199	.808	.123

Abbreviations: DC = discontinuation; DLX = duloxetine; and N = number of patients.

Visits 3-8

Patients continuing row refers to patients who completed the acute therapy phase (Visit 8) and entered the drug-tapering phase

*Frequencies are analyzed using Fisher's exact test

Primary Efficacy Measures

Table HMBR.3 summarizes the mean change analysis of the primary efficacy measure, HAMA total score for all randomly assigned patients. Both duloxetine 120 mg QD and duloxetine 60 mg QD were statistically significantly superior to placebo ($p \leq .001$) in improving symptoms of anxiety as measured by the HAMA total score.

Secondary Outcome Measures

Table HMBR.4 summarizes the mean change analysis (gatekeeper analysis) from baseline to endpoint on the SDS global functioning score for all randomly assigned patients in the acute therapy phase. The SDS global functioning score is the sum of the SDS scores for Item 1, work school; Item 2, social life; and on Item 3, family life home responsibilities. Compared with placebo, patients treated with either duloxetine 60 mg QD or duloxetine 120 mg QD experienced statistically significantly greater mean improvements on the SDS global functioning score ($p < .001$). Both duloxetine treatment groups demonstrated similar findings compared with the placebo treatment group on all SDS items (p -values $< .001$).

Table HMBR.5 summarizes the response rate at endpoint for all randomized patients in the acute-therapy phase. Statistically significantly greater percentages of patients treated with duloxetine 60 mg QD ($p < .001$) or duloxetine 120 mg QD ($p < .001$) met response criteria at endpoint compared with placebo-treated patients. Figure HMBR.3 presents Kaplan-Meier estimates of time to first response. Both duloxetine 60 mg QD- and duloxetine 120 mg QD-treated patients were statistically significantly more likely to achieve response earlier than placebo-treated patients.

For the HAMA psychic anxiety factor score, using mean change analyses, both duloxetine 60 mg QD and duloxetine 120 mg QD were statistically superior compared with placebo (Table HMBR.6).

For the HAMA somatic anxiety factor score, using mean change analyses, both duloxetine 60 mg QD ($p = .003$) and duloxetine 120 mg QD ($p = .001$) were statistically superior compared with placebo (Table HMBR.7).

Both duloxetine 60 mg QD and duloxetine 120 mg QD were statistically significantly superior ($p \leq .001$) compared with placebo for the mean change from baseline to endpoint analyses of the following secondary measures: the HADS Anxiety Subscale score (Table HMBR.8); the HADS Depression Subscale score (Table HMBR.9); the CGI-Improvement (Table HMBR.10); and the PGI-Improvement (Table HMBR.11). In the mean change from baseline to endpoint analyses of the VAS for pain items, both duloxetine 60 mg QD and duloxetine 120 mg QD were statistically significantly superior to placebo (p -values ranged from $p \leq .001$ to $p = .045$; Table HMBR.12).

There were no statistically significant differences for either duloxetine 60 mg QD or duloxetine 120 mg QD compared with placebo in the mean change from baseline to endpoint analysis of the SQ-SS total score (duloxetine 60 mg $p=.321$; duloxetine 120 mg $p=.053$; Table HMBR.13).

**Table HMBR.3. HAMA Total Score
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase**

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	173	25.82	7.66	26.0	7.0	44.0	17.19	9.96	17.0	0.0	53.0	-8.62	9.17	-7.0	-38.0	12.0
2) DLX60QD	165	25.05	7.18	25.0	2.0	40.0	12.32	8.79	10.0	0.0	49.0	-12.73	9.79	-13.0	-32.0	18.0
3) DLX120QD	169	25.13	7.24	26.0	6.0	44.0	12.74	9.55	11.0	0.0	44.0	-12.39	10.10	-13.0	-33.0	24.0

Main Effects (Type III SS)

Therapy	F=13.82	df=2,475	p=<.001
Investigator	F=2.06	df=28,475	p=0.001

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	-8.38	(SE= 0.67)
2) DLX60QD	-12.8	(SE= 0.68)
3) DLX120QD	-12.5	(SE= 0.67)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-4.38	Two-sided 95% CI : (-6.23 , -2.54)	t=-4.68	p=<.001
DLX120QD - PLACEBO	diff=-4.09	Two-sided 95% CI : (-5.92 , -2.26)	t=-4.39	p=<.001
DLX120QD - DLX60QD	diff= 0.29	Two-sided 95% CI : (-1.56 , 2.14)	t= 0.31	p=0.757

Abbreviations: DLX = duloxetine; Max = maximum; Min = minimum; N = number of patients; and SD = standard deviation.
Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.4. Sheehan Disability Scale
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase**

SDS GLOBAL SCORE

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	163	15.05	7.29	16.0	0.0	30.0	11.39	8.12	11.0	0.0	30.0	-3.66	7.49	-3.0	-26.0	13.0
2) DLX60QD	156	15.26	7.40	16.0	0.0	30.0	7.38	6.79	6.0	0.0	27.0	-7.88	8.50	-8.3	-30.0	27.0
3) DLX120QD	160	14.97	7.51	16.0	0.0	30.0	8.08	8.27	5.5	0.0	30.0	-6.89	8.86	-6.0	-25.0	23.0

Main Effects (Type III SS)

Therapy	F=14.01	df=2,447	p=<.001
Investigator	F=1.37	df=28,447	p=0.101

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	-3.83	(SE= 0.56)
2) DLX60QD	-7.76	(SE= 0.58)
3) DLX120QD	-7.04	(SE= 0.57)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-3.92	Two-sided 95% CI : (-5.48 , -2.36)	t=-4.95	p=<.001
DLX120QD - PLACEBO	diff=-3.20	Two-sided 95% CI : (-4.75 , -1.66)	t=-4.07	p=<.001
DLX120QD - DLX60QD	diff= 0.72	Two-sided 95% CI : (-0.85 , 2.28)	t= 0.90	p=0.367

Abbreviations: DLX = duloxetine; Max = maximum; Min = minimum; N = number of patients; and SD = standard deviation.
Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.
Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.4. Sheehan Disability Scale
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Continued)**

SDS ITEM 1: WORK SCHOOL

	Baseline						Endpoint						Change					
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max		
1) PLACEBO	126	4.94	2.65	5.0	0.0	10.0	3.86	2.92	4.0	0.0	10.0	-1.08	2.59	-1.0	-9.0	5.0		
2) DLX60QD	126	4.94	2.92	5.0	0.0	10.0	2.32	2.27	2.0	0.0	9.0	-2.62	3.22	-3.0	-10.0	7.0		
3) DLX120QD	130	4.99	2.88	5.0	0.0	10.0	2.65	2.94	2.0	0.0	10.0	-2.35	3.19	-2.0	-8.0	7.0		

Main Effects (Type III SS)

	F	df	p
Therapy	12.58	2, 350	<.001
Investigator	1.11	28, 350	0.322

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	-1.15	(SE= 0.23)
2) DLX60QD	-2.64	(SE= 0.23)
3) DLX120QD	-2.39	(SE= 0.22)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-1.48	Two-sided 95% CI : (-2.11 , -0.86)	t=-4.67	p=<.001
DLX120QD - PLACEBO	diff=-1.23	Two-sided 95% CI : (-1.85 , -0.62)	t=-3.94	p=<.001
DLX120QD - DLX60QD	diff= 0.25	Two-sided 95% CI : (-0.37 , 0.86)	t= 0.79	p=0.429

Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.4. Sheehan Disability Scale
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Continued)**

SDS ITEM 2: SOCIAL LIFE

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	163	5.07	2.73	5.0	0.0	10.0	3.86	2.83	3.0	0.0	10.0	-1.21	2.88	-1.0	-9.0	6.0
2) DLX60QD	156	5.26	2.74	5.5	0.0	10.0	2.61	2.54	2.0	0.0	10.0	-2.65	3.23	-3.0	-10.0	10.0
3) DLX120QD	160	5.06	2.80	5.0	0.0	10.0	2.71	2.89	2.0	0.0	10.0	-2.35	3.25	-2.0	-10.0	8.0

Main Effects (Type III SS)

	F	df	p	Raw Data
Therapy	11.44	2,447	<.001	
Investigator	1.30	28,447	0.140	

Least Squares Means for Change from Baseline

1) PLACEBO	-1.29	(SE= 0.20)
2) DLX60QD	-2.54	(SE= 0.21)
3) DLX120QD	-2.40	(SE= 0.21)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-1.25	Two-sided 95% CI : (-1.81 , -0.68)	t=-4.34	p=<.001
DLX120QD - PLACEBO	diff=-1.11	Two-sided 95% CI : (-1.67 , -0.55)	t=-3.89	p=<.001
DLX120QD - DLX60QD	diff= 0.14	Two-sided 95% CI : (-0.43 , 0.71)	t= 0.48	p=0.631

Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.4. Sheehan Disability Scale
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Concluded)**

SDS ITEM 3: FAMILY LIFE HOME RESPONSIBILITIES

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	163	4.96	2.72	5.0	0.0	10.0	3.79	2.85	4.0	0.0	10.0	-1.18	2.95	-1.0	-9.0	6.0
2) DLX60QD	156	4.92	2.62	5.0	0.0	10.0	2.34	2.39	2.0	0.0	10.0	-2.58	2.97	-3.0	-10.0	10.0
3) DLX120QD	160	4.97	2.68	6.0	0.0	10.0	2.66	2.78	2.0	0.0	10.0	-2.31	3.19	-2.0	-8.0	10.0

Main Effects (Type III SS)

	F	df	p
Therapy	13.75	2,447	<.001
Investigator	1.45	28,447	0.066

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	-1.21	(SE= 0.20)
2) DLX60QD	-2.58	(SE= 0.20)
3) DLX120QD	-2.33	(SE= 0.20)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-1.37	Two-sided 95% CI : (-1.91 , -0.82)	t=-4.89	p=<.001
DLX120QD - PLACEBO	diff=-1.12	Two-sided 95% CI : (-1.66 , -0.58)	t=-4.04	p=<.001
DLX120QD - DLX60QD	diff= 0.25	Two-sided 95% CI : (-0.30 , 0.80)	t= 0.88	p=0.380

Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.5. Response Rate at Endpoint
All Randomized Patients
Acute Therapy Phase**

Therapy	N	Responders n (%)	----- p-Values* -----		
			Overall	---- Pairwise ----	
				DLX60QD	DLX120QD
PLACEBO	173	53 (31%)	<.001	<.001	<.001
DLX60QD	165	95 (58%)			.729
DLX120QD	169	94 (56%)			

Abbreviations: DLX = duloxetine and N = number of patients.

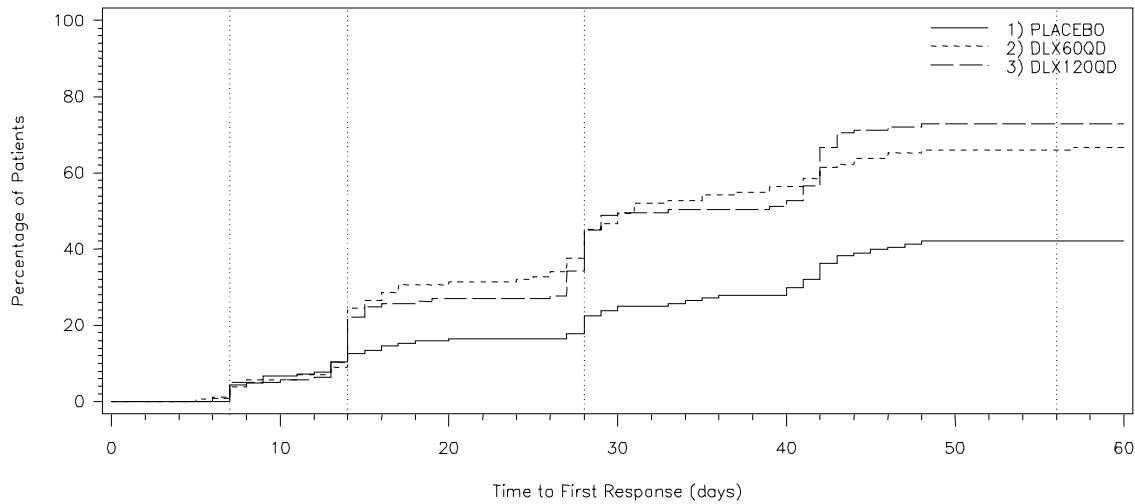
Response is defined as a 50% or greater reduction from baseline in HAMA total score.

*Frequencies are analyzed using CMH test stratified by investigator.

PRODUCTION DATA – PRODUCTION MODE

Kaplan–Meier Plot of Time to First Response
 All Randomized Patients
 F1J–MC–HMBR, Acute Therapy Phase
 Percentage(SE,n at risk) at Selected Times(t) in Days

TRTSORT	#Pts.	#Evs.	t=7	t=14	t=28	t=56
1	169	73	4.2(1.5, 158)	12.7(2.6, 139)	22.4(3.3, 116)	42.0(4.1, 71)
2	164	107	3.7(1.5, 149)	24.5(3.5, 111)	45.2(4.1, 79)	65.9(4.0, 41)
3	165	110	5.0(1.7, 151)	22.2(3.4, 115)	45.0(4.1, 72)	72.8(3.9, 35)



LOGRANK TEST Overall: $p < .0001$ Pairwise: 1vs2 $p < .0001$, 1vs3 $p < .0001$, 2vs3 $p = .5537$
 STRATIFIED LOGRANK TEST Overall: $p < .0001$ Pairwise: 1vs2 $p < .0001$, 1vs3 $p < .0001$, 2vs3 $p = .5339$

Response is defined as a 50% or greater reduction from baseline in HAMA total score

Figure HMBR.3. Kaplan-Meier plot of time to first response for all randomized patients in the acute therapy phase.

**Table HMBR.6. HAMA Psychic Anxiety Factor Score
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase**

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	173	14.17	4.00	14.0	2.0	23.0	9.66	5.64	10.0	0.0	26.0	-4.51	5.19	-4.0	-19.0	7.0
2) DLX60QD	165	13.96	3.65	14.0	2.0	22.0	6.47	4.89	5.0	0.0	23.0	-7.50	5.42	-8.0	-20.0	7.0
3) DLX120QD	169	14.06	3.77	14.0	3.0	24.0	6.94	5.64	5.0	0.0	23.0	-7.12	5.79	-8.0	-20.0	16.0

Main Effects (Type III SS)

	F	df	p
Therapy	18.74	2,475	<.001
Investigator	1.97	28,475	0.002

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	-4.53	(SE= 0.39)
2) DLX60QD	-7.57	(SE= 0.40)
3) DLX120QD	-7.15	(SE= 0.39)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-3.04	Two-sided 95% CI : (-4.11 , -1.98)	t=-5.61	p=<.001
DLX120QD - PLACEBO	diff=-2.63	Two-sided 95% CI : (-3.69 , -1.57)	t=-4.89	p=<.001
DLX120QD - DLX60QD	diff= 0.41	Two-sided 95% CI : (-0.66 , 1.48)	t= 0.76	p=0.449

Abbreviations: DLX = duloxetine; Max = maximum; Min = minimum; N = number of patients; and SD = standard deviation.

Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.7. HAMA Somatic Anxiety Factor Score
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase**

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	173	11.64	4.52	11.0	1.0	23.0	7.53	5.06	7.0	0.0	27.0	-4.12	4.78	-4.0	-22.0	7.0
2) DLX60QD	165	11.09	4.54	11.0	0.0	24.0	5.85	4.78	5.0	0.0	26.0	-5.24	5.24	-5.0	-18.0	11.0
3) DLX120QD	169	11.07	4.41	11.0	0.0	22.0	5.80	4.48	5.0	0.0	23.0	-5.27	5.13	-5.0	-18.0	15.0

Main Effects (Type III SS)

	F	df	p
Therapy	6.61	2,475	0.001
Investigator	2.20	28,475	<.001

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	-3.82	(SE= 0.33)
2) DLX60QD	-5.19	(SE= 0.34)
3) DLX120QD	-5.33	(SE= 0.33)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-1.37	Two-sided 95% CI : (-2.28 , -0.47)	t=-2.97	p=0.003
DLX120QD - PLACEBO	diff=-1.51	Two-sided 95% CI : (-2.41 , -0.61)	t=-3.28	p=0.001
DLX120QD - DLX60QD	diff=-0.13	Two-sided 95% CI : (-1.05 , 0.78)	t=-0.29	p=0.772

Abbreviations: DLX = duloxetine; Max = maximum; Min = minimum; N = number of patients; and SD = standard deviation.

Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.8. HADS Anxiety Subscale Score
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase**

HADS Anxiety Subscale Score

	Baseline						Endpoint						Change			
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	164	13.23	3.95	14.0	1.0	21.0	9.85	4.65	10.0	0.0	21.0	-3.38	4.10	-3.0	-15.0	4.0
2) DLX60QD	160	13.04	3.74	13.0	0.0	21.0	7.28	4.33	7.0	0.0	20.0	-5.76	4.67	-5.0	-16.0	6.0
3) DLX120QD	163	12.75	3.88	13.0	2.0	21.0	7.17	4.38	6.0	0.0	21.0	-5.58	4.72	-5.0	-21.0	9.0

Main Effects (Type III SS)

	F	df	p
Therapy	20.37	2,455	<.001
Investigator	2.40	28,455	<.001

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	-3.42	(SE= 0.31)
2) DLX60QD	-5.80	(SE= 0.31)
3) DLX120QD	-5.82	(SE= 0.31)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-2.39	Two-sided 95% CI : (-3.24 , -1.53)	t=-5.49	p=<.001
DLX120QD - PLACEBO	diff=-2.40	Two-sided 95% CI : (-3.25 , -1.55)	t=-5.55	p=<.001
DLX120QD - DLX60QD	diff=-0.01	Two-sided 95% CI : (-0.87 , 0.84)	t=-0.03	p=0.973

Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.9. HADS Depression Subscale Score
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase**

HADS Depression Subscale Score

	Baseline						Endpoint						Change					
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max		
1) PLACEBO	164	8.30	3.84	8.0	0.0	20.0	6.64	4.08	6.0	0.0	18.0	-1.66	3.88	-1.0	-13.0	15.0		
2) DLX60QD	160	8.37	3.78	8.0	1.0	21.0	4.83	3.72	4.0	0.0	17.0	-3.54	4.75	-4.0	-19.0	12.0		
3) DLX120QD	163	8.12	3.79	8.0	0.0	17.0	4.93	4.10	4.0	0.0	19.0	-3.19	4.31	-3.0	-14.0	15.0		

Main Effects (Type III SS)

	F	df	p
Therapy	11.75	2,455	<.001
Investigator	2.46	28,455	<.001

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	-1.75	(SE= 0.28)
2) DLX60QD	-3.47	(SE= 0.29)
3) DLX120QD	-3.32	(SE= 0.28)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-1.72	Two-sided 95% CI : (-2.49 , -0.94)	t=-4.36	p=<.001
DLX120QD - PLACEBO	diff=-1.57	Two-sided 95% CI : (-2.34 , -0.80)	t=-4.00	p=<.001
DLX120QD - DLX60QD	diff= 0.15	Two-sided 95% CI : (-0.63 , 0.92)	t= 0.37	p=0.712

Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.10. CGI-Improvement
Mean Score at Endpoint
All Randomized Patients
Acute Therapy Phase**

Clinical Global Impressions - Improvement Score

	Endpoint					
	N	Mean	SD	Median	Min	Max
1) PLACEBO	174	2.97	1.20	3.0	1.0	6.0
2) DLX60QD	165	2.33	1.21	2.0	1.0	6.0
3) DLX120QD	170	2.39	1.34	2.0	1.0	7.0

Main Effects (Type III SS)

	F	df	Raw Data	p
Therapy	13.00	2,478		<.001
Investigator	1.27	28,478		0.163

Least Squares Means for Endpoint

1) PLACEBO	2.94	(SE= 0.10)
2) DLX60QD	2.33	(SE= 0.10)
3) DLX120QD	2.38	(SE= 0.10)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-0.62	Two-sided 95% CI : (-0.88 , -0.35)	t=-4.56	p=<.001
DLX120QD - PLACEBO	diff=-0.57	Two-sided 95% CI : (-0.83 , -0.30)	t=-4.23	p=<.001
DLX120QD - DLX60QD	diff= 0.05	Two-sided 95% CI : (-0.22 , 0.32)	t= 0.36	p=0.720

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

Note: N=Number of patients with at least one non-missing post-baseline data.

**Table HMBR.11. PGI-Improvement
Mean Score at Endpoint
All Randomized Patients
Acute Therapy Phase**

Patient Global Impressions - Improvement Score

	Endpoint					
	N	Mean	SD	Median	Min	Max
1) PLACEBO	173	3.18	1.36	3.0	1.0	7.0
2) DLX60QD	165	2.56	1.43	2.0	1.0	7.0
3) DLX120QD	170	2.53	1.50	2.0	1.0	7.0

Main Effects (Type III SS)

	F	df	Raw Data	p
Therapy	10.95	2,477		<.001
Investigator	1.57	28,477		0.034

Least Squares Means for Endpoint

1) PLACEBO	3.17	(SE= 0.11)
2) DLX60QD	2.58	(SE= 0.11)
3) DLX120QD	2.53	(SE= 0.11)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-0.59	Two-sided 95% CI : (-0.89 , -0.29)	t=-3.82	p=<.001
DLX120QD - PLACEBO	diff=-0.65	Two-sided 95% CI : (-0.95 , -0.35)	t=-4.23	p=<.001
DLX120QD - DLX60QD	diff=-0.06	Two-sided 95% CI : (-0.36 , 0.25)	t=-0.38	p=0.707

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

Note: N=Number of patients with at least one non-missing post-baseline data.

**Table HMBR.12. VAS for Pain
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase**

VAS QUESTION 1: OVERALL PAIN

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	157	34.29	25.76	29.0	0.0	100.0	27.48	26.27	19.0	0.0	100.0	-6.81	26.44	-4.0	-78.0	87.0
2) DLX60QD	148	34.32	25.96	30.0	0.0	100.0	18.49	22.08	10.0	0.0	100.0	-15.83	24.25	-13.0	-82.0	68.0
3) DLX120QD	156	30.31	26.15	22.0	0.0	100.0	19.68	25.09	11.0	0.0	99.0	-10.63	25.93	-7.5	-75.0	90.0

Main Effects (Type III SS)

	F	df	p
Therapy	6.16	2,429	0.002
Investigator	1.29	28,429	0.149

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	-5.54	(SE= 1.76)
2) DLX60QD	-13.9	(SE= 1.80)
3) DLX120QD	-11.2	(SE= 1.74)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-8.39	Two-sided 95% CI : (-13.2 , -3.58)	t=-3.43	p=<.001
DLX120QD - PLACEBO	diff=-5.70	Two-sided 95% CI : (-10.5 , -0.93)	t=-2.35	p=0.019
DLX120QD - DLX60QD	diff= 2.69	Two-sided 95% CI : (-2.14 , 7.52)	t= 1.09	p=0.274

Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.12. VAS for Pain
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Continued)**

VAS QUESTION 2: HEADACHES

	Baseline						Endpoint						Change					
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max		
1) PLACEBO	157	22.61	24.85	13.0	0.0	89.0	21.08	26.57	10.0	0.0	100.0	-1.53	31.19	0.0	-89.0	100.0		
2) DLX60QD	148	23.72	25.17	16.0	0.0	95.0	15.45	22.62	5.0	0.0	95.0	-8.28	25.36	-2.0	-94.0	83.0		
3) DLX120QD	156	25.89	27.45	16.0	0.0	100.0	14.68	21.11	3.5	0.0	95.0	-11.21	29.79	-3.0	-100.0	73.0		

Main Effects (Type III SS)

	F	df	p
Therapy	3.86	2,429	0.022
Investigator	1.28	28,429	0.159

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	-2.98	(SE= 1.84)
2) DLX60QD	-8.12	(SE= 1.88)
3) DLX120QD	-9.71	(SE= 1.82)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-5.13	Two-sided 95% CI : (-10.2 , -0.11)	t=-2.01	p=0.045
DLX120QD - PLACEBO	diff=-6.72	Two-sided 95% CI : (-11.7 , -1.76)	t=-2.66	p=0.008
DLX120QD - DLX60QD	diff=-1.59	Two-sided 95% CI : (-6.62 , 3.44)	t=-0.62	p=0.535

Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.12. VAS for Pain
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Continued)**

VAS QUESTION 3: BACK PAIN

	Baseline						Endpoint						Change					
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max		
1) PLACEBO	157	24.55	25.18	17.0	0.0	100.0	21.62	24.86	12.0	0.0	98.0	-2.93	27.35	-1.0	-85.0	74.0		
2) DLX60QD	148	25.45	26.78	15.5	0.0	93.0	13.38	20.75	2.0	0.0	88.0	-12.07	20.74	-3.0	-80.0	46.0		
3) DLX120QD	156	25.08	27.48	13.5	0.0	100.0	13.22	22.80	3.0	0.0	99.0	-11.86	25.01	-6.0	-80.0	87.0		

Main Effects (Type III SS)

	F	df	p
Therapy	8.85	2,429	<.001
Investigator	1.49	28,429	0.054

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	-3.36	(SE= 1.60)
2) DLX60QD	-11.2	(SE= 1.64)
3) DLX120QD	-11.6	(SE= 1.59)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-7.89	Two-sided 95% CI : (-12.3 , -3.50)	t=-3.54	p=<.001
DLX120QD - PLACEBO	diff=-8.23	Two-sided 95% CI : (-12.6 , -3.89)	t=-3.73	p=<.001
DLX120QD - DLX60QD	diff=-0.33	Two-sided 95% CI : (-4.73 , 4.06)	t=-0.15	p=0.882

Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.12. VAS for Pain
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Continued)**

VAS QUESTION 4: SHOULDER PAIN

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	157	24.80	28.37	13.0	0.0	100.0	19.32	25.72	8.0	0.0	99.0	-5.48	26.20	0.0	-95.0	76.0
2) DLX60QD	147	22.14	27.22	8.0	0.0	98.0	11.65	20.38	1.0	0.0	91.0	-10.48	21.29	-2.0	-86.0	57.0
3) DLX120QD	156	23.06	27.48	12.0	0.0	100.0	13.19	22.97	4.0	0.0	100.0	-9.87	24.43	-2.0	-90.0	80.0

Main Effects (Type III SS)

	F	df	Raw Data	p
Therapy	4.38	2,428		0.013
Investigator	1.20	28,428		0.226

Least Squares Means for Change from Baseline

1) PLACEBO	-4.63	(SE= 1.58)
2) DLX60QD	-10.5	(SE= 1.63)
3) DLX120QD	-9.86	(SE= 1.56)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-5.89	Two-sided 95% CI : (-10.2 , -1.57)	t=-2.68	p=0.008
DLX120QD - PLACEBO	diff=-5.23	Two-sided 95% CI : (-9.50 , -0.97)	t=-2.41	p=0.016
DLX120QD - DLX60QD	diff= 0.66	Two-sided 95% CI : (-3.67 , 4.99)	t= 0.30	p=0.765

Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.12. VAS for Pain
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Continued)**

VAS QUESTION 5: INTERFERENCE WITH DAILY ACTIVITIES

	Baseline						Endpoint						Change					
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max		
1) PLACEBO	157	29.14	25.83	21.0	0.0	100.0	24.85	27.59	14.0	0.0	100.0	-4.29	27.19	-1.0	-79.0	92.0		
2) DLX60QD	147	25.10	25.20	15.0	0.0	92.0	15.63	21.92	4.0	0.0	100.0	-9.47	25.53	-4.0	-85.0	78.0		
3) DLX120QD	156	25.44	25.68	16.0	0.0	100.0	15.28	24.15	5.0	0.0	99.0	-10.16	25.00	-6.5	-74.0	93.0		

Main Effects (Type III SS)

	F	df	p
Therapy	5.59	2,428	0.004
Investigator	1.09	28,428	0.350

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	-3.00	(SE= 1.82)
2) DLX60QD	-9.86	(SE= 1.86)
3) DLX120QD	-10.5	(SE= 1.79)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-6.87	Two-sided 95% CI : (-11.8 , -1.92)	t=-2.73	p=0.007
DLX120QD - PLACEBO	diff=-7.52	Two-sided 95% CI : (-12.4 , -2.63)	t=-3.03	p=0.003
DLX120QD - DLX60QD	diff=-0.65	Two-sided 95% CI : (-5.61 , 4.30)	t=-0.26	p=0.796

Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.12. VAS for Pain
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Concluded)**

VAS QUESTION 6: PAIN WHILE AWAKE

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	157	37.62	29.63	33.0	0.0	100.0	32.01	31.22	22.0	0.0	100.0	-5.61	32.54	-1.0	-97.0	99.0
2) DLX60QD	147	35.56	28.16	30.0	0.0	100.0	20.01	24.22	10.0	0.0	97.0	-15.55	26.42	-10.0	-96.0	72.0
3) DLX120QD	156	33.26	30.27	25.0	0.0	100.0	20.01	26.69	9.0	0.0	100.0	-13.26	28.98	-6.5	-91.0	92.0

Main Effects (Type III SS)

	F	df	p	Raw Data
Therapy	8.81	2,428	<.001	
Investigator	1.38	28,428	0.097	

Least Squares Means for Change from Baseline

1) PLACEBO	-4.55	(SE= 2.01)
2) DLX60QD	-15.0	(SE= 2.06)
3) DLX120QD	-14.2	(SE= 1.98)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-10.4	Two-sided 95% CI : (-15.9 , -4.96)	t=-3.75	p=<.001
DLX120QD - PLACEBO	diff=-9.61	Two-sided 95% CI : (-15.0 , -4.19)	t=-3.49	p=<.001
DLX120QD - DLX60QD	diff= 0.83	Two-sided 95% CI : (-4.66 , 6.32)	t= 0.30	p=0.766

Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

Table HMBR.13. SQ-SS
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase

SQSS Total Score

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	166	9.47	3.30	9.0	2.0	18.0	8.16	3.32	7.5	1.0	17.0	-1.31	3.15	-1.0	-12.0	7.0
2) DLX60QD	161	9.29	3.54	9.0	2.0	17.0	7.73	3.27	7.0	2.0	17.0	-1.56	3.15	-1.5	-10.0	8.0
3) DLX120QD	165	9.28	3.30	9.0	3.0	18.0	7.50	2.85	7.0	2.0	17.0	-1.78	3.25	-2.0	-11.0	6.0

Main Effects (Type III SS)

	F	df	p
Therapy	1.88	2,460	0.154
Investigator	1.12	28,460	0.304

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	-1.30	(SE= 0.21)
2) DLX60QD	-1.60	(SE= 0.22)
3) DLX120QD	-1.87	(SE= 0.21)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-0.30	Two-sided 95% CI : (-0.88 , 0.28)	t=-1.01	p=0.312
DLX120QD - PLACEBO	diff=-0.57	Two-sided 95% CI : (-1.15 , 0.01)	t=-1.94	p=0.053
DLX120QD - DLX60QD	diff=-0.27	Two-sided 95% CI : (-0.86 , 0.31)	t=-0.91	p=0.364

Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

Safety

No patient deaths occurred during the acute-therapy phase and one placebo-treated patient reported an SAE of erysipelas. Which was considered by the principle investigator not to be related to study drug.

Of the 513 randomly assigned patients, 386 (75.2%) patients reported at least 1 TEAE. Overall, statistically significantly more duloxetine-treated patients, duloxetine 60 mg QD and duloxetine 120 mg QD, reported TEAEs than placebo-treated patients ($p=.009$ and $p<.001$, respectively). Table HMBR.14 summarizes TEAEs reported by $\geq 5\%$ of patients from any treatment group. During the acute therapy phase 49 patients discontinued due to an AE (see Table HMBR.15). Duloxetine-treated patients (both treatment groups) reported AEs as the reason for discontinuation statistically significantly more frequently compared with placebo-treated patients (p -values $<.001$), with nausea being the most common AE associated with discontinuation. The majority of the AEs were categorized as moderate or mild.

During the drug-tapering phase, no deaths occurred and one placebo-treated patient reported an SAE of myocardial infarction. In the opinion of the investigator, the myocardial infarction was possibly related to study drug.

A total of 79 patients experienced a DEAE in the drug-taper phase. Table HMBR.16 summarizes DEAEs in order of decreasing frequency. There was no statistical significance among the treatment groups in the study drug stopping methods (taper compared with abrupt) during the drug-tapering phase.

In total, 3 patients discontinued during the drug-taper phase (1 placebo, 1 duloxetine 60 mg QD-abrupt, and 1 duloxetine 120 mg QD-taper). Table HMBR.17 includes a summary of DEAEs by decreasing frequency by drug-tapering dose as reported by $\geq 0.5\%$ of patients entering the drug-tapering phase. Overall, statistically significantly more duloxetine-treated patients (both 60 mg QD and 120 mg QD in both the taper and abrupt groups) reported DEAEs compared with placebo. Among duloxetine treatment groups (both 60 mg QD and 120 mg QD in both the taper and abrupt groups) there were no statistically significant differences.

Table HMBR.14. Treatment-Emergent Adverse Events Preferred Term Experienced by ≥5% of Randomized Patients from any Treatment Group Acute Therapy Phase

Event	1) PLACEBO	2) DLX60QD	3) DLX120QD	Total	----- p-Value* -----			
	(N=175) n (%)	(N=168) n (%)	(N=170) n (%)	(N=513) n (%)	Overall	1 vs. 2	1 vs. 3	2 vs. 3
PATIENTS WITH ≥1 TREATMENT-EMERGENT EVENT	112 (64.0%)	130 (77.4%)	144 (84.7%)	386 (75.2%)	<.001	.009	<.001	.096
Nausea	13 (7.4%)	70 (41.7%)	74 (43.5%)	157 (30.6%)	<.001	<.001	<.001	.743
Headache	24 (13.7%)	28 (16.7%)	35 (20.6%)	87 (17.0%)	.237	.456	.115	.403
Dizziness	12 (6.9%)	19 (11.3%)	32 (18.8%)	63 (12.3%)	.003	.188	.001	.068
Dry mouth	6 (3.4%)	18 (10.7%)	31 (18.2%)	55 (10.7%)	<.001	.010	<.001	.063
Fatigue	3 (1.7%)	21 (12.5%)	24 (14.1%)	48 (9.4%)	<.001	<.001	<.001	.749
Hyperhidrosis	8 (4.6%)	14 (8.3%)	26 (15.3%)	48 (9.4%)	.003	.188	<.001	.063
Insomnia	6 (3.4%)	18 (10.7%)	14 (8.2%)	38 (7.4%)	.024	.010	.067	.463
Constipation	4 (2.3%)	13 (7.7%)	14 (8.2%)	31 (6.0%)	.024	.024	.015	1.00
Nasopharyngitis	18 (10.3%)	5 (3.0%)	4 (2.4%)	27 (5.3%)	.002	.009	.003	.749
Diarrhoea	5 (2.9%)	5 (3.0%)	13 (7.6%)	23 (4.5%)	.070	1.00	.054	.088
Libido decreased	2 (1.1%)	11 (6.5%)	8 (4.7%)	21 (4.1%)	.025	.010	.058	.489
Anorexia	2 (1.1%)	9 (5.4%)	8 (4.7%)	19 (3.7%)	.052	.033	.058	.809
Somnolence	2 (1.1%)	6 (3.6%)	10 (5.9%)	18 (3.5%)	.050	.167	.019	.443
Vomiting	1 (0.6%)	5 (3.0%)	11 (6.5%)	17 (3.3%)	.007	.115	.003	.199
Sedation	1 (0.6%)	6 (3.6%)	9 (5.3%)	16 (3.1%)	.023	.063	.010	.599
Back pain	9 (5.1%)	2 (1.2%)	1 (0.6%)	12 (2.3%)	.017	.062	.020	.622

MedDRA Version: 8

N=Number of randomized patients, n=Number of patients with treatment-emergent adverse event

*Frequencies are analyzed using a Fisher's exact test

**Table HMBR.15. Adverse Events Reported as Reason for Discontinuation
By Decreasing Frequency
All Randomized Patients
Acute Therapy Phase**

Event	1) PLACEBO	2) DLX60QD	3) DLX120QD	Total	----- p-Values* -----			
	(N=175) n(%)	(N=168) n(%)	(N=170) n(%)	(N=513) n(%)	Overall	1 vs. 2	1 vs. 3	2 vs. 3
Patients Discontinued for	4 (2.3)	19 (11.3)	26 (15.3)	49 (9.6)	<.001	<.001	<.001	.337
Any AE								
Nausea	0 (0.0)	10 (6.0)	4 (2.4)	14 (2.7)	<.001	<.001	.058	.109
Vomiting	0 (0.0)	1 (0.6)	4 (2.4)	5 (1.0)	.069	.490	.058	.371
Dizziness	1 (0.6)	0 (0.0)	3 (1.8)	4 (0.8)	.227	1.00	.366	.248
Headache	0 (0.0)	1 (0.6)	1 (0.6)	2 (0.4)	.550	.490	.493	1.00
Libido decreased	0 (0.0)	2 (1.2)	0 (0.0)	2 (0.4)	.107	.239		.246
Abdominal pain upper	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)	1.00	1.00	1.00	
Anorgasmia	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	.659		.493	1.00
Anxiety	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	.659		.493	1.00
Asthenia	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	.659		.493	1.00
Asthma	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	.659		.493	1.00
Blood creatine phosphokinase increased	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)	.327	.490		.497
Convulsion	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	.659		.493	1.00
Depressed mood	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)	1.00	1.00	1.00	
Diarrhoea	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	.659		.493	1.00
Fatigue	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	.659		.493	1.00
Gastric disorder	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)	.327	.490		.497
Hot flush	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	.659		.493	1.00
Hypoaesthesia	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)	.327	.490		.497
Insomnia	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	.659		.493	1.00
Loss of libido	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)	1.00	1.00	1.00	
Mental impairment	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)	.327	.490		.497
Muscle rigidity	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	.659		.493	1.00
Orthostatic hypotension	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	.659		.493	1.00
Pain in extremity	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)	.327	.490		.497
Sedation	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	.659		.493	1.00
Somnolence	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	.659		.493	1.00
Vertigo	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	.659		.493	1.00

MedDRA Version: 8

N = Number of randomized patients, n = Number of patients with event

*Frequencies are analyzed using a Fisher's exact test

**Table HMBR.16. Discontinuation-Emergent Adverse Events
Preferred Term by Decreasing Frequency by Drug-Tapering Dose
Reported by ≥0.5% of Patients Entering Drug-Tapering Phase**

Event	1) PLACEBO (N=130) n (%)	2) DLX60QD -Abrupt (N=71) n (%)	3) DLX60QD -Taper (N=64) n (%)	4) DLX120QD -Abrupt (N=58) n (%)	5) DLX120QD -Taper (N=66) n (%)	Total (N=389) n (%)
PATIENTS WITH ≥1 DISCONTINUATION-EMERGENT EVENT	21 (16.2%)	22 (31.0%)	20 (31.3%)	21 (36.2%)	16 (24.2%)	100 (25.7%)
Dizziness	2 (1.5%)	7 (9.9%)	9 (14.1%)	5 (8.6%)	7 (10.6%)	30 (7.7%)
Headache	4 (3.1%)	4 (5.6%)	4 (6.3%)	6 (10.3%)	4 (6.1%)	22 (5.7%)
Insomnia	1 (0.8%)	1 (1.4%)	3 (4.7%)	3 (5.2%)	3 (4.5%)	11 (2.8%)
Nausea	0 (0.0%)	3 (4.2%)	3 (4.7%)	2 (3.4%)	0 (0.0%)	8 (2.1%)
Irritability	1 (0.8%)	3 (4.2%)	1 (1.6%)	0 (0.0%)	2 (3.0%)	7 (1.8%)
Paraesthesia	0 (0.0%)	3 (4.2%)	1 (1.6%)	2 (3.4%)	1 (1.5%)	7 (1.8%)
Anxiety	1 (0.8%)	2 (2.8%)	2 (3.1%)	0 (0.0%)	1 (1.5%)	6 (1.5%)
Hyperhidrosis	0 (0.0%)	2 (2.8%)	1 (1.6%)	0 (0.0%)	1 (1.5%)	4 (1.0%)
Tremor	0 (0.0%)	1 (1.4%)	1 (1.6%)	1 (1.7%)	1 (1.5%)	4 (1.0%)
Vertigo	0 (0.0%)	1 (1.4%)	2 (3.1%)	0 (0.0%)	1 (1.5%)	4 (1.0%)
Nasopharyngitis	1 (0.8%)	2 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.8%)
Palpitations	0 (0.0%)	2 (2.8%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	3 (0.8%)
Abnormal dreams	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (1.5%)	2 (0.5%)
Back pain	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	2 (0.5%)
Blood creatine phosphokinase increased	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)	2 (0.5%)
Diarrhoea	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	2 (0.5%)
Feeling hot and cold	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (1.5%)	2 (0.5%)
Influenza	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	2 (0.5%)
Nightmare	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (1.7%)	0 (0.0%)	2 (0.5%)
Tachycardia	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	2 (0.5%)
Vision blurred	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	2 (0.5%)

MedDRA Version: 8

N=Number of patients entering drug-tapering phase, n=Number of patients with discontinuation-emergent adverse event

*Frequencies are analyzed using a Fisher's exact test

Table HMBR.16. Discontinuation-Emergent Adverse Events Preferred Term by Decreasing Frequency by Drug-Tapering Dose Reported by ≥0.5% of Patients Entering Drug-Tapering Phase (Continued)

Event	p-Values*						
	Overall	1 vs. 2	1 vs. 3	1 vs. 4	1 vs. 5	2 vs. 3	2 vs. 4
PATIENTS WITH ≥1 DISCONTINUATION-EMERGENT EVENT	.016	.019	.024	.004	.181	1.00	.576
Dizziness	.005	.010	<.001	.030	.007	.595	1.00
Headache	.360	.457	.443	.071	.446	1.00	.343
Insomnia	.159	1.00	.106	.088	.112	.345	.326
Nausea	.021	.043	.035	.094		1.00	1.00
Irritability	.265	.127	.552	1.00	.263	.621	.252
Paraesthesia	.091	.043	.330	.094	.337	.621	1.00
Anxiety	.474	.285	.254	1.00	1.00	1.00	.501
Hyperhidrosis	.201	.124	.330		.337	1.00	.501
Tremor	.362	.353	.330	.309	.337	1.00	1.00
Vertigo	.169	.353	.108		.337	.603	1.00
Nasopharyngitis	.405	.285	1.00	1.00	1.00	.498	.501
Palpitations	.134	.124		.309		.498	1.00
Abnormal dreams	.210			.309	.337		.450
Back pain	.264	.353		.309		1.00	1.00
Blood creatine phosphokinase increased	.878	1.00	1.00	1.00	1.00		
Diarrhoea	.543	1.00	1.00	.523	1.00		.450
Feeling hot and cold	.320		.330		.337	.474	
Influenza	.543	1.00	1.00	.523	1.00		.450
Nightmare	.159		.330	.309		.474	.450
Tachycardia	.264	.353		.309		1.00	1.00
Vision blurred	.264	.353		.309		1.00	1.00

MedDRA Version: 8

N=Number of patients entering drug-tapering phase, n=Number of patients with discontinuation-emergent adverse event

*Frequencies are analyzed using a Fisher's exact test

Table HMBR.16. Discontinuation-Emergent Adverse Events Preferred Term by Decreasing Frequency by Drug-Tapering Dose Reported by ≥0.5% of Patients Entering Drug-Tapering Phase (Concluded)

Event	----- p-Values* -----			
	2 vs. 5	3 vs. 4	3 vs. 5	4 vs. 5
PATIENTS WITH ≥1 DISCONTINUATION-EMERGENT EVENT	.447	.572	.435	.171
Dizziness	1.00	.404	.602	.769
Headache	1.00	.516	1.00	.513
Insomnia	.352	1.00	1.00	1.00
Nausea	.245	1.00	.116	.217
Irritability	1.00	1.00	1.00	.498
Paraesthesia	.620	.604	1.00	.599
Anxiety	1.00	.497	.616	1.00
Hyperhidrosis	1.00	1.00	1.00	1.00
Tremor	1.00	1.00	1.00	1.00
Vertigo	1.00	.497	.616	1.00
Nasopharyngitis	.497			
Palpitations	.497	.475		.468
Abnormal dreams	.482	.475	1.00	1.00
Back pain	1.00	.475		.468
Blood creatine phosphokinase increased	.482		1.00	1.00
Diarrhoea		.475		.468
Feeling hot and cold	.482	1.00	1.00	1.00
Influenza		.475		.468
Nightmare		1.00	.492	.468
Tachycardia	1.00	.475		.468
Vision blurred	1.00	.475		.468

MedDRA Version: 8

N=Number of patients entering drug-tapering phase, n=Number of patients with discontinuation-emergent adverse event

*Frequencies are analyzed using a Fisher's exact test

Table HMBR.17 summarizes the mean change from baseline to endpoint analysis for chemistry analytes in the acute therapy phase. Duloxetine 60 mg QD-treated patients experienced statistically significantly greater mean increases in alanine transaminase (ALT/SGPT) ($p=.032$) and creatine phosphokinase ($p=.031$) compared with placebo-treated patients. Duloxetine 120 mg QD-treated patients experienced a statistically significantly greater mean increase in alkaline phosphatase ($p=.003$), ALT/SGOT ($p=.018$), and aspartate aminotransferase (AST/SGOT) ($p=.018$) compared with placebo-treated patients. Duloxetine 120 mg QD-treated patients experienced a statistically significantly greater mean decrease in inorganic phosphorus ($p=.034$) and uric acid ($p=.008$) compared with placebo-treated patients. Duloxetine 120 mg QD-treated patients experienced a statistically significantly greater mean decrease in uric acid ($p<.001$) compared with patients treated with duloxetine 60 mg QD.

Table HMBR.18 summarizes the mean change from baseline to endpoint analysis for hematology analytes. Duloxetine 60 mg QD-treated patients experienced a statistically significantly greater mean decrease in lymphocytes compared with placebo-treated patients ($p=.007$). Duloxetine 120 mg QD-treated patients a statistically significantly greater mean increase in erythrocyte count ($p=.009$) and segmented neutrophils ($p=.033$) compared with placebo-treated patients. Duloxetine 120 mg QD-treated patients experienced a statistically significantly greater mean decrease in lymphocytes ($p=.009$) compared with placebo-treated patients.

Table HMBR.19 summarizes the mean change from baseline to endpoint analysis for vital signs and weight in acute therapy phase. Compared with placebo-treated patients, duloxetine 120 mg QD-treated patients experienced a statistically significantly greater mean increase in pulse rate ($p=.001$) and sitting diastolic blood pressure ($p=.014$). Duloxetine 120 mg QD-treated patients experienced a statistically significantly greater mean increase in pulse rate compared to patients treated with duloxetine 60 mg QD-treated patients ($p=.037$).

In the acute therapy phase, duloxetine 60 mg QD- and duloxetine 120 mg QD-treated patients experienced a statistically significantly greater mean decrease in QT interval ($p=.002$ and $p=.003$ respectively) and a statistically significantly greater mean increase in QTc Bazetts interval and heart rate compared with placebo-treated patients. Duloxetine 120 mg QD-treated patients also experienced a statistically significantly greater mean increase in QTc regression interval compared with placebo-treated patients ($p=.007$) (Table HMBR.20). No other differences in ECG parameters were statistically significant between treatment groups. Both duloxetine 60 mg QD and duloxetine 120 mg QD were statistically significant compared to placebo in heart ($p\leq.001$).

No statistically significant differences between treatment groups were observed for chemistry or hematology analytes, vital signs and weight during the drug-taper phase.

**Table HMBR.17. Laboratory Values – Chemistry Analytes
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase**

Lab Test	Lab Unit	Therapy	N	---Baseline---		Change to ---Endpoint---		-----p-Value*-----		
				Mean	STD	Mean	STD	Overall	vs. 2	vs. 3
ALKALINE PHOSPHATASE	Units/Liter	1) PLACEBO	136	65.794	18.413	0.059	8.457	.102	.146	.037
		2) DLX60QD	144	67.014	18.938	0.729	7.867			.505
		3) DLX120QD	139	65.158	18.822	1.734	9.148			
ALT/SGPT	Units/Liter	1) PLACEBO	135	22.704	11.151	-0.274	6.937	.034	.032	.018
		2) DLX60QD	142	22.246	11.350	0.838	9.206			.803
		3) DLX120QD	136	23.037	11.799	2.110	14.227			
AST/SGOT	Units/Liter	1) PLACEBO	133	21.398	6.174	-0.143	5.014	.045	.060	.018
		2) DLX60QD	141	21.972	6.778	0.525	5.636			.597
		3) DLX120QD	135	22.052	6.560	1.741	10.216			
BICARBONATE, HCO3	millimole/Liter	1) PLACEBO	136	23.371	2.680	0.648	3.002	.254	.169	.136
		2) DLX60QD	142	23.573	2.088	1.145	2.277			.893
		3) DLX120QD	136	23.554	2.290	1.070	2.524			
BILIRUBIN, TOTAL	micromole/Liter	1) PLACEBO	136	9.195	5.273	-0.574	4.131	.643	.607	.677
		2) DLX60QD	142	9.113	5.641	-0.268	3.959			.349
		3) DLX120QD	136	9.283	4.939	-0.743	4.916			
CALCIUM	millimole/Liter	1) PLACEBO	137	2.418	0.090	-0.005	0.083	.197	.286	.073
		2) DLX60QD	144	2.435	0.096	-0.020	0.091			.451
		3) DLX120QD	139	2.426	0.094	-0.025	0.098			
CHLORIDE	millimole/Liter	1) PLACEBO	137	104.226	2.179	-0.153	2.497	.097	.064	.058
		2) DLX60QD	144	104.042	2.041	-0.611	2.374			.945
		3) DLX120QD	139	104.338	2.696	-0.590	2.587			

* Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: Model=Treatment and PINVID.
Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.17. Laboratory Values – Chemistry Analytes
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Continued)**

Lab Test	Lab Unit	Therapy	N	---Baseline---		Change to ---Endpoint---		-----p-Value*-----		
				Mean	STD	Mean	STD	Overall	vs. 2	vs. 3
CHOLESTEROL	millimole/Liter	1) PLACEBO	137	5.279	0.976	0.052	0.781	.572	.764	.305
		2) DLX60QD	144	5.452	0.983	0.029	0.724			
		3) DLX120QD	139	5.484	1.005	0.130	0.779			
CREATINE PHOSPHOKINASE	Units/Liter	1) PLACEBO	135	98.896	46.803	8.267	110.438	.077	.031	.091
		2) DLX60QD	142	117.521	89.626	11.514	89.753			
		3) DLX120QD	136	107.978	58.901	10.463	65.234			
CREATININE	micromole/Liter	1) PLACEBO	137	101.044	15.098	1.547	7.742	.237	.144	.138
		2) DLX60QD	144	101.618	13.199	0.632	7.804			
		3) DLX120QD	139	101.439	13.356	0.669	8.646			
GGT (GGPT/SGGT/YGGT)	Units/Liter	1) PLACEBO	136	26.382	20.632	-0.338	15.789	.347	.777	.170
		2) DLX60QD	144	25.979	20.385	-1.063	10.971			
		3) DLX120QD	139	25.475	17.960	-1.676	10.090			
INORGANIC PHOSPHORUS	millimole/Liter	1) PLACEBO	137	1.079	0.155	0.026	0.176	.076	.074	.034
		2) DLX60QD	144	1.142	0.180	-0.014	0.199			
		3) DLX120QD	139	1.122	0.161	-0.018	0.184			
POTASSIUM	millimole/Liter	1) PLACEBO	136	4.350	0.402	-0.026	0.411	.862	.895	.698
		2) DLX60QD	143	4.297	0.336	0.007	0.377			
		3) DLX120QD	139	4.336	0.360	-0.012	0.386			
SODIUM	millimole/Liter	1) PLACEBO	137	141.022	2.981	-0.124	3.248	.761	.637	.466
		2) DLX60QD	144	140.944	2.673	-0.444	3.117			
		3) DLX120QD	139	141.029	2.784	-0.309	3.198			

* Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: Model=Treatment and PINVID.
Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.17. Laboratory Values – Chemistry Analytes
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Concluded)**

Lab Test	Lab Unit	Therapy	N	---Baseline---		Change to ---Endpoint---		-----p-Value*-----		
				Mean	STD	Mean	STD	Overall	vs. 2	vs. 3
TOTAL PROTEIN	gram/Liter	1) PLACEBO	137	73.620	4.086	-0.613	3.216	.677	.694	.379
		2) DLX60QD	144	74.194	4.370	-0.979	3.724			
		3) DLX120QD	139	73.655	4.257	-1.151	3.780			
UREA NITROGEN	millimole/Liter	1) PLACEBO	137	5.084	1.466	0.266	1.278	.099	.048	.084
		2) DLX60QD	144	5.077	1.518	0.017	1.267			
		3) DLX120QD	139	5.188	1.384	0.029	1.248			
URIC ACID	micromole/Liter	1) PLACEBO	137	311.956	89.709	-1.241	44.074	<.001	.207	<.001
		2) DLX60QD	144	305.639	88.870	-4.063	42.618			
		3) DLX120QD	139	297.496	85.331	-17.727	40.057			

* Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: Model=Treatment and PINVID.
Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.18. Laboratory Values – Hematology Analytes
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase**

Lab Test	Lab Unit	Therapy	N	---Baseline---		Change to ---Endpoint---		-----p-Value*-----			
				Mean	STD	Mean	STD	Overall	vs. 2	vs. 3	
BASOPHILS	BILL/L	1) PLACEBO	118	0.043	0.025	0.004	0.027	.768	.524	.532	
		2) DLX60QD	130	0.047	0.022	0.004	0.028				.997
		3) DLX120QD	118	0.040	0.022	0.003	0.025				
EOSINOPHILS	BILL/L	1) PLACEBO	118	0.150	0.100	0.012	0.081	.593	.311	.528	
		2) DLX60QD	130	0.151	0.100	0.027	0.207				.713
		3) DLX120QD	118	0.145	0.083	0.028	0.205				
ERYTHROCYTE COUNT	TRIL/L	1) PLACEBO	118	4.753	0.372	-0.058	0.225	.033	.146	.009	
		2) DLX60QD	130	4.778	0.450	-0.030	0.253				.218
		3) DLX120QD	118	4.751	0.368	0.012	0.253				
HEMATOCRIT	ACTUAL COUNT	1) PLACEBO	117	0.430	0.039	-0.002	0.026	.509	.765	.264	
		2) DLX60QD	127	0.434	0.040	-0.001	0.027				.399
		3) DLX120QD	117	0.433	0.040	0.002	0.028				
HEMOGLOBIN	mmol/Liter (Fe)	1) PLACEBO	118	8.907	0.776	-0.124	0.401	.152	.272	.053	
		2) DLX60QD	130	8.958	0.831	-0.083	0.474				.372
		3) DLX120QD	118	8.982	0.720	-0.033	0.429				
LEUKOCYTE COUNT	BILL/L	1) PLACEBO	118	6.532	2.002	0.035	1.402	.304	.618	.319	
		2) DLX60QD	130	6.580	1.564	-0.054	1.546				.128
		3) DLX120QD	118	6.195	2.005	0.217	1.826				
LYMPHOCYTES	BILL/L	1) PLACEBO	118	2.013	0.592	0.096	0.469	.009	.007	.009	
		2) DLX60QD	130	2.135	0.586	-0.071	0.455				.985
		3) DLX120QD	118	1.960	0.622	-0.063	0.476				

* Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: Model=Treatment and PINVID.
Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.18. Laboratory Values – Hematology Analytes
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Concluded)**

Lab Test	Lab Unit	Therapy	N	---Baseline---		Change to ---Endpoint---		-----p-Value*-----			
				Mean	STD	Mean	STD	Overall	vs. 2	vs. 3	
MEAN CELL HEMOGLOBIN (MCH)	femtomole (Fe)	1) PLACEBO	118	1.885	0.090	-0.005	0.057	.675	.377	.601	
		2) DLX60QD	130	1.886	0.113	-0.009	0.052				.728
		3) DLX120QD	118	1.897	0.093	-0.010	0.060				
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)	mmol/Liter (Fe)	1) PLACEBO	117	20.784	0.839	-0.213	0.901	.866	.715	.601	
		2) DLX60QD	127	20.694	0.916	-0.139	0.875				.864
		3) DLX120QD	117	20.760	0.804	-0.130	0.818				
MEAN CELL VOLUME (MCV)	femtoliter	1) PLACEBO	117	90.615	4.670	0.590	3.660	.587	.367	.373	
		2) DLX60QD	127	91.063	6.026	0.268	3.615				.992
		3) DLX120QD	117	91.316	5.119	0.222	3.353				
MONOCYTES	BILL/L	1) PLACEBO	118	0.343	0.126	0.006	0.104	.209	.235	.605	
		2) DLX60QD	130	0.376	0.140	-0.008	0.127				.086
		3) DLX120QD	118	0.328	0.120	0.018	0.125				
NEUTROPHILS, SEGMENTED	BILL/L	1) PLACEBO	118	3.983	1.536	-0.083	1.181	.075	.678	.033	
		2) DLX60QD	130	3.870	1.189	-0.005	1.301				.076
		3) DLX120QD	118	3.722	1.591	0.231	1.735				
PLATELET COUNT	BILL/L	1) PLACEBO	118	269.19	66.205	0.847	33.731	.559	.537	.659	
		2) DLX60QD	130	284.56	63.630	-0.931	49.373				.285
		3) DLX120QD	117	276.03	70.447	2.812	44.846				

* Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: Model=Treatment and PINVID.
Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.19. Vital Signs and Weight
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase**

PULSE RATE

	Baseline						Endpoint						Change					
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max		
1) PLACEBO	173	71.61	8.67	70.0	53.0	104.0	71.06	9.93	70.0	48.0	104.0	-0.55	9.11	0.0	-24.0	28.0		
2) DLX60QD	166	72.20	9.54	72.0	48.0	102.0	72.84	10.47	72.0	48.0	100.0	0.64	10.61	2.0	-28.0	30.0		
3) DLX120QD	170	71.21	9.56	70.0	46.0	95.0	74.11	10.06	74.5	52.0	110.0	2.90	10.66	2.0	-28.0	36.0		

Main Effects (Type III SS)

	F	df	p
Therapy	5.38	2,478	0.005
Investigator	1.40	28,478	0.087

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	-0.53	(SE= 0.78)
2) DLX60QD	0.68	(SE= 0.80)
3) DLX120QD	2.98	(SE= 0.78)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff= 1.21	Two-sided 95% CI : (-0.94 , 3.36)	t= 1.11	p=0.270
DLX120QD - PLACEBO	diff= 3.51	Two-sided 95% CI : (1.38 , 5.64)	t= 3.23	p=0.001
DLX120QD - DLX60QD	diff= 2.30	Two-sided 95% CI : (0.14 , 4.46)	t= 2.10	p=0.037

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

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.19. Vital Signs and Weight
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Continued)**

SYSTOLIC BLOOD PRESSURE(SITTING)

	Baseline						Endpoint						Change					
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max		
1) PLACEBO	173	126.47	14.73	125.0	92.0	185.0	125.88	14.15	125.0	90.0	174.0	-0.58	12.83	0.0	-65.0	27.0		
2) DLX60QD	166	123.62	15.74	121.0	90.0	201.0	124.43	15.32	122.5	90.0	177.0	0.81	13.10	0.0	-50.0	38.0		
3) DLX120QD	170	122.90	16.13	120.0	88.0	185.0	123.95	14.53	122.0	90.0	176.0	1.05	11.92	1.5	-53.0	36.0		

Main Effects (Type III SS)

	F	df	p
Therapy	0.89	2,478	0.411
Investigator	1.07	28,478	0.366

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	-0.65	(SE= 0.98)
2) DLX60QD	0.71	(SE= 1.00)
3) DLX120QD	1.07	(SE= 0.98)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff= 1.36	Two-sided 95% CI : (-1.33 , 4.06)	t= 0.99	p=0.321
DLX120QD - PLACEBO	diff= 1.73	Two-sided 95% CI : (-0.95 , 4.40)	t= 1.27	p=0.206
DLX120QD - DLX60QD	diff= 0.36	Two-sided 95% CI : (-2.35 , 3.07)	t= 0.26	p=0.794

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

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.19. Vital Signs and Weight
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Continued)**

DIASTOLIC BLOOD PRESSURE (SITTING)

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	173	77.76	9.54	79.0	55.0	102.0	77.10	9.76	78.0	55.0	102.0	-0.65	8.12	0.0	-23.0	20.0
2) DLX60QD	166	76.79	10.56	75.0	60.0	106.0	77.75	10.88	78.0	50.0	104.0	0.96	8.90	0.0	-35.0	22.0
3) DLX120QD	170	76.52	10.41	78.0	50.0	110.0	78.13	11.01	80.0	50.0	110.0	1.61	8.68	1.0	-26.0	30.0

Main Effects (Type III SS)

	F	df	p	Raw Data
Therapy	3.17	2,478	0.043	
Investigator	1.58	28,478	0.031	

Least Squares Means for Change from Baseline

1) PLACEBO	-0.54	(SE= 0.66)
2) DLX60QD	0.96	(SE= 0.67)
3) DLX120QD	1.72	(SE= 0.66)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff= 1.51	Two-sided 95% CI : (-0.30 , 3.31)	t= 1.64	p=0.102
DLX120QD - PLACEBO	diff= 2.26	Two-sided 95% CI : (0.46 , 4.05)	t= 2.47	p=0.014
DLX120QD - DLX60QD	diff= 0.75	Two-sided 95% CI : (-1.06 , 2.56)	t= 0.81	p=0.416

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

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.19. Vital Signs and Weight
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Concluded)**

WEIGHT (kg)

	Baseline						Endpoint						Change					
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max		
1) PLACEBO	160	75.69	15.57	74.0	46.0	122.0	75.79	15.69	73.5	49.0	123.0	0.10	2.25	0.0	-18.0	6.0		
2) DLX60QD	157	72.03	15.59	70.0	40.0	111.0	71.96	15.60	70.0	39.0	114.0	-0.08	2.01	0.0	-5.0	5.0		
3) DLX120QD	159	71.31	15.26	70.0	42.0	133.0	70.94	15.28	69.0	42.0	129.0	-0.36	2.57	0.0	-10.0	13.0		

Main Effects (Type III SS)

	F	df	p
Therapy	1.56	2,445	0.211
Investigator	0.95	28,445	0.541

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	0.08	(SE= 0.19)
2) DLX60QD	-0.09	(SE= 0.19)
3) DLX120QD	-0.37	(SE= 0.19)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-0.17	Two-sided 95% CI : (-0.68 , 0.34)	t=-0.66	p=0.510
DLX120QD - PLACEBO	diff=-0.45	Two-sided 95% CI : (-0.96 , 0.06)	t=-1.75	p=0.081
DLX120QD - DLX60QD	diff=-0.28	Two-sided 95% CI : (-0.79 , 0.23)	t=-1.08	p=0.280

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

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.20. ECG Intervals and Heart Rate
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase**

PR Interval

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	119	159.46	19.87	158.0	113.0	235.0	158.45	25.84	157.0	0.0	213.0	-1.01	22.83	-1.0	-213.0	33.0
2) DLX60QD	115	154.43	18.60	152.0	106.0	200.0	150.90	18.87	150.0	104.0	196.0	-3.53	11.45	-4.0	-32.0	35.0
3) DLX120QD	115	156.22	21.96	154.0	113.0	253.0	153.01	21.39	149.0	118.0	215.0	-3.21	13.63	-3.0	-62.0	36.0

Main Effects (Type III SS)

	F	df	p
Therapy	1.24	2, 318	0.291
Investigator	0.69	28, 318	0.878

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	-0.14	(SE= 1.71)
2) DLX60QD	-3.35	(SE= 1.79)
3) DLX120QD	-3.08	(SE= 1.79)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-3.21	Two-sided 95% CI : (-7.68 , 1.25)	t=-1.42	p=0.158
DLX120QD - PLACEBO	diff=-2.94	Two-sided 95% CI : (-7.39 , 1.50)	t=-1.30	p=0.194
DLX120QD - DLX60QD	diff= 0.27	Two-sided 95% CI : (-4.20 , 4.73)	t= 0.12	p=0.906

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

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.20. ECG Intervals and Heart Rate
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Continued)**

QRS Interval

	Baseline						Endpoint						Change			
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	119	98.84	11.35	98.0	78.0	156.0	100.11	11.43	98.0	79.0	147.0	1.27	8.93	1.0	-33.0	25.0
2) DLX60QD	115	100.32	11.01	98.0	73.0	144.0	99.97	11.69	99.0	78.0	152.0	-0.35	7.63	0.0	-19.0	19.0
3) DLX120QD	115	96.38	9.17	97.0	69.0	125.0	96.40	9.12	97.0	78.0	118.0	0.02	8.51	0.0	-18.0	27.0

Main Effects (Type III SS)

	F	df	p
Therapy	1.00	2, 318	0.369
Investigator	1.11	28, 318	0.322

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	0.99	(SE= 0.84)
2) DLX60QD	-0.58	(SE= 0.88)
3) DLX120QD	0.11	(SE= 0.88)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-1.57	Two-sided 95% CI : (-3.76 , 0.62)	t=-1.41	p=0.159
DLX120QD - PLACEBO	diff=-0.88	Two-sided 95% CI : (-3.06 , 1.30)	t=-0.80	p=0.426
DLX120QD - DLX60QD	diff= 0.69	Two-sided 95% CI : (-1.50 , 2.88)	t= 0.62	p=0.537

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

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.20. ECG Intervals and Heart Rate
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Continued)**

QT Interval

	Baseline						Endpoint						Change					
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max		
1) PLACEBO	119	387.23	30.10	388.0	330.0	481.0	395.23	31.09	392.0	329.0	498.0	8.00	24.47	5.0	-74.0	85.0		
2) DLX60QD	115	388.39	28.50	389.0	318.0	484.0	386.39	28.19	386.0	332.0	453.0	-2.00	20.75	-2.0	-89.0	49.0		
3) DLX120QD	115	387.56	29.77	388.0	332.0	484.0	385.89	28.44	386.0	311.0	464.0	-1.67	25.41	0.0	-81.0	84.0		

Main Effects (Type III SS)

	F	df	p
Therapy	6.27	2, 318	0.002
Investigator	0.92	28, 318	0.586

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	8.09	(SE= 2.39)
2) DLX60QD	-1.72	(SE= 2.49)
3) DLX120QD	-1.46	(SE= 2.49)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff=-9.80	Two-sided 95% CI : (-16.0 , -3.58)	t=-3.10	p=0.002
DLX120QD - PLACEBO	diff=-9.54	Two-sided 95% CI : (-15.7 , -3.35)	t=-3.03	p=0.003
DLX120QD - DLX60QD	diff= 0.26	Two-sided 95% CI : (-5.97 , 6.48)	t= 0.08	p=0.935

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

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.20. ECG Intervals and Heart Rate
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Continued)**

QTc Bazetts Interval

	Baseline						Endpoint						Change					
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max		
1) PLACEBO	119	414.97	19.57	415.0	375.0	489.0	411.65	19.73	411.0	370.0	481.0	-3.33	15.98	-4.0	-44.0	33.0		
2) DLX60QD	115	410.28	21.18	410.0	355.0	475.0	412.75	20.87	413.0	357.0	472.0	2.47	18.72	1.0	-36.0	49.0		
3) DLX120QD	115	407.90	20.83	405.0	354.0	476.0	412.97	22.13	411.0	360.0	474.0	5.06	17.83	5.0	-38.0	59.0		

Main Effects (Type III SS)

	F	df	p
Therapy	7.98	2, 318	<.001
Investigator	1.33	28, 318	0.128

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	-3.58	(SE= 1.74)
2) DLX60QD	2.78	(SE= 1.82)
3) DLX120QD	5.34	(SE= 1.82)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff= 6.36	Two-sided 95% CI : (1.82 , 10.91)	t= 2.76	p=0.006
DLX120QD - PLACEBO	diff= 8.92	Two-sided 95% CI : (4.40 , 13.44)	t= 3.88	p=<.001
DLX120QD - DLX60QD	diff= 2.55	Two-sided 95% CI : (-1.99 , 7.10)	t= 1.11	p=0.269

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

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.20. ECG Intervals and Heart Rate
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Continued)**

QTc Fredericias Interval

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	119	405.17	17.85	404.6	367.3	463.1	405.83	18.40	405.3	357.6	455.7	0.67	14.10	1.3	-33.6	32.6
2) DLX60QD	115	402.55	17.65	402.6	361.3	452.4	403.57	18.31	406.4	351.0	454.8	1.02	14.52	0.8	-50.9	32.2
3) DLX120QD	115	400.71	18.39	398.9	363.0	451.0	403.44	19.78	401.3	356.0	471.6	2.73	14.45	2.1	-40.6	42.5

Main Effects (Type III SS)

	F	df	p
Therapy	0.87	2, 318	0.419
Investigator	1.37	28, 318	0.103

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	0.54	(SE= 1.43)
2) DLX60QD	1.34	(SE= 1.49)
3) DLX120QD	2.97	(SE= 1.49)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff= 0.80	Two-sided 95% CI : (-2.91 , 4.51)	t= 0.42	p=0.673
DLX120QD - PLACEBO	diff= 2.43	Two-sided 95% CI : (-1.26 , 6.13)	t= 1.30	p=0.196
DLX120QD - DLX60QD	diff= 1.64	Two-sided 95% CI : (-2.07 , 5.35)	t= 0.87	p=0.386

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

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.20. ECG Intervals and Heart Rate
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Continued)**

QTc Regression Interval

	Baseline						Endpoint						Change					
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max		
1) PLACEBO	119	409.76	17.88	409.5	373.0	475.7	408.59	18.17	407.6	363.3	467.7	-1.17	14.32	-0.4	-36.2	30.0		
2) DLX60QD	115	406.21	18.46	404.4	358.9	454.3	407.96	18.79	409.8	353.7	461.0	1.75	15.99	2.0	-42.1	40.4		
3) DLX120QD	115	404.11	18.74	401.6	362.5	461.7	407.92	20.29	405.8	358.4	473.4	3.81	15.18	3.3	-33.2	50.5		

Main Effects (Type III SS)

	F	df	p
Therapy	3.80	2, 318	0.023
Investigator	1.41	28, 318	0.087

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	-1.33	(SE= 1.50)
2) DLX60QD	2.09	(SE= 1.57)
3) DLX120QD	4.07	(SE= 1.57)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff= 3.43	Two-sided 95% CI : (-0.49 , 7.34)	t= 1.72	p=0.086
DLX120QD - PLACEBO	diff= 5.40	Two-sided 95% CI : (1.50 , 9.30)	t= 2.72	p=0.007
DLX120QD - DLX60QD	diff= 1.97	Two-sided 95% CI : (-1.94 , 5.89)	t= 0.99	p=0.323

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

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

**Table HMBR.20. ECG Intervals and Heart Rate
Mean Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase (Concluded)**

Heart Rate

	Baseline						Endpoint						Change					
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max		
1) PLACEBO	119	70.08	11.39	70.0	40.0	96.0	66.25	11.06	66.0	45.0	110.0	-3.83	10.18	-4.0	-38.0	43.0		
2) DLX60QD	115	68.11	11.69	67.0	46.0	106.0	69.58	11.24	68.0	43.0	102.0	1.47	9.44	1.0	-34.0	26.0		
3) DLX120QD	115	67.64	11.48	66.0	45.0	100.0	69.75	11.24	68.0	46.0	102.0	2.10	11.11	2.0	-34.0	29.0		

Main Effects (Type III SS)

	F	df	p
Therapy	11.49	2, 318	<.001
Investigator	0.81	28, 318	0.743

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	-3.78	(SE= 1.04)
2) DLX60QD	1.59	(SE= 1.09)
3) DLX120QD	2.21	(SE= 1.09)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff= 5.38	Two-sided 95% CI : (2.66 , 8.09)	t= 3.90	p=<.001
DLX120QD - PLACEBO	diff= 5.99	Two-sided 95% CI : (3.29 , 8.70)	t= 4.36	p=<.001
DLX120QD - DLX60QD	diff= 0.62	Two-sided 95% CI : (-2.10 , 3.33)	t= 0.45	p=0.656

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

Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.

Health Outcomes

The effect of duloxetine treatment (both treatment groups) on functional impairment also demonstrated superiority compared with placebo on the Q-LES-Q-SF and the EQ-5D. Table HMBR.21 summarizes the mean change from baseline to endpoint analysis of the Q-LES-Q-SF. Both duloxetine 60 mg QD and duloxetine 120 mg QD were statistically significantly superior to placebo in total score and percent in the total score. Table HMBR.16 summarizes the mean change from baseline to endpoint analysis of the EQ-5D. Both duloxetine 60 mg QD and duloxetine 120 mg QD were statistically significantly superior to placebo for index score and VAS health state score.

Table HMBR.22 summarizes the mean change analysis from baseline to endpoint on the SDS for all randomly assigned patients in the acute therapy phase. Compared with placebo, patients treated with either duloxetine 120 mg QD or duloxetine 60 mg QD experienced statistically significantly ($p < .001$) greater mean improvements on the SDS global functioning score; on Item 1, work school; on Item 2, social life; and on Item 3, family life home responsibilities.

**Table HMBR.21. Q-LES-Q-SF
Mean Change from Baseline to Endpoint
Completers Analysis
Acute Therapy Phase**

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	135	41.30	7.37	41.0	22.6	62.0	46.48	9.27	47.0	22.6	69.0	5.18	9.05	5.0	-19.4	30.0
2) DLX60QD	136	40.45	8.43	41.0	17.0	69.0	50.93	9.90	51.0	20.0	70.0	10.48	10.06	11.0	-12.0	47.0
3) DLX120QD	129	40.68	8.52	40.0	16.0	66.0	50.98	9.99	53.0	24.0	68.0	10.30	9.26	10.0	-20.0	34.0

Main Effects (Type III SS)

	F	df	p
Therapy	14.50	2, 368	<.001
Investigator	3.21	28, 368	<.001

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	6.25	(SE= 0.72)
2) DLX60QD	10.50	(SE= 0.72)
3) DLX120QD	11.23	(SE= 0.74)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff= 4.25	Two-sided 95% CI : (2.29 , 6.21)	t= 4.26	p=<.001
DLX120QD - PLACEBO	diff= 4.98	Two-sided 95% CI : (3.00 , 6.95)	t= 4.96	p=<.001
DLX120QD - DLX60QD	diff= 0.72	Two-sided 95% CI : (-1.26 , 2.71)	t= 0.72	p=0.474

Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.

Note: N=Number of patients with a baseline and completed the acute therapy phase through Visit 8.

**Table HMBR.22. EQ-5D
Mean Change from Baseline to Endpoint
Completers Analysis
Acute Therapy Phase**

EQ-5D INDEX SCORE

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1) PLACEBO	135	0.59	0.28	0.7	-0.2	1.0	0.73	0.24	0.7	-0.2	1.0	0.14	0.28	0.1	-0.6	0.9
2) DLX60QD	137	0.58	0.29	0.7	-0.1	1.0	0.81	0.18	0.8	-0.1	1.0	0.23	0.27	0.2	-0.5	0.9
3) DLX120QD	129	0.63	0.26	0.7	-0.1	1.0	0.81	0.23	0.8	-0.1	1.0	0.18	0.27	0.1	-0.5	1.1

Main Effects (Type III SS)

	F	df	p
Therapy	5.17	2, 369	0.006
Investigator	1.45	28, 369	0.069

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	0.15	(SE= 0.02)
2) DLX60QD	0.22	(SE= 0.02)
3) DLX120QD	0.22	(SE= 0.02)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff= 0.07	Two-sided 95% CI : (0.02 , 0.12)	t= 2.82	p=0.005
DLX120QD - PLACEBO	diff= 0.07	Two-sided 95% CI : (0.02 , 0.11)	t= 2.73	p=0.007
DLX120QD - DLX60QD	diff=-0.00	Two-sided 95% CI : (-0.05 , 0.05)	t=-0.06	p=0.951

Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.

Note: N=Number of patients with a baseline and completed the acute therapy phase through Visit 8.

**Table HMBR.22. EQ-5D
Mean Change from Baseline to Endpoint
Completers Analysis
Acute Therapy Phase (Concluded)**

EQ-5D VAS HEALTH STATE

	Baseline						Endpoint						Change					
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max		
1) PLACEBO	132	56.68	20.82	59.0	9.0	95.0	68.01	19.34	70.0	5.0	100.0	11.33	20.60	10.0	-45.0	71.0		
2) DLX60QD	135	53.88	18.62	59.0	15.0	100.0	74.87	18.64	80.0	13.0	100.0	20.99	22.85	21.0	-45.0	75.0		
3) DLX120QD	125	59.20	20.71	60.0	10.0	98.0	77.78	17.62	81.0	10.0	100.0	18.58	18.79	15.0	-25.0	73.0		

Main Effects (Type III SS)

	F	df	p
Therapy	9.90	2, 360	<.001
Investigator	1.62	28, 360	0.026

Raw Data

Least Squares Means for Change from Baseline

1) PLACEBO	12.47	(SE= 1.50)
2) DLX60QD	19.69	(SE= 1.48)
3) DLX120QD	20.98	(SE= 1.54)

Pairwise Comparison of LS Means

DLX60QD - PLACEBO	diff= 7.22	Two-sided 95% CI : (3.18 , 11.26)	t= 3.52	p=<.001
DLX120QD - PLACEBO	diff= 8.51	Two-sided 95% CI : (4.42 , 12.60)	t= 4.09	p=<.001
DLX120QD - DLX60QD	diff= 1.29	Two-sided 95% CI : (-2.84 , 5.42)	t= 0.62	p=0.539

Type III Sums of Squares from ANOVA: Model=Treatment,PINVID and Baseline.

Note: N=Number of patients with a baseline and completed the acute therapy phase through Visit 8.