Summary ID# 7108

Clinical Study Summary: Study F1J-MC-HMDV

Duloxetine 60 to 120 mg Once Daily Compared with Placebo in the Prevention of Relapse in Generalized Anxiety Disorder

Date summary approved by Lilly: 07 December 2007

Brief Summary of Results

This was a multicenter study with open-label acute therapy phase (26 weeks) followed by a randomized, double-blind, placebo-controlled continuation therapy phase (26 weeks) for patients who responded to duloxetine 60 to 120 mg once daily (QD) during the open-label acute therapy phase. The results of study are summarized below.

- Of 887 patients who entered the open-label acute therapy phase, 429 (216 duloxetine and 213 placebo) were randomized in the double-blind continuation therapy phase. Statistically significantly ($p \leq .001$) more duloxetine-treated patients than placebo-treated patients, 167 (77.3%) and 116 (54.5%), respectively completed the double-blind continuation therapy phase.
- Of the patients who responded to duloxetine during open-label acute therapy phase, placebo-treated patients ($p \leq .001$) compared with duloxetine-treated patients relapsed faster in the double-blind continuation therapy phase.
- A statistically significant ($p < .001$) greater number of placebo-treated patients (84, 41.8%) compared with duloxetine-treated patients (28, 13.7%) met relapse criteria during the 26-week double-blind continuation therapy phase.

- In the double-blind continuation therapy phase, placebo-treated patients reported statistically significantly greater loss in function (p<.001) compared with duloxetine-treated patients on the change in Sheehan Disability Scale **(**SDS) Global score.
- Statistically significant (p<.001, within treatment t-test) improvement from baseline to endpoint was reported for all efficacy, quality-of-life, and functional outcomes.
- Statistically significant (p<.001) improvements in duloxetine compared with placebo were reported for Hamilton Anxiety Rating Scale (HAMA), Hospital Anxiety and Depression Scale (HADS), Clinical Global Impressions-Severity (CGI-Severity) Scale, CGI-Improvement Scale, Patient's Global Impression of Improvement (PGI-Improvement) Scale, Visual Analog Scale (VAS) for Pain, Symptom Questionnaire-Somatic Subscale (SQ-SS), Composite Cognitive score; Health Outcomes Scales: SDS, Quality-of-Life-Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF), and the EuroQol Questionnaire-5-Dimension (EQ-5D) during double-blind continuation phase. Statistically significant differences between duloxetine and placebo were not demonstrated for Composite Cognitive score in the double-blind continuation therapy.
- There were 307 patients out of 658 who responded continuously for 14, 10, and 6 weeks prerandomization. Of these patients treated with placebo, the time to relapse was statistically significantly (p<.001) faster than that of duloxetine-treated patients in the group of responders.
- There was no statistically significant within-group change (p=.84) from baseline to endpoint in the Beck Scale for Suicide Ideation (BSSI) during the open-label acute therapy phase.
- There were 2 deaths—1 due to cerebral hemorrhage and 1 completed suicide—reported during the open-label acute therapy phase. Neither were related to study drug or procedure according to investigators. A total of 11 patients (1.2%) out of 887 patients experienced serious adverse events (SAEs) during the open-label acute therapy phase, and 3 (1.4%) out of 216 duloxetine-treated patients and 1 (0.5%) out of 213 placebo-treated patients reported at least 1 SAE during double-blind continuation therapy phase.
- A total of 121 (13.6%) patients discontinued during the open-label therapy phase due to an adverse event (AE); nausea (11 patients, 1.2%) was the most commonly reported AE.
- A total of 4 duloxetine-treated patients (1.9%) and 2 placebo-treated patients (0.9%) discontinued for any AE during double-blind continuation therapy phase. There were no statistically significant differences between treatment groups in the incidence of individual AEs.

- The most frequently reported treatment-emergent adverse events (TEAEs) during open-label therapy phase were nausea [251 (28.3%)], headache [166 (18.7%)], dry mouth [127 (14.3%)], and diarrhea [126 (14.2%)].
- During the double-blind continuation therapy phase, statistically significantly (p=.012) more [21 (9.9%)] placebo-treated patients reported dizziness than did duloxetine-treated patients [8 (3.7%)]. No other TEAEs were statistically significant in the double-blind continuation therapy phase.
- In duloxetine-treated patients during the open-label acute therapy phase there was a statistically significant (p<.05) mean increase from baseline to endpoint for alkaline phosphatase, alanine transaminase, aspartate transaminase, bicarbonate, cholesterol, fasting glucose, basophiles, eosinophils, hemoglobin A1C, mean cell hemoglobin concentration, monocytes, platelet count, and a statistically significant mean decrease for total bilirubin, calcium, chloride, sodium, total protein, uric acid, erythrocyte count, hematocrit, hemoglobin, lymphocytes, and mean cell volume.
- During double-blind therapy phase, statistically significant treatment-group differences were noted for eosinophils (p=.031), alkaline phosphatase (p=.017), and cholesterol (p<.001) where duloxetine-treated patients showed a mean increase, while placebo-treated patients showed a mean decrease from baseline to endpoint. Statistically significant treatment-group differences (p=.001) were observed for chloride, with a mean decrease for duloxetine-treated and mean increase for placebo-treated patients.
- Duloxetine-treated patients reported a significant mean increase from baseline to endpoint for sitting pulse rate (2.22 beats per minutes; p<.001) and sitting diastolic blood pressure (1.09 mm Hg; p<.001) at open-label acute therapy phase.
- During the double-blind continuation therapy phase, the increase in weight was statistically significant (p=.010) for duloxetine-treated patients (0.84 kg) compared with a decrease for placebo-treated patients (-0.01 kg).

Title of Study: Duloxetine 60 to 120 mg Once Daily Compared with Placebo in the Prevention of Relapse in Generalized Anxiety Disorder	
Investigators: This multicenter study included 52 principal investigators.	
Study Centers: This study was conducted at 52 study centers in 7 countries.	
Length of Study: 26 months Date first patient enrolled: 19 January 2005 Date last patient completed: 17 March 2007	**Phase of Development:** 3

Objectives: The primary objective

To assess the long-term maintenance of efficacy of duloxetine 60 to 120 mg once daily (QD) compared with placebo by a comparison of the time to relapse among patients with *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition-Text Revised (DSM-IV-TR)-defined generalized anxiety disorder (GAD) who responded to duloxetine during the open-label acute therapy phase after 26 weeks. Patients were assessed for relapse during the 26-week double-blind continuation therapy phase.

Secondary Gatekeeper Objective

A gatekeeper strategy was employed for testing the secondary hypotheses.

To evaluate the efficacy of duloxetine 60 to 120 mg QD compared with placebo during a 26-week, double-blind continuation therapy phase, measured by the mean change on the Sheehan Disability Scale (SDS) Global Functional Impairment score.

Additional Secondary Objectives

Open-Label Acute Therapy Phase

- To assess the efficacy and safety of duloxetine during the open-label acute therapy phase, using the efficacy and safety measures completed during this phase.

Double-Blind Continuation Therapy Phase

- To evaluate the efficacy of duloxetine 60 to 120 mg QD compared with placebo during a 26 week, double-blind continuation therapy phase as measured by the mean change on the following measures:
  - the Hamilton Anxiety Rating Scale (HAMA) Total score, Psychic Factor score, Somatic Factor score, anxious mood item, and tension item
  - the Anxiety and Depression Subscale scores of the Hospital Anxiety Depression Scale (HADS)
  - the Clinical Global Impressions of Severity (CGI-Severity) Scale
  - the Clinical Global Impressions of Improvement (CGI-Improvement) Scale
  - the Patient's Global Impressions of Improvement (PGI-Improvement) Scale
  - the Visual Analog Scale (VAS) for Pain: headache, back pain, shoulder pain, pain interference with daily activities, and proportion of the day with pain
  - the Symptom Questionnaire-Somatic Subscale (SQ-SS) Total score
  - using a composite cognitive score derived from the Verbal Learning and Recall Test (VLRT), the Symbol Digit Substitution Test (SDST), 2-Digit Cancellation Test (2DCT), and the Letter- Number Sequencing Test (LNST).
- To evaluate the efficacy of treatment with duloxetine 60 to 120 mg QD compared with placebo as measured by relapse rates during the 26-week double-blind continuation therapy phase.
- To compare the effects of duloxetine 60 to 120 mg QD with placebo during a 26-week, double-blind continuation therapy phase on patients' quality of life using the SDS Impairment scores, the Quality-of-Life-Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF), and the EuroQol Questionnaire-5-Dimension (EQ-5D).
- To assess the maintenance of effect of duloxetine compared with placebo by a comparison of the time to relapse among patients who responded to open-label acute treatment based on the number of weeks a patient was in responder status prior to randomization (ie, 6, 10, or 14 weeks). Patients were assessed for

relapse during the 26-week double-blind continuation therapy phase. ● To compare the safety and tolerability of duloxetine 60 to 120 mg QD with placebo during a 26-week, double-blind continuation therapy phase as measured by discontinuation rates, treatment-emergent adverse events (TEAEs), vital signs, weight, and laboratory analyses.
Study Design: This was a multicenter, randomized, double-blind, placebo-controlled relapse prevention study with an open-label acute therapy phase and double-blind continuation therapy phase as summarized in Figure HMDV.1
Number of Patients: **Open Label Acute Therapy Phase:** Planned: 760 Enrolled: 887 Met criteria to enter double blind phase: 429 **Double Blind Continuation Therapy Phase:** Randomized: 216 duloxetine, 213 placebo Completed: 167 duloxetine, 116 placebo
Diagnosis and Main Criteria for Inclusion: Male and female outpatients at least 18 years of age with generalized anxiety disorder (GAD), absence of major depression as defined by the DSM-IV-TR, were eligible to participate in this study.
Study Drug, Dose, and Mode of Administration: Duloxetine 60 to 120 mg/day, given daily as capsules orally.
Comparator, Dose, and Mode of Administration: Placebo given daily as capsules, orally.
Duration of Treatment: Open-Label Acute Therapy Phase: 26 weeks. Double-Blind Continuation Therapy Phase: 26 weeks

Variables: Efficacy:

● Time to relapse: Relapse was defined as an increase in CGI-Severity score compared with randomization by at least 2 points to a score greater than or equal to 4 and a Mini International Neuropsychiatric Interview (MINI) diagnosis of GAD (excluding duration) or discontinuation due to lack of efficacy.

Response was defined as a decrease from baseline (Visit 2) Hamilton Anxiety Rating Scale (HAMA) Total score by at least 50% to a score no higher than 11 and a CGI-Improvement score of 1 or 2 for the last 2 consecutive visits

● HAMA
● HADS
● CGI-Severity
● CGI-Improvement Scale
● PGI-Improvement Scale
● VAS for Pain
● SQ-S Scale
● Composite Cognitive score
● Cognitive assessment battery

VLRT
SDST
2DCT
LNST

Safety:

● Beck Scale for Suicide Ideation
● AEs
● Laboratory tests
● Vital Sign determination, electrocardiogram, physical examination

Health Outcomes:

● SDS
● Q-LES-Q-SF
● EQ-5D

Evaluation Methods:
Statistical:
Unless otherwise specified, all analyses were conducted on an intent-to-treat (ITT) basis, meaning that data were analyzed by the therapy groups to which patients were randomly assigned, even if the patient was not assigned the treatment, did not receive the correct treatment, or did not comply with the protocol.

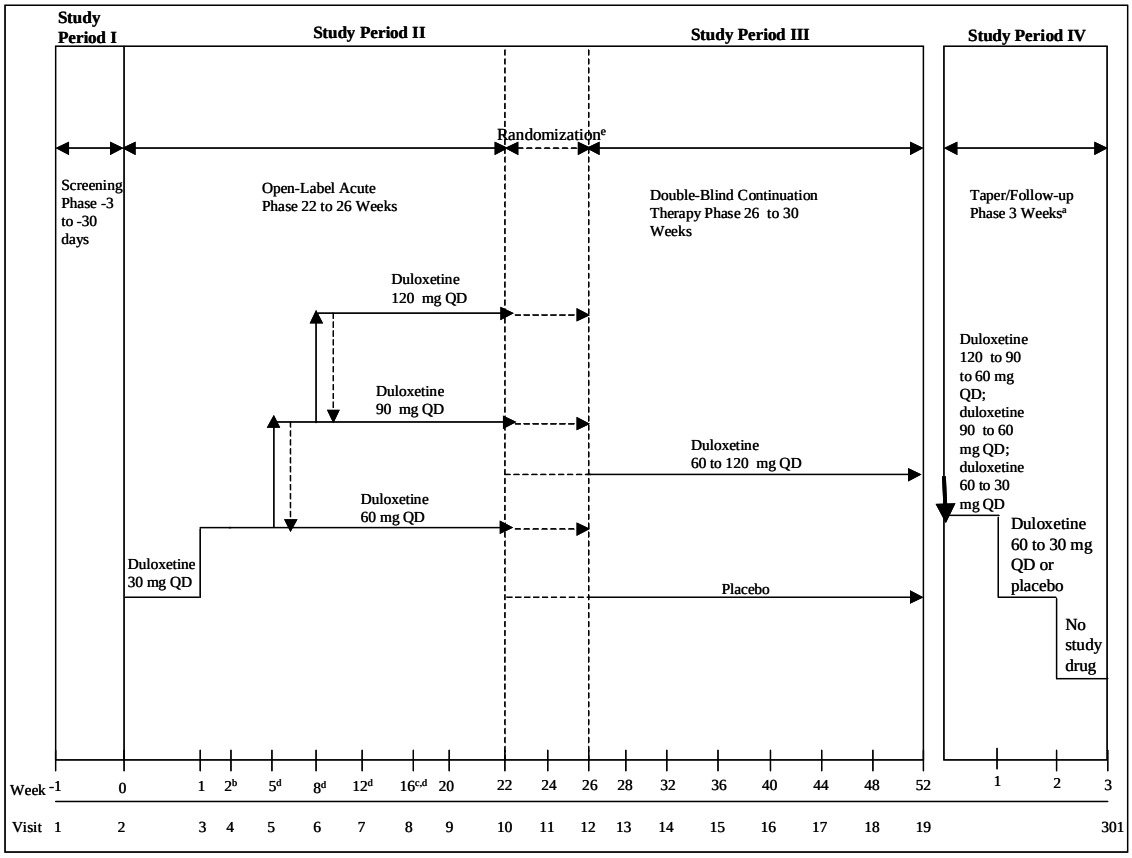
Open-label baseline values were determined by the last nonmissing values collected at screening or when the patient was given study drug. Double-blind baseline values were determined by the last value collected in the open-label acute therapy phase.

Treatment effects were evaluated based on a two-sided significance level of .05 and interaction effects at .05. No adjustments for multiple comparisons were made. The primary efficacy analysis was the comparison of duloxetine 60 to 120 mg QD with placebo in time to relapse during the double-blind continuation therapy phase using the log-rank test. The log-rank test measured the treatment differences in time to event while accounting for patient dropout. For patients who did not relapse during the double-blind continuation therapy phase, the time to censoring was the time from the randomization visit to the patient's last nonmissing observation during the double-blind continuation therapy phase. Survival curves were constructed using the Kaplan-Meier product limit method.

Unless otherwise specified, when an analysis of variance (ANOVA) model was used to analyze a continuous efficacy variable, the model contained the main effects of treatment and investigator. Similar logic was applied to an analysis of covariance (ANCOVA) model, which in general, refers to the ANOVA model with baseline values added as a covariate. Difference in the least-squares mean derived from Type III sums of squares were used for the statistical comparison using ANOVA or ANCOVA. Open-label acute therapy continuous outcome variables, including laboratory data, were evaluated using a t-test to assess if mean change from baseline to endpoint was significant from zero. Frequencies were reported only for open-label categorical outcome variables. Double-blind categorical outcome variables were analyzed using Fisher's exact test. Laboratory data during double-blind studies were analyzed by the ANOVA model on rank-transformed data.

Study Design

The study design is represented schematically in Figure HMDV.1. Following the screening phase, patients received open-label treatment with duloxetine 30 mg once daily (QD) at Visit 2 for 1 week and then were titrated to 60 mg QD at Visit 3. Patients who were unable to tolerate duloxetine 60 mg QD by Visit 3 were discontinued from the study. Patients increased their dose of duloxetine to 90 mg QD beginning at Visit 5 (Week 5), and to 120 mg QD beginning at Visit 6 (Week 8). Patients returned to the previously tolerated dose of duloxetine at any time up to Visit 8 when the increased dose was not tolerated. Titration occurred if CGI-Improvement score was 3 or higher and the patient could tolerate a dose increase. Patients were required to be on a stable dose at Visit 8. Patients who met response criteria at the end of the open-label acute therapy phase were then randomly assigned to treatment with duloxetine or placebo for up to 26 weeks during the double-blind continuation therapy phase.



Abbreviations: QD = once daily.

a Dose reductions.

b Patients discontinuing from treatment who have completed at least two weeks of treatment enter the 3-week taper/follow-up phase.

c Patients were on a stable dose of study drug starting at Visit 8 (Week 16). No other dose adjustments were allowed after this visit.

d Titration occurred if CGI-Improvement score was 3 or higher and the patient could tolerate a dose increase.

e Patients randomized to placebo underwent a 2-week downtitration in study medication. Patients taking duloxetine 60 mg QD received duloxetine 30 mg QD for 2 weeks. Patients taking duloxetine 90 mg QD received 60 mg QD for 1 week followed by 30 mg QD for 1 week. Patients taking duloxetine 120 mg QD received 90 mg QD for 4 days and 60 mg QD for the remainder of the week, followed by 30 mg QD for 1 week.

Figure HMDV.1. Study design.

Results

Patient Demographics

The study was composed predominantly of Caucasian females between 18 and 80 years of age, with a mean age of 43.32 years (open-label phase) and 45.33 years (double-blind phase). Table HMDV.1 summarizes patient demographics and psychiatric history for the open-label acute therapy phase and the double-blind continuation therapy phase. Table

HMDV.2 summarizes baseline severity of illness for all randomized patients for the double-blind continuation phase. There were no statistically significant differences between treatment groups.

Table HMDV.1. Demographics and Baseline Characteristics

Variable	Open-Label Acute Therapy Phase Duloxetine (N = 887)	Double-Blind Continuation Therapy Phase			
		Placebo (N = 213)	Duloxetine (N = 216)	Total (N = 429)	p-Value*
Age at Consent (years) Mean (SD)	43.32 (13.39)	45.68 (14.05)	44.98 (13.20)	45.33 (13.62)	.598
Weight (kg)[a] Mean (SD)	76.72 (18.45)	76.60 (19.47)	75.75 (17.86)	76.17 (18.66)	.635
Gender, n (%)					
Male	346 (39.01)	88 (41.31)	84 (38.89)	172 (40.09)	
Female	541 (60.99)	125 (58.69)	132 (61.11)	257 (59.91)	.623
Race, n (%)					
Caucasian	754 (85.01)	191 (89.67)	185 (85.65)	376 (87.65)	
African	17 (1.92)	3 (1.41)	7 (3.24)	10 (2.33)	
Hispanic	98 (11.05)	15 (7.04)	18 (8.33)	33 (7.69)	
East Asian	11 (1.24)	1 (0.47)	3 (1.39)	4 (0.93)	
West Asian	7 (0.79)	3 (1.41)	3 (1.39)	6 (1.40)	.586
Historical Diagnoses, n (%)					
Significant Historical Diagnosis ≥1	188 (21.2)	46 (21.6)	40 (81.5)	8.6 (20)	.470
Psychiatric History (years)					
Age at First Diagnosis GAD Mean (SD)	36.84 (14.39)	39.02 (15.25)	38.74 (14.60)	38.88 (14.91)	.842
Duration of GAD	6.69 (9.26)	6.79 (9.42)	6.38 (9.01)	6.58 (9.21)	.645
Previous and Concomitant Therapy, n (%)					
Patients with ≥1 Benzodiazepine	204 (23)	49 (23)	47 (21.8)	96 (22.4)	.817
Previous Therapy ≥1 Drug	372 (41.9)	90 (42.3)	96 (44.4)	186 (43.4)	.697
Patients with ≥1 Concomitant Drug Therapy	672 (75.8)	155 (72.8)	151 (69.9)	306 (71.3)	.524

Abbreviations: GAD = generalized anxiety disorder; N = Number of randomized patients; SD = standard deviation.

*Frequencies are analyzed using Fisher's exact test.

Table HMDV.2. Baseline Severity of Illness
All Randomized Patients
Double-Blind Phase

Variable	Placebo N = 213 Mean (SD)	Duloxetine N = 216 Mean (SD)	Total N = 429 Mean (SD)	p-Value*
HAMA Total Score	5.62 (3.09)	5.30 (2.94)	5.46 (3.01)	.274
HAMA Psychic Anxiety Factor Score	3.00 (1.86)	2.75 (1.87)	2.87 (1.87)	.150
HAMA Somatic Anxiety Factor Score	2.62 (2.02)	2.56 (1.94)	2.59 (1.98)	.756
HAMA item 1 (Anxious Mood)	0.62 (0.61)	0.59 (0.56)	0.60 (0.59)	.692
HAMA item 2 (Tension)	0.57 (0.62)	0.56 (0.63)	0.57 (0.63)	.835
HADS Anxiety Subscale Score	4.64 (2.95)	4.66 (3.30)	4.65 (3.13)	.938
HADS Depression Subscale Score	3.05 (3.01)	3.06 (3.31)	3.06 (3.16)	.966
CGI-Severity Score	1.61 (0.63)	1.59 (0.60)	1.60 (0.62)	.708
SQ-SS (Total Score)	5.06 (4.32)	4.85 (4.07)	4.95 (4.19)	.614
VAS (Overall Pain)	17.13 (20.74)	15.16 (20.17)	16.14 (20.46)	.319
VAS (Headaches)	12.77 (19.81)	11.46 (18.38)	12.11 (19.09)	.481
VAS (Back Pain)	15.15 (22.21)	12.53 (18.12)	13.83 (20.27)	.181
VAS (Shoulder Pain)	11.04 (17.10)	11.82 (19.08)	11.43 (18.10)	.655
VAS (Interference with Daily Activities)	12.77 (19.56)	11.48 (17.81)	12.12 (18.69)	.474
VAS (Pain While Awake)	18.08 (23.57)	16.64 (23.17)	17.36 (23.35)	.525
SDS Impairment in Work/School[a]	1.42 (1.65)	1.41 (1.86)	1.42 (1.76)	.943
SDS Social/Leisure activities	1.49 (1.80)	1.50 (2.03)	1.50 (1.92)	.697
SDS Family Life/Home Responsibilities	1.46 (1.74)	1.50 (2.08)	1.50 (1.92)	.950
SDS (Global Score)	4.47 (4.83)	4.56 (5.72)	4.52 (5.29)	.859

Abbreviations: CGI-Severity = Clinical Global Impressions of Severity; HADS = Hospital Anxiety and Depression Scale; HAMA = Hamilton Anxiety Rating Scale; SD = standard deviation; SDS = Sheehan Disability Scale; SQ-SS = Symptom Questionnaire-Somatic Subscale; VAS = Visual Analog Scale for Pain.

[a] N = 194 for placebo, 200 for duloxetine (394 total).

*Means are analyzed using a Type III sums of squares (ANOVA): Model=Treatment.

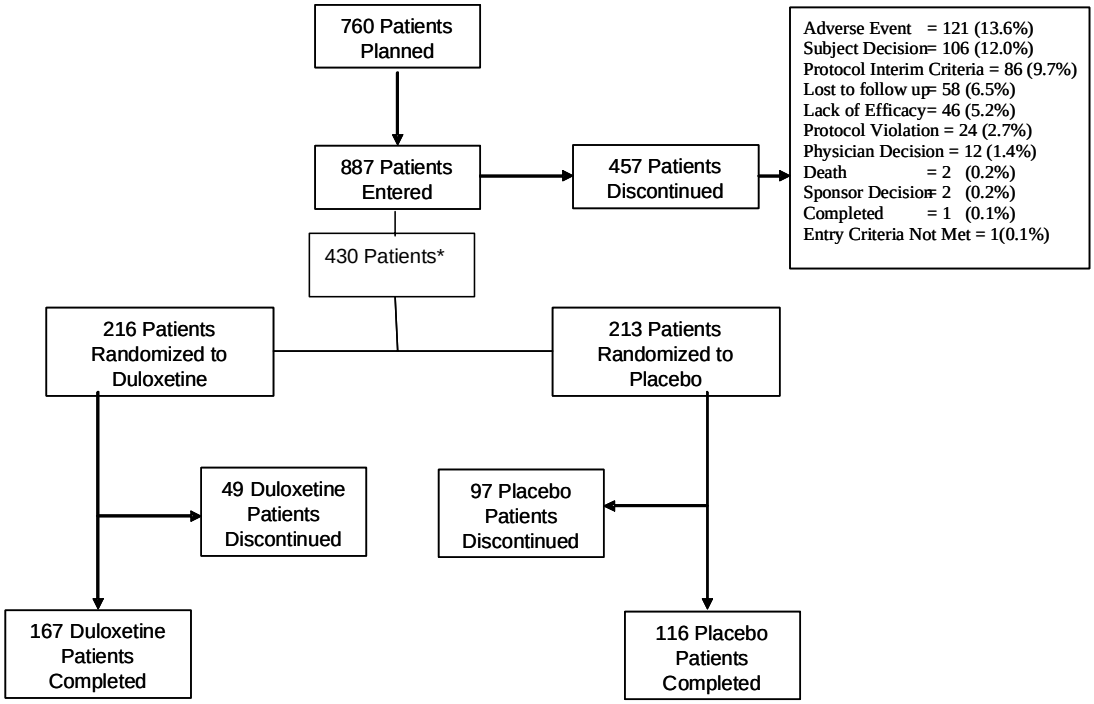
Patient Disposition

Of 887 patient enrolled in the open-label phase, 121 (13.6%) patients discontinued due to adverse events. Out of 429 patients who continued to double-blind continuation therapy phase, 213 patients were randomly assigned to placebo and 216 to duloxetine 60 to 120 mg QD.

Figure HMDV.2 and Table HMDV.3 summarize patient disposition and reason for study discontinuation for all enrolled patients in the open-label acute therapy phase and the double-blind continuation therapy phase. Of the patients who discontinued in the open-label phase, the most reported reason was adverse event (AE; 121, 13.6%).

In the double-blind treatment phase, statistically significantly more placebo-treated patients discontinued due to lack of efficacy compared with duloxetine-treated patients. There was a statistically significant ($p<.001$) difference between the numbers of patient

who completed the study in the duloxetine treatment group (77.3%) compared with the placebo treated treatment group (54.5%).



* One patient who was eligible for the study was never randomized.

Figure HMDV.2. Patient disposition.

Table HMDV.3. Reasons for Discontinuation
All Randomized Patients
Double-Blind Continuation Therapy Phase

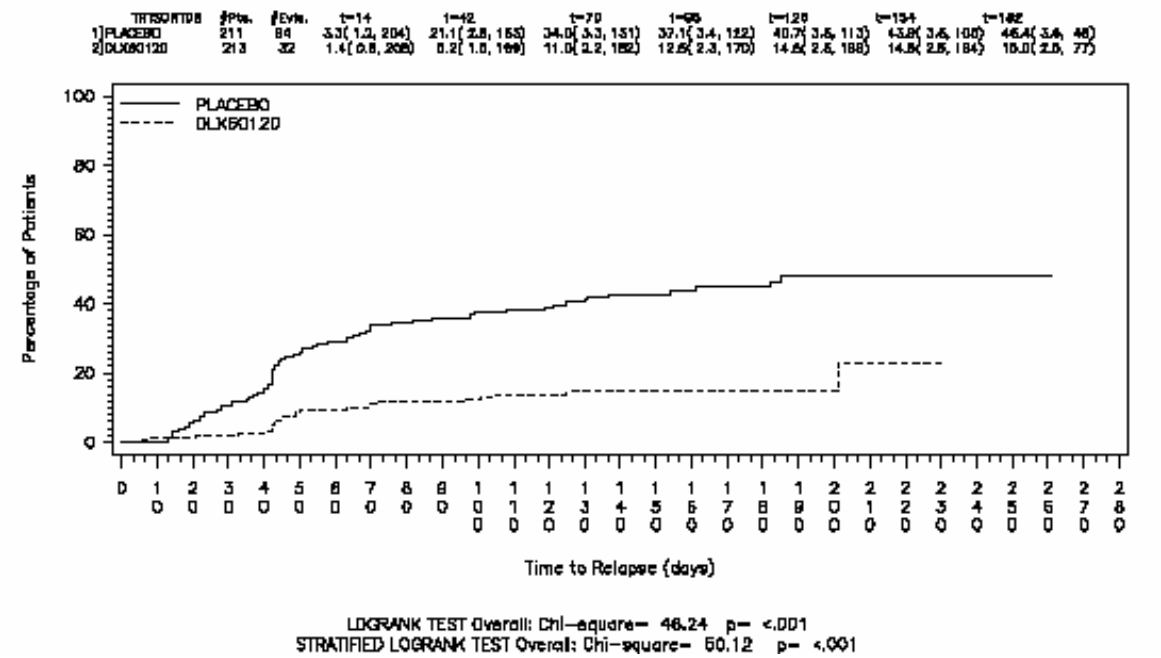
Primary Reason for Discontinuation	Placebo (N = 213) n (%)	Duloxetine (N = 216) n (%)	Total (N = 429) n (%)	p-Value*
Discontinuation Due to any Reason	213 (100)	216 (100)	429 (100)	
Lack of Efficacy	66 (31)	21 (9.7)	87 (20.3)	<.001
Patient Decision	20 (9.4)	15 (6.9)	35 (8.2)	.382
Lost to Follow-up	5 (2.3)	7 (3.2)	12 (2.8)	.771
Adverse Events	2 (0.9)	4 (1.9)	6 (1.4)	.685
Physician Decision	4 (1.9)	0	4 (0.9)	.060
Protocol Violation	0	1 (0.5)	1 (0.2)	1.000
Sponsor Decision	0	1 (0.5)	1 (0.2)	1.000
Completed	116 (54.5)	167 (77.3)	283 (66.0)	<.001

*Frequencies are analyzed using Fisher's exact test.

Primary Efficacy Measures

Time to Relapse

Relapse was defined as an increase in Clinical Global Impressions of Severity (CGI-Severity) score compared with randomization by at least 2 points to a score ≥4 and a Mini International Neuropsychiatric Interview (MINI) diagnosis of generalized anxiety disorder (GAD; excluding duration) or discontinuation due to lack of efficacy. Figure HMDV.3 shows the Kaplan-Meier plot of time to relapse for all randomized patients during the double-blind continuation therapy phase. Of the patients who responded to duloxetine during the open-label acute therapy phase, placebo-treated patients relapsed faster in the double-blind continuation therapy phase (p≤.001) compared with the duloxetine-treated patients.



Abbreviations: DLX60120 = Duloxetine.

Figure HMDV.3. Kaplan-Meier plot for time to relapse (double-blind continuation therapy phase).

Relapse Rate Analysis

There was a statistically significant (p<.001) difference between the number of placebo-treated patients (84, 41.8%) who met relapse criteria compared with duloxetine-treated patients (28, 13.7%).

Secondary Efficacy Measures

Sheehan Disability Scale and Global Functional Impairment Score

In the double-blind continuation therapy phase, placebo-treated patients reported a statistically significantly greater decrease in function (p<.001) compared with duloxetine-treated patients from baseline to endpoint on the Sheehan Disability Scale **(**SDS) item 1 (work/school), item 2 (social life), item 3 (family life/home responsibilities), and the Global Functional Improvement Score, as summarized in Table HMDV.4.

Table HMDV.4. Sheehan Disability Scale LS Mean Change from Baseline to Endpoint All Randomized Patients Double-Blind Continuation Therapy Phase

N	Therapy	Baseline Mean (SD)	LS Mean Change	SE	Pairwise Comparison p-Value*
SDS (Global Score)					
211	Placebo	4.49 (4.84)	5.03	0.47	
213	Duloxetine	4.60 (5.74)	0.60	0.48	<.001
SDS item 1(Impairment In Work/School)					
187	Placebo	1.43 (1.65)	1.70	0.17	
187	Duloxetine	1.35 (1.79)	0.11	0.17	<.001
SDS item 2 (Social/Leisure Activities)					
211	Placebo	1.50 (1.81)	1.68	0.17	
213	Duloxetine	1.52 (2.04)	0.21	0.17	<.001
SDS item 3 (Family Life/Home Responsibilities)					
211	Placebo	1.47 (1.75)	1.59	0.17	
213	Duloxetine	1.55 (2.09)	0.23	0.17	<.001

Abbreviations: LS = least square; N = number of patients with a baseline and at least one nonmissing postbaseline data; SDS = Sheehan Disability Scale; SE = standard error.

*Type III Sums of Squares from ANCOVA: Model = Treatment Investigator Baseline.

Additional Secondary Objectives

Open-Label Acute Phase

Efficacy

There were statistically significant (p<.001) within-treatment improvements on all efficacy measures during the 26-week open-label acute therapy phase, as summarized in Table HMDV.5.

Table HMDV.5. Efficacy Measures
All Randomized Patients
Open-Label Acute Therapy Phase

n	Therapy (N = 887)	Baseline Mean (SD)	Change Mean (SD)	Within treatment p-Value
858	HAMA Total Score	26.44 (6.56)	-14.91 (10.11)	<.001
858	HAMA Psychic Anxiety Factor Score	14.91 (3.21)	-8.47 (5.56)	<.001
858	HAMA Somatic Anxiety Factor Score	11.52 (4.56)	-6.44 (5.62)	<.001
858	HAMA Item 1 (Anxious Mood)	2.98 (0.62)	-1.69 (1.21)	<.001
858	HAMA Item 2 (Tension)	2.75 (0.72)	-1.55 (1.19)	<.001
743	HADS Anxiety Subscale Score	14.01 (2.97)	-6.98 (5.03)	<.001
744	HADS Depression Subscale Score	8.50 (4.12)	-3.76 (4.49)	<.001
761	CGI-Severity Score	4.71 (0.72)	-2.24 (1.46)	<.001
861	CGI-Improvement Score[a]	-	2.26 (1.27)	<.001
425	PGI-Improvement Score[a]	-	2.35 (1.55)	<.001
456[b]	SDS (Global Score)	17.04 (6.84)	-11.78 (8.13)	<.001
368[b]	SDS Impairment in work/school	5.55 (2.78)	-3.89 (3.09)	<.001
456[b]	SDS-Social/Leisure Activities	5.80 (2.56)	-4.07 (3.02)	<.001
456[b]	SDS Family life/Home Responsibilities	5.56 (2.53)	-3.81 (2.96)	<.001
679	Composite Cognitive Score Baseline	30.33 (6.43)	0.80 (4.59)	<.001
460[b]	Q-LES-Q-SF Percent Score	48.41 (14.84)	24.43 (17.21)	<.001
460[b]	EQ-5D Index Score	0.52 (0.28)	0.32 (0.31)	<.001
461[b]	EQ-5D Visual Analog Scale HASS	55.62 (21.19)	23.78 (22.64)	<.001

Abbreviations: CGI-Improvement = Clinical Global Impressions of Improvement; CGI-Severity = Clinical Global Impressions of Severity; EQ-5D = EuroQol Questionnaire 5-Dimension Index Score; HADS = Hospital Anxiety Depression Scale; HAMA = Hamilton Anxiety Rating Scale; N = number of patients with a baseline and at least one nonmissing postbaseline data; PGI-Improvement = Patient's Global Impression of Improvement; Q-LES-Q-SF = Quality-of Life-Enjoyment and Satisfaction Questionnaire; SD = standarad deviation; SDS = Sheehan Disability Scale.

a CGI and PGI-I reported as mean endpoint.

b Complete analysis was performed. Completer = patient with a baseline and postbaseline data who completed the open-label.

For HAMA, HADS, SDS negative mean change indicates improvement.

For CGI-Improvement and -Severity scores, PGI-I score, Composite Cognitive score, Q-LES-Q-SF Percent score, EQ-5D Index score, and EQ-5D Visual Analog Scale HASS, positive mean change indicates improvement.

Double-Blind Continuation Therapy Phase

Placebo-treated patients reported a statistically significant increase ($p<.001$) in symptom severity (worsening) compared with duloxetine-treated patients on the Hamilton Anxiety Rating Scale (HAMA) Total score, Psychic Anxiety Factor score, Somatic Anxiety Factor score, item 1 (anxious mood) and item 2 (tension), as summarized in Table HMDV.6.

Table HMDV.6. Hamilton Anxiety Rating Scale Factor Scores Mean Change from Baseline to Endpoint All Randomized Patients Double-Blind Continuation Therapy Phase

N	Therapy	Baseline Mean (SD)	LS Mean Change	SE	Pairwise comparison p-Value*
HAMA Total Score					
211	Placebo	5.63 (3.06)	7.52	0.57	
213	Duloxetine	5.35 (2.93)	1.63	0.58	<.001
HAMA Psychic Anxiety Factor Score					
211	Placebo	3.02 (1.86)	4.52	0.33	
213	Duloxetine	2.76 (1.87)	1.23	0.34	<.001
HAMA Somatic Anxiety Factor Score					
211	Placebo	2.60 (1.99)	2.98	0.28	
213	Duloxetine	2.59 (1.93)	0.34	0.28	<.001
HAMA item 1 (Anxious Mood)					
211	Placebo	0.62 (0.61)	0.89	0.07	
213	Duloxetine	0.59 (0.56)	0.22	0.07	<.001
HAMA item 2 (Tension)					
211	Placebo	0.57 (0.62)	0.80	0.07	
213	Duloxetine	0.56 (0.63)	0.15	0.07	<.001

Abbreviations: HAMA = Hamilton Anxiety Rating Scale; LS = least square; N = number of patients with a baseline and at least one nonmissing postbaseline data; SE = standard error.

* Type III Sums of Squares from ANCOVA: Model = Treatment Investigator Baseline.

Placebo-treated patients demonstrated a statistically significant (p<.001) greater increase in symptom severity (worsening) compared with duloxetine-treated patients on the Hospital Anxiety Depression Scale (HADS) Anxiety Subscale score and Depression Subscale score, as summarized in Table HMDV.7.

Placebo-treated patients demonstrated a statistically significant greater increase in symptom severity (worsening) compared with duloxetine-treated patients on Visual Analog Scale for Pain (VAS) for pain measurements: overall pain (p<.001), headaches (p<.001), back pain (p=.012), shoulder pain (p<.001), interference with daily activities (p<.001), and pain while awake (p<.001), as summarized in Table HMDV.7.

Placebo-treated patients demonstrated a statistically significant (p<.001) increase in symptom severity (worsening) compared with duloxetine-treated patients on the Symptom Questionnaire-Somatic Subscale (SQ-SS) total score during the double-blind continuation phase (Table HMDV.7).

Duloxetine-treated patients reported statistically significant (p<.001) improvement compared with placebo-treated patients on mean score at endpoint on the Clinical Global Impressions of Improvement (CGI-Improvement) and Patient's Global Impressions of Improvement (PGI-Improvement; Table HMDV.7).

Table HMDV.7. Efficacy Measures
All Randomized Patients
Double-Blind Continuation Therapy Phase

N	Therapy*	Baseline (SD)	LS Mean Change	SE	Pairwise comparison p-Value*
HADS Anxiety Subscale Score					
198	Placebo	4.68 (2.92)	3.53	0.29	
209	Duloxetine	4.65 (3.33)	0.05	0.29	<.001
HADS Depression Subscale Score					
198	Placebo	3.06 (2.98)	2.23	0.25	
209	Duloxetine	3.08 (3.33)	0	0.24	<.001
Clinical Global Impressions- Severity					
211	Placebo	1.61 (0.63)	1.21	0.09	
213	Duloxetine	1.60 (0.60)	0.17	0.09	<.001
Clinical Global Impressions-Improvement Score					
211	Placebo	2.58 (1.46)	2.59	0.09	
213	Duloxetine	1.66 (1.03)	1.65	0.09	<.001
Patient Global Impressions-Improvement Score					
211	Placebo	2.90 (1.71)	2.88	0.10	
213	Duloxetine	1.80 (1.13)	1.77	0.10	<.001
VAS (Overall Pain)					
190	Placebo	17.30 (20.91)	8.72	1.38	
202	Duloxetine	15.08 (20.30)	-1.56	1.34	<.001
VAS (Headaches)					
190	Placebo	12.40 (19.93)	7.24	1.49	
202	Duloxetine	11.48 (18.59)	0.30	1.45	<.001
VAS (Back Pain)					
190	Placebo	14.42 (21.32)	5.19	1.42	
202	Duloxetine	12.38 (18.08)	0.37	1.39	.012
VAS (Shoulder Pain)					
190	Placebo	11.02 (17.52)	6.32	1.30	
202	Duloxetine	11.21 (18.38)	-0.38	1.27	<.001
VAS (Interference with Daily Activities)					
190	Placebo	12.72 (19.77)	8.60	1.42	
202	Duloxetine	11.35 (17.15)	-0.03	1.38	<.001
VAS (Pain while Awake)					
190	Placebo	17.59 (23.32)	7.93	1.59	
202	Duloxetine	16.20 (22.85)	0.57	1.54	<.001
Symptom-Questionnaire-Somatic Scale (Total Score)					
194	Placebo	5.03 (4.30)	3.16	0.32	
206	Duloxetine	4.88 (4.08)	0.12	0.31	<.001

Abbreviations: HADS = Hospital Anxiety Depression Scale; LS = least squares; N = Number of patients with a baseline and at least one nonmissing postbaseline data; SD = standard deviation; SE = standard error; VAS = Visual Analog Scale for Pain.

*Type III Sums of Squares from ANCOVA: Model = Treatment Investigator Baseline.

Cognitive Assessment Battery

Least square (LS) mean change from baseline to endpoint for the cognitive assessment battery during the double-blind continuation phase was not statistically significantly different (p=.289) between the two treatment groups (1.07 for placebo and 1.55 for duloxetine).

Health Outcomes/Quality-of-Life Evaluation

In the double-blind continuation therapy phase, placebo-treated patients reported a statistically significantly greater decrease in quality-of-life satisfaction (p<.001) compared with duloxetine-treated patients on LS mean change on the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF) Questionnaire, EuroQol Questionnaire 5 Dimension (EQ-5D) index score, and VAS, as summarized in Table HMDV.8.

Table HMDV.8. Health Outcome Measures
All Randomized Patients
Double-Blind Continuation Therapy Phase

N	Therapy	Baseline Mean (SD)	LS Mean Change	SE	Pair wise Comparison	
					t	p-Value*
Q-LES-Q-SF Percent Score						
198	Placebo	74.38 (14.61)	-12.53	1.18		
209	Duloxetine	74.41 (14.97)	-0.29	1.15	7.67	<.001
EQ-5D Index Score						
198	Placebo	0.85 (0.16)	-0.12	0.01		
209	Duloxetine	0.86 (0.18)	0	0.01	6.16	<.001
EQ-5D Visual Analog Scale						
198	Placebo	80.40 (13.65)	-12.65	1.28		
209	Duloxetine	80.24 (14.77)	1.30	1.25	8.05	<.001

Abbreviations: EQ-5D = EuroQol Questionnaire 5 Dimension index score; LS = least squares; N = number of patients; Q-LES-Q-SF = Quality-of Life-Enjoyment and Satisfaction Questionnaire; SD = standard deviation; SE = standard error; t = t-test.

*Type III Sums of Squares from ANCOVA: Model = Treatment Investigator Baseline.

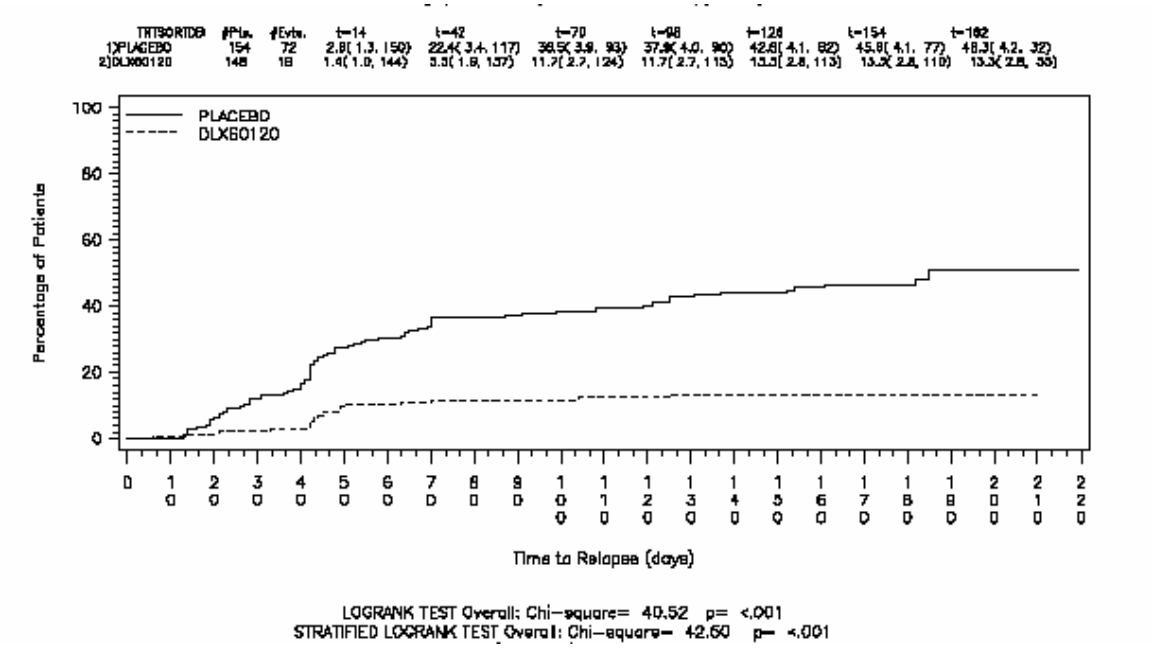
Remission Rate Analysis

A statistically significantly (p<.001) greater number of duloxetine-treated patients (145, 68.1%) met remission criteria compared with placebo-treated patients (83, 39.3%).

Maintenance of Effect

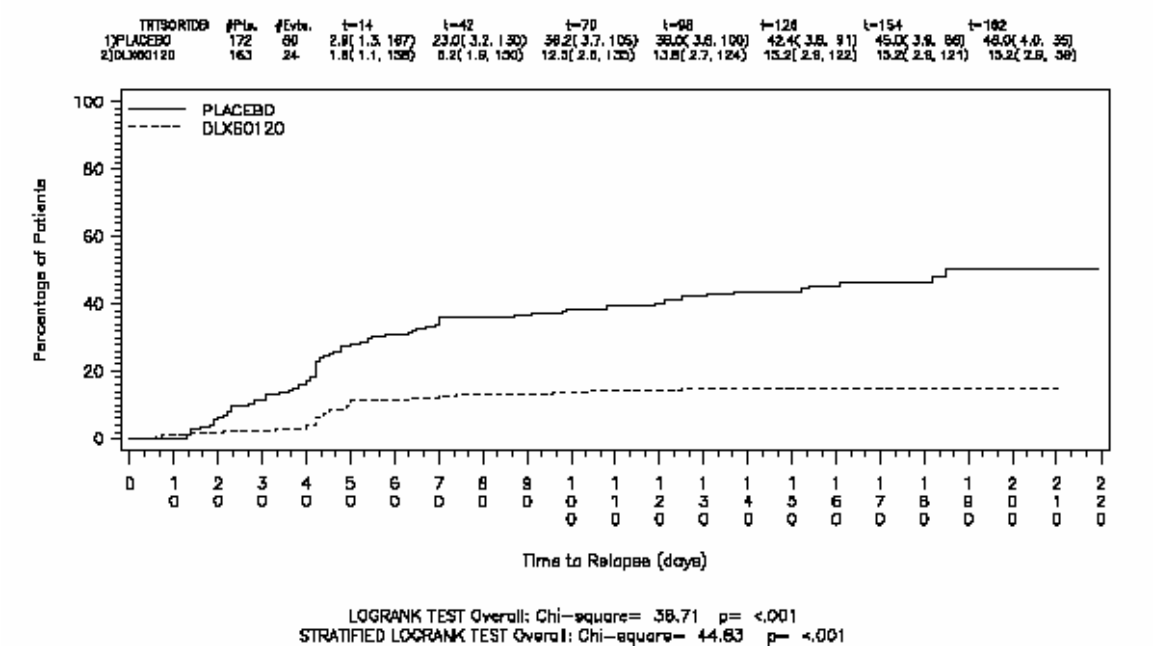
In the open-label acute therapy phase, 64.1%, 54.8%, and 46.7% of patients responded continuously for 6 weeks, 10 weeks, and 14 weeks prerandomization, respectively. Among those patients who responded continuously, duloxetine-treated patients were reported to have statistically significantly longer time to relapse compared with placebo-treated patients (p<.001) for 6 weeks,10 weeks, and 14 weeks prerandomization.

Figures HMDV.4, HMDV.5, and HMDV.6 show the Kaplan-Meier plot of time to relapse for all randomized patients who responded continuously for 14 weeks, 10 weeks, or 6 weeks prerandomization, respectively.



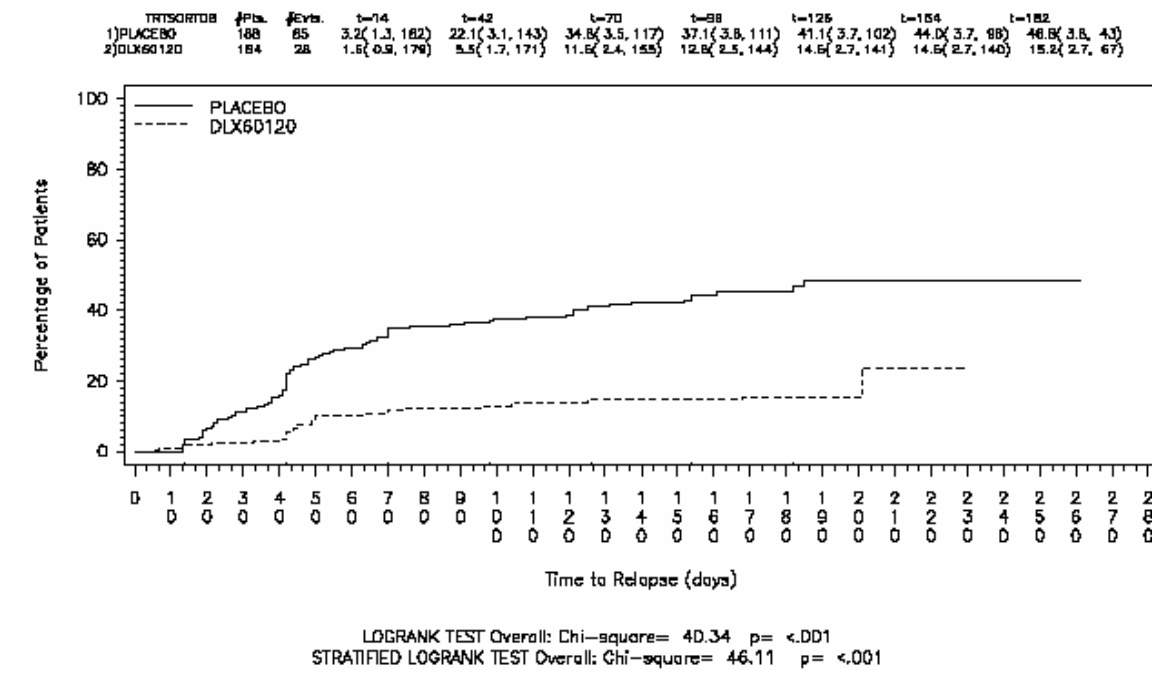
Abbreviation: DLX60120 = Duloxetine.

Figure HMDV.4. Kaplan-Meier plot of time to relapse for all randomized patients who responded continuously for 14 weeks during the open-label treatment phase and entered the double-blind continuation therapy phase.



Abbreviations: DLX60120 = Duloxetine.

Figure HMDV.5. **Kaplan-Meier plot of time to relapse for all randomized patients who responded continuously for 10 weeks during the open-label treatment phase and entered the double-blind continuation therapy phase.**



Abbreviations: DLX60120 = Duloxetine.

Figure HMDV.6. Kaplan-Meier plot of time to relapse for all randomized patients who responded continuously for 6 weeks during the open-label treatment phase and entered the double-blind continuation therapy phase.

Safety

Beck Scale for Suicide Ideation

Eighteen patients (2.0%) had a positive response to the initial screening questions of the Beck Scale for Suicide Ideation (BSSI) during the open-label phase. Patients with a positive response indicated that they have a weak to moderate desire to kill themselves or that if they found themselves in a life-threatening situation they may take a chance on life and death or would not take the necessary steps to avoid death. At endpoint, these patients had a mean BSSI score of 5.7 (values observed ranged 0 to 19, SD = 6.1), which did not differ statistically significantly from their baseline mean value of 5.4 (values observed ranged 0 to 26; SD = 6.6; p=.84).

Death, Overview and Discontinuation

Table HMDV.9 provides an overview of deaths, searious adverse events (SAEs), treatment-emergent adverse events (TEAEs), and discontinuations due to an AE for all randomized patients in the open-label and double-blind therapy phases.

Table HMDV.9. Overview of Adverse Events
All Randomized Patients
Open-Label and Double-Blind Continuation Therapy Phase

Adverse Event	Open-Label Therapy Phase N = 887 n (%)	Double-Blind Continuation Therapy Phase		
		Placebo N = 213 n (%)	Duloxetine N = 216 n (%)	p-value
Deaths	2 (0.2)	0 (0)	0 (0)	0.00
Serious Adverse Events	11 (2.2)	1 (0.5)	3 (1.4)	.623
Discontinuations Due to an Adverse Event	121 (13.6)	2 (0.9)	4 (1.4)	.685
Treatment-emergent Adverse Events	732 (82.5)	117 (54.9)	113 (52.3)	.629

Abbreviations: N= number of randomized patients; n = number of patients with adverse event.

A total of 11 patients (2.2%) experienced SAEs during the open-label acute therapy phase. An SAE of suicide attempt was reported by 2 patients (0.2%), and alcohol poisoning, alcoholism, anxiety, arrhythmia, cellulitis, cerebral hemorrhage, syncope, stress, nephrolithiasis, mania, diverticulitis, depression and completed suicide were each reported by 1 (0.1%) patient.

The SAEs cerebral hemorrhage and completed suicide resulted in death during open-label phase. According to investigators, neither death was related to study drug or procedure.

A total of 3 (1.4%) duloxetine-treated patients and 1 (0.5%) placebo-treated patient reported at least 1 SAE in the double-blind continuation therapy phase. Duloxetine-treated patients reported acute bronchitis, diarrhea, and GAD. The placebo-treated patient reported fall and tendon rupture. There were no statistically significant or clinically important treatment differences in the incidence of individual SAEs between treatment groups.

Discontinuation due to AE

A total of 121 patients discontinued during the open-label therapy phase because an AE, as summarized in Table HMDV.10. Nausea (11, 1.2%) was the most commonly reported AE.

A total of 4 duloxetine-treated patients (1.9%) and 2 placebo-treated patients (0.9%) discontinued for any AE in the double-blind continuation therapy phase. There were no statistically significant differences between treatment groups in the incidence of individual AE, as summarized in Table HMDV.11.

Table HMDV.10. Adverse Events (n ≥2) Reported as Reason for Discontinuation
All Enrolled Patients
Open-Label Acute Therapy Phase

Adverse Events	(N = 887) n (%)
Patients Discontinued for Any AE	121 (13.6)
Nausea	11 (1.2)
Insomnia	6 (0.7)
Dizziness	5 (0.6)
Sedation	5 (0.6)
Fatigue	4 (0.5)
Somnolence	4 (0.5)
Vomiting	4 (0.5)
Anxiety	3 (0.3)
Constipation	3 (0.3)
Libido decreased	3 (0.3)
Pregnancy	3 (0.3)
Sleep disorder	3 (0.3)
Vertigo	3 (0.3)
Depression	2 (0.2)
Diarrhea	2 (0.2)
Disturbance in attention	2 (0.2)
Ejaculation failure	2 (0.2)
Erectile dysfunction	2 (0.2)
Gastritis	2 (0.2)
Headache	2 (0.2)
Migraine	2 (0.2)
Suicidal ideation	2 (0.2)

Abbreviations: N = number of enrolled patients, n = number of patients who discontinued because of adverse event or death.

Table HMDV.11. Adverse Events Reported as Reason for Discontinuation
All Randomized Patients
Double-Blind Continuation Therapy Phase

Adverse Event	Placebo N = 213 n (%)	Duloxetine N = 216 n (%)	Total N = 429 n (%)	p-Value*
Patient Discontinued for any AE	2 (0.9)	4 (1.9)	6 (1.4)	.685
Pregnancy	0	2 (0.9)	2 (0.5)	.499
Bronchitis Acute	0	1 (0.5)	1 (0.2)	1.000
Dizziness	1 (0.5)	0	1 (0.2)	.497
Epilepsy	0	1 (0.5)	1 (0.2)	1.000
Weight Increased	1 (0.5)	0	1 (0.2)	.497

Abbreviations: AE = adverse event; N = number of randomized patients; n = number of patients who discontinued because of adverse event or death.

*Frequencies are analyzed using Fisher's exact test.

Treatment-Emergent Adverse Events

Table HMDV.12 summarizes TEAEs occurring in ≥5% of patients in order of decreasing frequency in the open-label acute therapy phase. Nausea (251, 28.3%) was the most commonly reported TEAE.

In the double-blind therapy phase, 117 (54.9%) patients and 113 (52.3%) patients reported ≥1 TEAE in the placebo- and duloxetine-treatment groups, respectively. There was a statistically significant (p=.012) difference between placebo-treated patients[21 (9.9%)] and duloxetine-treated patients [8 (3.7%)] for dizziness.

Headache was reported in 11 (5.2%) patients in the placebo treatment group and in 12 (5.6%) patients in the duloxetine group; however, the difference between duloxetine and placebo was not statistically significant (p=1.000).

Table HMDV.12. Treatment-Emergent Adverse Events in ≥5% of Patients
All Enrolled Patients
Open-Label Acute Therapy Phase

Events	Open-Label Phase Therapy N = 887 n (%)
Nausea	251 (28.3)
Headache	166 (18.7)
Dry Mouth	127 (14.3)
Diarrhea	126 (14.2)
Dizziness	119 (13.4)
Constipation	111 (12.5)
Fatigue	102 (11.5)
Hyperhidrosis	89 (10.0)
Insomnia	87 (9.8)
Somnolence	73 (8.2)
Decreased Appetite	54 (6.1)
Upper Respiratory Tract Infection	49 (5.5)
Libido decreased	48 (5.4)
Vomiting	48 (5.4)
Nasopharyngitis	44 (5.0)

Abbreviations: N = number of enrolled patients; n = number of patients with treatment-emergent adverse event.

Laboratory Analysis

Table HMDV.13 and Table HMDV.14 summarize the laboratory analytes with statistically significant changes from baseline to endpoint in open-label acute therapy phase and double-blind continuation therapy phase, respectively.

Table HMDV.13. Summary of Laboratory Values with Statistically Significant Changes from Baseline to Endpoint
All Randomized Patients
Open-Label Acute Therapy Phase

Lab Analyte (units)	N	Baseline Mean (SD)	Change Mean (SD)	p-Value*
Alkaline Phosphatase (units/liter)	801	71.07 (22.26)	2.95 (12.37)	<.001
ALT/SGPT (units/liter)	799	23.67 (14.35)	1.68 (23.73)	.045
AST/SGOT(units/liter)	790	22.59 (8.88)	1.06 (12.16)	.015
Bicarbonate (millimole/liter)	799	23.34 (2.59)	1.64 (2.98)	<.001
Total Bilirubin (micromole/liter)	800	9.20 (4.99)	-0.87 (4.10)	<.001
Calcium (millimole/liter)	802	2.46 (0.11)	-0.02 (0.11)	<.001
Chloride (millimole/liter)	803	103.86 (2.58)	-0.75 (2.73)	<.001
Cholesterol (millimole/liter)	802	5.40 (1.07)	0.06 (0.74)	.016
Glucose Fasting (millimole/liter)	607	5.35 (1.08)	0.14 (1.07)	.002
Sodium (millimole/liter)	803	141.47 (2.74)	-0.89 (3.18)	<.001
Total Protein (gram/liter)	802	74.07 (4.50)	-1.36 (3.98)	<.001
Uric Acid (micromole/liter)	802	312.10 (82.78)	-8.71 (47.09)	<.001
Basophils (billion/liter)	635	0.05 (0.03)	0 (0.03)	.010
Eosinophils (billion/liter)	635	0.13 (0.10)	0.01 (0.09)	.014
Erythrocyte Count (trillion/liter)	636	4.87 (0.45)	-0.07 (0.26)	<.001
Hematocrit (actual count)	628	0.44 (0.04)	-0.01 (0.03)	<.001
Hemoglobin (millimole/liter)	636	8.88 (0.84)	-0.13 (0.47)	<.001
Hemoglobin A1C (actual count)	640	0.05 (0.01)	0 (0)	.007
Lymphocytes (billion/liter)	635	2.07 (0.61)	-0.04 (0.47)	.040
MCHC (millimole/liter)	628	20.21 (0.86)	0.17 (0.98)	<.001
MCV (femoliter)	628	90.60 (5.47)	-0.75 (4.07)	<.001
Monocytes (billion/liter)	635	0.36 (0.12)	0.02 (0.12)	.002
Platelet Count (billion/liter)	624	267.34 (67.57)	11.92 (45.97)	<.001

Abbreviations: ALT/SGPT = alanine transaminase; AST/SGOT = aspartate transaminase; MCHC = mean cell hemoglobin concentration; MCV = mean cell volume; N = number of patients with a baseline and at least one nonmissing postbaseline data; SD = standard deviation.

*Type III Sums of Squares from an analysis of variance (ANOVA) on rank-transformed data.

Table HMDV.14. Summary of Laboratory Values with Statistically Significant Changes from Baseline to Endpoint
All Randomized Patients
Double-Blind Continuation Therapy Phase

Lab Analytes (units)	Therapy	N	Baseline Mean (SD)	Change Mean (SD)	p-Value*
Alkaline Phosphatase (unit/liter)	Placebo	169	73.32 (21.11)	-1.72 (10.92)	.017
	Duloxetine	190	73.68 (23.13)	1.15 (10.93)	
Chloride (millimole/liter)	Placebo	168	103.21 (2.56)	0.79 (2.70)	.001
	Duloxetine	189	103.16 (2.40)	-0.03 (2.28)	
Cholesterol (millimole/liter)	Placebo	169	5.41 (1.04)	-0.20 (0.68)	<.001
	Duloxetine	190	5.58 (1.15)	0.16 (0.84)	
Eosinophil Billion/liter)	Placebo	142	0.15 (0.11)	-0.01 (0.09)	.031
	Duloxetine	154	0.14 (0.11)	0.01 (0.08)	

Abbreviations: N = number of patients with a baseline and at least one nonmissing postbaseline data; SD = standard deviation.

*Type III Sums of Squares from an analysis of variance (ANOVA) on rank-transformed data.

Vital Signs

Table HMDV.15 and Table HMDV.16 summarize vital signs and weight changes from baseline to endpoint for the open-label therapy phase and double-blind continuation therapy phase. Patients in the duloxetine treatment group reported a statistically significant (p<.001) mean increase from baseline to endpoint for sitting pulse rate and sitting diastolic blood pressure during the open-label therapy phase. A total of 35 patients (3.9%) experienced a sustained elevation of blood pressure.

Table HMDV.15. Vital Signs and Weight Mean Change from Baseline to Endpoint
All Enrolled Patients
Open-Label Acute Therapy Phase

Vital Signs (units)	N	Baseline Mean (SD)	Change Mean (SD)	t*	p-Value
Sitting Pulse Rate (beats per minute)	859	71.23 (9.48)	2.22 (10.25)	6.34	<.001
Sitting Diastolic BP (millimeter of mercury)	860	75.62 (9.35)	1.09 (8.69)	3.67	<.001
Sitting Systolic BP (millimeter of mercury)	860	122.66 (13.66)	0.68 (12.23)	1.63	.104
Weight (kilogram)	751	76.54 (18.51)	0.16 (4.05)	1.11	.269

Abbreviations: BP = blood pressure; N = number of patients with a baseline and at least one nonmissing postbaseline data; SD = standard deviation; t = t-test.

*T-test used to assess if mean changes from baseline to endpoint were significant from zero.

During the double-blind continuation therapy phase, the increase in weight was statistically significant (p=.010) for duloxetine-treated patients (0.84), compared with a decrease for placebo-treated patients (-0.01).

One patient (0.5%) reported sustained elevation of blood pressure, defined as diastolic blood pressure ≥90 and increase from baseline ≥10 for 3 consecutive visits or systolic blood pressure ≥140 and increase from baseline ≥10 for 3 consecutive visits.

Table HMDV.16. Vital Signs and Weight Mean Change from Baseline to Endpoint
All Enrolled Patients
Double-Blind Continuation Therapy Phase

Lab Analytes (units)	Therapy	N	Baseline Mean (SD)	LS mean for Change from Baseline	SE	p-Value
Sitting Pulse Rate (beats per minute)	Placebo	211	73.68 (10.43)	-1.26	0.70	.359
	Duloxetine	213	72.81 (10.31)	-0.38	0.70	
Sitting Diastolic BP (millimeter of mercury)	Placebo	211	76.91 (8.82)	0.54	0.57	.371
	Duloxetine	213	76.85 (9.73)	1.24	0.57	
Sitting Systolic BP (millimeter of mercury)	Placebo	211	124.02 (12.13)	0.03	0.80	.891
	Duloxetine	213	124.55 (13.37)	-0.12	0.80	
Weight (kilogram)	Placebo	198	76.18 (19.20)	-0.01	0.24	.010
	Duloxetine	205	75.67 (18.11)	0.84	0.24	

Abbreviations: BP = blood pressure; LS = least squares; N = number of patients with a baseline and at least one nonmissing postbaseline data; SD = standard deviation; SE = standard error.