Summary ID# 8606

Clinical Study Summary: Study F1J-MC-HMDI

Duloxetine Versus Placebo in the Prevention of Recurrence of Major Depressive Disorder

Date summary approved by Lilly: 20 November 2008

Title of Study: Duloxetine Versus Placebo in the Prevention of Recurrence of Major Depressive Disorder	
Investigators: This multicenter study included 43 principal investigators.	
Study Centers: This study was conducted at 44 study centers in 6 countries.	
Length of Study: Date of first patient enrolled: 29 March 2005 Date of last patient completed: 23 January 2008	**Phase of Development:** 3b

Objectives: The primary objective of this study was to assess the efficacy of duloxetine 60 mg to 120 mg once daily (QD) compared with placebo in the prevention of depressive recurrences, as measured by time to recurrence, among patients with recurrent major depressive disorder (MDD) who had responded to duloxetine during a 4- to 10-week acute treatment period and a 24-week continuation treatment period.

The secondary objectives of this study were:

- To evaluate the efficacy of maintenance treatment with duloxetine compared with placebo as measured by:
  - Recurrence rates
  - Time to ≥50% worsening in the 17-item Hamilton Depression Rating Scale ($HAMD_{17}$) and Clinical Global Impression-Severity (CGI-Severity) ≥3
  - Loss of response ($HAMD_{17}$ >9 and CGI-Severity >2) at any time
  - $HAMD_{17}$ total score
  - CGI-Severity scale
  - Patient Global Impression-Improvement (PGI-Improvement) scale
  - Hamilton Depression Rating Scale (HAMD) subscales, including the Core, Maier, Anxiety/Somatization, Retardation/Somatization, and Sleep subscales, and the depressed mood item (Item 1)
  - Visual Analog Scale (VAS) for pain
  - Symptom Questionnaire-Somatic Subscale (SQ-SS).

- To assess the efficacy of maintenance treatment with duloxetine compared with placebo on quality of life and health outcome measures, as measured by:
  - Sheehan Disability Scale (SDS)
  - 36-item Short-Form Health Survey (SF-36)
  - Resource Utilization and Hospitalization Module.
- To evaluate the safety and tolerability of maintenance treatment with duloxetine compared with

placebo as measured by:
  - Treatment-emergent adverse events (TEAEs)
  - Vital signs
  - Laboratory measurements
  - Arizona Sexual Experience Scale (ASEX).
- To assess the efficacy and safety of duloxetine during the 4- to 10-week, open-label acute therapy phase and the 24-week open-label continuation therapy phase, using the above measures (if applicable).

Study Design: This was an 86-week study (4-10 weeks open-label acute therapy, 24 weeks open-label continuation therapy, followed by 52 weeks double-blind maintenance therapy) in which outpatients who met the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revised (DSM-IV-TR) diagnostic criteria for recurrent MDD without psychotic features, and who had responded to duloxetine 60 mg QD to 120 mg QD after 4 to 10 weeks of open-label acute therapy and 24 weeks of open-label continuation therapy were randomized to double-blind treatment for 52 weeks with either duloxetine or placebo. Patients who discontinued the study had the option to enter a 3-week follow-up taper phase. The study design is illustrated in Figure HMDI.1.

Number of Patients:
Planned: A total of 490 patients were planned to be enrolled into the open-label acute therapy phase of the study, with approximately 257 patients estimated to be randomly assigned into the double-blind maintenance therapy phase of the study.
Enrolled/Randomized: A total of 514 patients were enrolled into the open-label acute therapy phase; 413 continued into the open-label continuation therapy phase; and 288 patients were subsequently randomized to placebo (N=142) or duloxetine (N=146) during the double-blind maintenance therapy phase of the study.
Completed: 169 patients (73 placebo and 96 duloxetine) completed the double-blind maintenance therapy phase of the study.

Diagnosis and Main Criteria for Inclusion: Patients were outpatients of at least 18 years of age who met DSM-IV-TR diagnostic criteria for recurrent MDD and who had experienced at least three episodes of depression, including the current episode, within the past 5 years. Patients had to have been in remission between episodes of depression and stable and off antidepressant medication for at least 2 months prior to the onset of the current episode. Patients had to have a $HAMD_{17}$ total score $\geq$18 at Visits 1 and 2, and a CGI-Severity $\geq$4 at Visits 1 and 2.

Test Product, Dose, and Mode of Administration: Duloxetine 60 to 120 mg/day, given orally once a day as two to four 30-mg capsules.

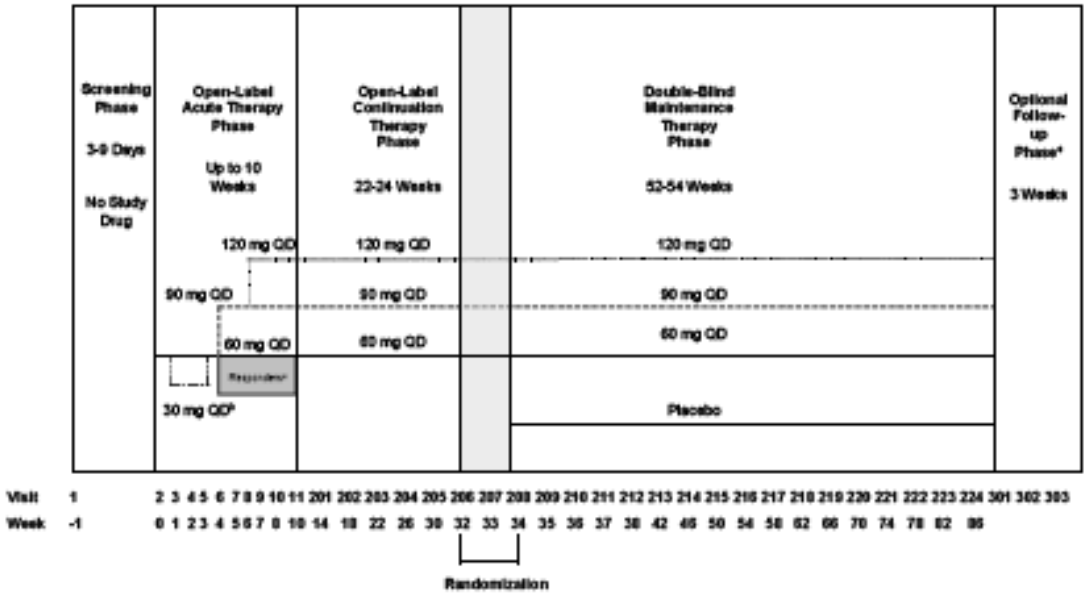
Reference Therapy, Dose, and Mode of Administration: During the double-blind maintenance therapy phase only, placebo, given orally once a day as capsules.

Duration of Treatment: The duration of treatment was 4 to 10 weeks for the open-label acute therapy phase, 24 weeks for the open-label continuation therapy phase, 52 weeks for the double-blind maintenance therapy phase, and up to 3 weeks for the optional follow-up phase.

Variables:
Efficacy: The primary efficacy variable was time to recurrence during the double-blind maintenance therapy phase of the study. Secondary efficacy variables included recurrence rates, time to $\geq$50% worsening in the $HAMD_{17}$ and CGI-Severity $\geq$3; loss of response ($HAMD_{17}$ >9 and CGI-Severity >2) at any time; $HAMD_{17}$ total score; HAMD subscales, including the Core, Maier, Anxiety/Somatization, Retardation/Somatization, and Sleep subscales, and the depressed mood item (Item 1); CGI-Severity scale; VAS for pain; SQ-SS; and PGI-Improvement scale.
Health Outcomes: SDS; SF-36; Resource Utilization and Hospitalization Module.
Safety: TEAEs, laboratory measurements, vital signs, ECGs, and ASEX. For the ASEX scale, Item 1=sex drive; Item 2=arousal; Item 3=vaginal lubrication/penile erection; Item 4=orgasm; Item 5=satisfaction

Evaluation Methods:
Statistical: All analyses were conducted on an intent-to-treat (ITT) basis. An ITT analysis is an analysis of data by the groups to which patients were randomly assigned, even if the patient did not take the assigned treatment, did not receive the correct treatment, or did not follow the protocol.
In each phase, all patients on duloxetine formed one duloxetine treatment group, regardless of their doses of duloxetine. Treatment comparisons during the double-blind maintenance therapy phase compared the duloxetine treatment group and the placebo treatment group; no statistical comparisons were made between dose groups, although the summary statistics by dose may have been reported. Treatment effects were evaluated based on a two-sided significance level of 0.05 and interaction effects at a significance level of 0.10 unless otherwise stated. No adjustments were made for multiple comparisons.

A display of the study design is presented in Figure HMDI.1.



Abbreviation: QD = once daily.
a Patients who meet response criteria during Week 4 to Week 10 moved directly to the open-label continuation therapy phase.
b Patients who could not tolerate 60 mg QD may have decreased their doses to 30 mg QD during Visit 3 through Visit 5.

Figure HMDI.1. Study design.

Disposition:

A total of 514 patients were screened and enrolled into the open-label acute therapy phase of the study. Of these, 413 patients completed the open-label acute therapy phase, met response criteria, and entered the open-label continuation therapy phase of the study. Of these 413 patients, 288 patients completed the open-label continuation therapy phase of the study, continued to meet response criteria, and advanced to the double-blind maintenance therapy phase of the study. Of the 288 patients who advanced to the double-blind maintenance therapy phase of the study, 146 patients were randomized to

duloxetine and 142 patients were randomized to placebo. A total of 169 patients completed the double-blind maintenance therapy phase of the study (73/142 [51.4%] patients in the placebo group and 96/146 [65.8%] patients in the duloxetine group; p=.017). A total of 119 patients discontinued the double-blind maintenance therapy phase of the study (69/142 [48.6%] placebo and 50/146 [34.2%] duloxetine). A total of 109 patients entered the optional follow-up taper phase (61/96 [63.5%] in the duloxetine group and 48/73 [65.8%] in the placebo group). A summary of patient disposition is provided in Figure HMDI.2.

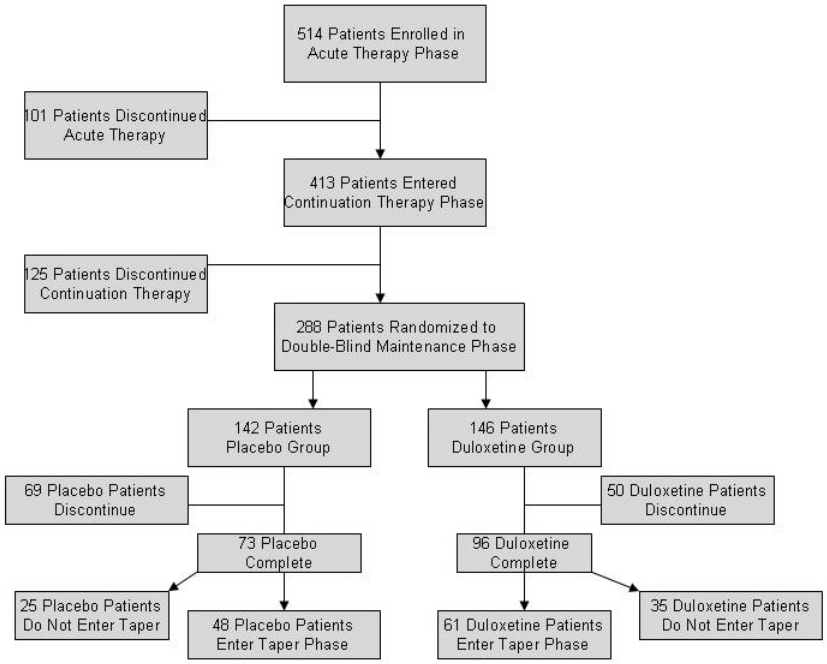


Figure HMDI.2. Patient disposition.

The most common reasons for discontinuation from the open-label acute therapy phase were adverse events, followed by patient decision (33/514 [6.4%] and 24/514 [4.7%], respectively). The most common reason for discontinuation from the open-label continuation therapy phase was patient decision (50/413 [12.1%]). For patients who entered the double-blind maintenance therapy phase, there was a statistically significant difference in the number of patients who discontinued because the recurrence criteria were met between the duloxetine group (14/146 [9.6%] patients) and the placebo group (43/142 [30.3%] patients; p<.001). For patients who entered the optional follow-up taper phase, the most common reasons for discontinuation were patient decision for the

duloxetine group (4/61 [6.6%]) and physician decision for the placebo group (3/48 [6.3%]).

Demographics:

Open-label Acute Therapy Phase:

Most patients were female (69.8%) and Caucasian (98.1%). The average age of patients was 47.62 years and the ages ranged from 18.04 to 79.64. The mean HAMD17 total score was 23.07 and the mean CGI-Severity score was 4.49 at baseline. The average age at the first episode of depression was 33.16 years of age. The average duration of the current depressive episode was approximately 4 months and the average number of previous depressive episodes was 4.22. A summary of patient demographic and disease characteristics at baseline of the open-label acute therapy phase is provided in Table HMDI.1.

Table HMDI.1. Patient Demographic and Disease Characteristics at Baseline of Open-label Acute Therapy Phase - All Enrolled Patients

Variable	Duloxetine (N=514)
Sex [n (%)]	
Male	155 (30.2)
Female	359 (69.8)
Origin [n (%)]	
Caucasian	504 (98.1)
Hispanic	5 (1.0)
African	3 (0.6)
South Asian	1 (0.2)
East Asian	1 (0.2)
Age (years)	
Mean (SD)	47.62 (13.30)
Median	48.60
Minimum, maximum	18.04, 79.64
Height (cm)	
Mean (SD)	167.60 (9.23) [a]
Minimum, maximum	144.00, 195.00
Weight (kg)	
Mean (SD)	74.66 (16.14)[b]
Minimum, maximum	37.00, 163.00
$HAMD_{17}$ Total Score	
Mean (SD)	23.07 (3.57)
Minimum, maximum	16.00, 36.00
CGI-Severity	
Mean (SD)	4.49 (0.6)
Minimum, maximum	4.00, 6.00
Age at First Episode (years)	
Mean (SD)	33.16 (13.38)
Minimum, maximum	3.00, 73.00
Duration of Current Episode (months)	
Mean (SD)	4.02 (4.65)
Minimum, maximum	1.00, 72.00
Number of Previous Episodes	
Mean (SD)	4.22 (3.48)
Minimum, maximum	2.00, 71.00

Abbreviations: N = number of enrolled patients in treatment phase, SD = standard deviation.

[a] N=508

[b] N=513

Open-label Continuation Therapy Phase:

Most patients were female (70.5%) and Caucasian (97.8%). The average age of patients was 47.42 years and the ages ranged from 18.04 to 79.64. The mean HAMD17 total score was 6.65 and the mean CGI-Severity score was 1.83 at baseline. The average age

at the first episode of depression was 32.94 years of age. The average duration of the current depressive episode was approximately 4 months and the average number of previous depressive episodes was 4.25. A summary of patient demographic and disease characteristics at baseline of the open-label continuation therapy phase is provided in Table HMDI.2.

Table HMDI.2. Patient Demographic and Disease Characteristics at Baseline of Open-label Continuation Therapy Phase - All Patients Continuing from Open-label Acute Therapy Phase

Variable	Duloxetine (N=413)
Sex [n (%)]	
Male	122 (29.5)
Female	291 (70.5)
Origin [n (%)]	
Caucasian	404 (97.8)
Hispanic	4 (1.0)
African	3 (0.7)
South Asian	1 (0.2)
East Asian	1 (0.2)
Age (years)	
Mean (SD)	47.42 (13.04)
Median	48.55
Minimum, maximum	18.04, 79.64
Height (cm)	
Mean (SD)	167.35 (9.17) [a]
Minimum, maximum	144.00, 195.00
Weight (kg)	
Mean (SD)	74.21 (15.87)
Minimum, maximum	44.00, 158.00
$HAMD_{17}$ Total Score	
Mean (SD)	6.65 (2.06)
Minimum, maximum	1.00, 12.00
CGI-Severity	
Mean (SD)	1.83 (0.39)
Minimum, maximum	1.00, 3.00
Age at First Episode (years)	
Mean (SD)	32.94 (13.12)
Minimum, maximum	3.00, 73.00
Duration of Current Episode (months)	
Mean (SD)	3.92 (4.85)
Minimum, maximum	1.00, 72.00
Number of Previous Episodes	
Mean (SD)	4.25 (3.79)
Minimum, maximum	3.00, 71.00

Abbreviations: N = number of enrolled patients in treatment phase, SD = standard deviation.

[a] N=410

Double-blind Maintenance Therapy Phase:

There were no statistically significant differences between treatment groups for patient demographic or disease characteristics at baseline of the double-blind maintenance therapy phase. Most patients included in this study were female and Caucasian. For the double-blind maintenance therapy phase, 74.6% of placebo and 68.5% of duloxtine subjects were female and 97.9% of placebo and 97.9% of duloxetine subjects were Caucasian.

For the double-blind maintenance therapy phase, the average age of patients was 48.01 years for placebo and 47.07 years for duloxetine and aged from 18.04 to 75.72 for placebo and 18.05 to 79.64 for duloxetine. The mean HAMD17 total score was 4.49 for placebo and 4.12 for duloxetine. The mean CGI-Severity score was 1.46 for placebo and 1.49 for duloxetine. The average age at the first episode of depression was 33.49 years of age for placebo and 32.37 years of age for duloxetine. The average duration of the current depressive episode was approximately 3.49 months for placebo and 3.85 months for duloxetine and the average number of previous depressive episodes was 3.97 months for placebo and 4.36 months for duloxetine.

A summary of patient demographic and disease characteristics at baseline of the double-blind maintenance therapy phase is provided in Table HMDI.3.

Table HMDI.3. Patient Demographic and Baseline Characteristics at Baseline of the Double-blind Maintenance Therapy Phase - All Randomized Patients

Variable	Placebo (N=142)	Duloxetine (N=146)	p-value
Sex [n (%)][b]			
Male	36 (25.4)	46 (31.5)	.296
Female	106 (74.6)	100 (68.5)	
Origin [n (%)][b]			
Caucasian	139 (97.9)	143 (97.9)	.903
Hispanic	2 (1.4)	1 (0.7)	
African	1 (0.7)	1 (0.7)	
South Asian	0	0	
East Asian	0	1 (0.7)	
Age (years) [b]			
Mean (SD)	48.01 (12.29)	47.07 (12.84)	.529
Median	49.23	47.29	
Minimum, maximum	18.04, 75.72	18.05, 79.64	
Height (cm) [b]			
Mean (SD)	166.95 (8.70)[a]	167.42 (9.34)	.658
Minimum, maximum	146.00, 192.00	144.00, 190.00	
Weight (kg) [b]			
Mean (SD)	76.09 (16.24)	74.47 (16.42)	.401
Minimum, maximum	43.00, 139.00	45.00, 128.00	
$HAMD_{17}$ Total Score [c]			
Mean (SD)	4.49 (2.51)	4.12 (2.52)	.214
Minimum, maximum	0.00, 10.00	0.00, 10.00	
CGI-Severity [c]			
Mean (SD)	1.46 (0.50)	1.49 (0.52)	.720
Minimum, maximum	1.00, 2.00	1.00, 3.00	
Age at First Episode (years) [c]	33.49 (13.91)	32.37 (12.33)	.472
Mean (SD)	3.00, 73.00	10.00, 63.00	
Minimum, maximum			
Duration of Current Episode (months) [c]			
Mean (SD)	3.49 (3.42)	3.85 (3.38)	.374
Minimum, maximum	1.00, 30.00	1.00, 27.00	
Number of Previous Episodes [c]	3.97 (1.47)	4.36 (2.25)	.082
Mean (SD)	3.00, 11.00	3.00, 20.00	
Minimum, maximum			

Abbreviations: N = number of patients randomized to the double-blind maintenance therapy phase, SD = standard deviation.

[a] N=139

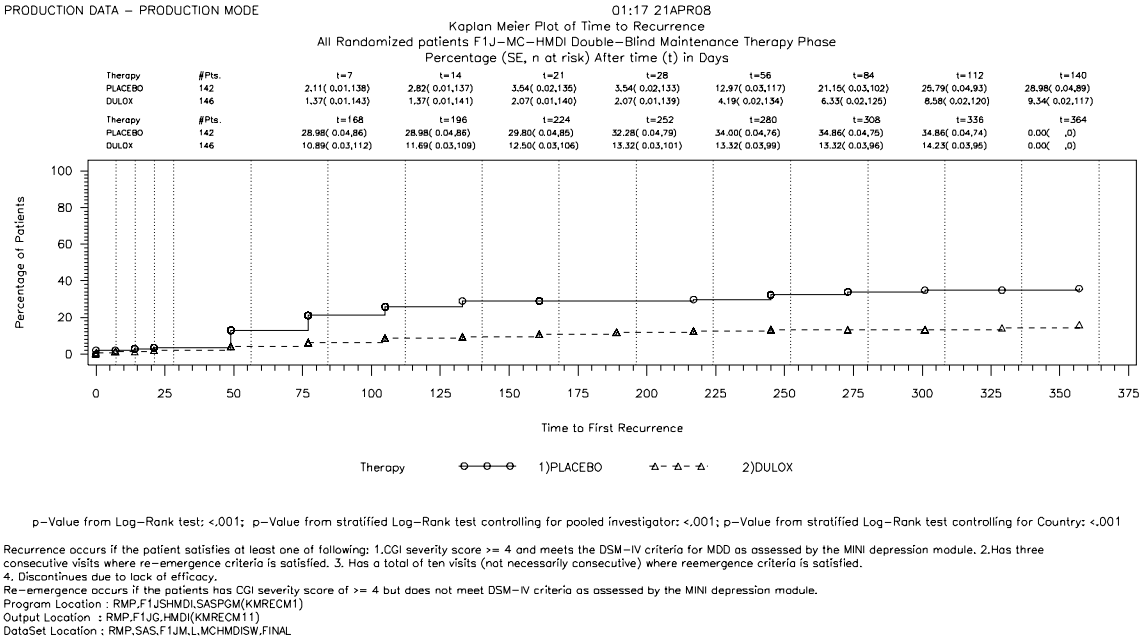
[b] p-values analyzed for means using Type II sum of squares analyses;

[c] p-values analyzed for means using Type II sum of sqares analysis of variance (ANOVA): model=treatment

Summary:

Primary Efficacy:

The primary efficacy measure was time to recurrence during the double-blind maintenance therapy phase of the study. Time to a depressive recurrence was statistically significantly longer in patients treated with duloxetine compared with patients treated with placebo (p<.001). A Kaplan-Meier plot of time to recurrence during the double-blind maintenance therapy phase of the study is provided in Figure HMDI.3.



p–Value from Log–Rank test: <.001; p–Value from stratified Log–Rank test controlling for pooled investigator: <.001; p–Value from stratified Log–Rank test controlling for Country: <.001

Recurrence occurs if the patient satisfies at least one of following: 1.CGI severity score >= 4 and meets the DSM–IV criteria for MDD as assessed by the MINI depression module. 2.Has three consecutive visits where re–emergence criteria is satisfied. 3. Has a total of ten visits (not necessarily consecutive) where reemergence criteria is satisfied. 4. Discontinues due to lack of efficacy.
Re–emergence occurs if the patients has CGI severity score of >= 4 but does not meet DSM–IV criteria as assessed by the MINI depression module.
Program Location : RMP,F1JSHMDI,SASPGM(KMRECM1)
Output Location : RMP,F1JG,HMDI(KMRECM11)
DataSet Location : RMP.SAS.F1JM.L.MCHMDISW.FINAL

Figure HMDI.3. Kaplan-Meier plot of time to recurrence.

Secondary Efficacy:

HAMD17, CGI-Severity, PGI-Improvement, VAS pain, and SQ-SS Scores

Among the 146 duloxetine-treated patients and 142 placebo-treated patients who entered the double-blind maintenance therapy phase, duloxetine had a statistically significant lower recurrence rate at any time (47/142 [33.1%] placebo vs 21/146 [14.4%] duloxetine; p<.001) and a statistically significant lower rate of loss of response at any time (66/142 [46.5%] placebo vs 44/146 [30.1%] duloxetine; p=.003). During the double-blind maintenance therapy phase of the study, there was statistically significant worsening of $HAMD_{17}$ total score, all $HAMD_{17}$ subscales, except for sleep, and CGI-Severity in placebo-treated patients compared with duloxetine-treated patients, and a statistically significant difference between treatment groups in mean PGI-Improvement at endpoint favoring duloxetine. There were no statistically significant differences between treatment groups in the mean change from baseline to endpoint in mean VAS for pain or SQ-SS scores.

A summary of secondary efficacy parameters during the double-blind maintenance therapy phase is presented in Table HMDI.4.

Table HMDI.4. Secondary Endpoints ($HAMD_{17}$, CGI-Severity, VAS for Pain, SQ-SS, and PGI-Improvement) Mean Changes from Baseline to Endpoint – Double-blind Maintenance Therapy Phase – All Randomized Patients

Variable	Change from Baseline to Endpoint	
	Placebo (N=142)	Total Duloxetine (N=145)
$HAMD_{17}$ Total Score***		
Mean (SD)	4.01 (6.75)	1.65 (5.31)
$HAMD_{17}$ Item 1 – Depressed Mood Subscale*		
Mean (SD)	0.62 (1.22)	0.30 (0.91)
$HAMD_{17}$ Sleep Subscale		
Mean (SD)	0.71 (1.60)	0.14 (1.33)
$HAMD_{17}$ Retardation Subscale*		
Mean (SD)	1.30 (2.61)	0.66 (2.12)
$HAMD_{17}$ Maier Subscale*		
Mean (SD)	2.11 (3.68)	1.04 (2.88)
$HAMD_{17}$ Core Subscale*		
Mean (SD)	1.59 (2.93)	0.82 (2.09)
$HAMD_{17}$ Anxiety Subscale*		
Mean (SD)	1.36 (2.61)	0.55 (2.17)
CGI-Severity Total Score***		
Mean (SD)	0.85 (1.38)	0.27 (0.94)
VAS for Pain – Overall Pain		
Mean (SD)	3.09 (20.85)[a]	3.64 (23.49)
VAS for Pain – Headache		
Mean (SD)	1.58 (20.34)[a]	5.19 (21.79)
VAS for Pain – Back Pain		
Mean (SD)	3.60 (20.26)[a]	1.86 (21.53)
VAS for Pain – Shoulder Pain		
Mean (SD)	3.34 (17.95)[a]	0.21 (21.09)
VAS for Pain – Interference with Daily Activities		
Mean (SD)	1.79 (18.75)[a]	3.74 (24.24)
VAS for Pain – Pain While Awake		
Mean (SD)	3.38 (24.95)[a]	3.96 (28.38)
SQ-SS		
Mean (SD)	0.72 (4.77)[b]	0.77 (4.68)
PGI-Improvement Mean at Endpoint***		
Mean (SD)	2.32 (1.35)	1.76 (1.02)

Abbreviations: CGI = Clinical Global Impressions, $HAMD_{17}$ = 17-item Hamilton Depression Rating Scale score, N = number of randomized patients with a baseline and at least one non-missing post-baseline measurement, SD = standard deviation, SQ-SS = Symptom Questionnaire – Somatic Subscale, VAS = Visual Analog Scale; PGI=Patient Global Improvement.

*Pairwise comparison of LS means; $p<.05$; ***Pairwise comparison of LS means; $p<.001$

[a] N=141; [b] N=140

Note: An increase in score indicates worsening for all secondary endpoints, except for PGI-Improvement.

During the open-label acute therapy phase, there were statistically significant improvements in the mean change from baseline to endpoint for the $HAMD_{17}$ total score (mean change -14.37; p<.001), all $HAMD_{17}$ subscales (range of mean changes -2.37 to -7.46; all p<.001), CGI-Severity (mean change -2.30; p<.001), SQ-SS score (mean change -5.37; p<.001), and for the VAS for pain scores (range of mean changes -10.47 to -16.79; all p<.001). At endpoint, mean PGI-Improvement score was 2.12 (p<.001).

During the open-label continuation therapy phase, there were statistically significant improvements in the mean change from baseline to endpoint for the $HAMD_{17}$ total score (mean change -0.61; p=.016), the $HAMD_{17}$ retardation subscale (mean change -0.48; p<.001), the $HAMD_{17}$ Maier subscale (mean change -0.29; p=.046), and the $HAMD_{17}$ core subscale (mean change -0.29; p=.019). At endpoint, mean PGI-Improvement score was 1.76 (p<.001). No statistically significant mean changes from baseline to endpoint were observed for CGI-Severity score (mean change -0.07; p=.153), VAS for pain scores (range of mean changes -0.39 to 1.16; p>.273), or SQ-SS score (mean change -0.35; p=.157).

During the optional follow-up taper phase, there was statistically significant worsening in the mean change from baseline to endpoint in the CGI-severity score (placebo -0.17, duloxetine 0.15; p=.027). No statistically significant mean changes from baseline to endpoint were observed for $HAMD_{17}$ total score (placebo -0.70, duloxetine 0.47; p=.590) or VAS for pain scores (all p≥.180).

Quality of Life and Health Outcome Measures

Additional secondary measures included quality of life and health outcome measures. For the open-label acute therapy phase of the study, there were statistically significant improvements (increases) in mean changes from baseline to endpoint for general quality of life measures (as measured by the SF-36; p<.001 for all 12 scores) and statistically significant decreases for mean disability scores (as measured by the SDS) for global score, social life item, and family life/home responsibilities item (all p<.001), but not for the work/school item (p=.606).

For the open-label continuation therapy phase of the study, there were statistically significant increases in the SF-36 mean changes from baseline to endpoint for mental component summary, role limitations due to emotional problems, mental health, social function, vitality, and health compared to a year ago (all p<.001), role limitations due to physical (p=.025), and general health perceptions (p=.002). Also, there were statistically significant decreases in mean changes from baseline to endpoint in all SDS scores (p<.008 for work/school item, p<.001 for all others).

During the double-blind maintenance therapy phase of the study, treatment with duloxetine was associated with statistically significant higher scores on general quality of life (as measured by the SF-36) and statistically lower disability scores (as measured by the SDS) compared with placebo. Table HMDI.5 provides a summary of the statistically

significant mean changes from baseline to endpoint for the SDS and SF-36 for all randomized patients during the double-blind maintenance therapy phase of the study.

Table HMDI.5. Sheehan Disability Scale and 36-item Short-Form Health Survey (SF-36)
Mean Change from Baseline to Endpoint – Double-blind Maintenance Therapy Phase – All Randomized Patients

	Change from Baseline to Endpoint	
Variable	**Placebo (N=142)**	**Total Duloxetine (N=146)**
Sheehan Disability Scale		
SDS – Global Score*		
Number of patients	117	128
Mean (SD)	2.15 (8.98)	-0.06 (7.90)
SDS – Family Life/Home Responsibilities item*		
Number of patients	117	128
Mean (SD)	0.77 (3.05)	-0.04 (2.76)
36-item Short-Form Health Survey		
Mental Component Summary**		
Number of patients	117	129
Mean (SD)	-5.87 (13.81)	-1.06 (11.72)
Role Limitations Due to Physical Problems*		
Number of patients	118	129
Mean (SD)	-0.40 (1.89)	-0.02 (1.45)
Role Limitations Due to Emotional Problems**		
Number of patients	117	129
Mean (SD)	-0.45 (1.35)	0.02 (1.22)
Mental Health**		
Number of patients	118	129
Mean (SD)	-2.85 (6.26)	-0.62 (5.40)

Abbreviations: N = number of randomized patients with a baseline and at least one non-missing post-baseline measurement, SD = standard deviation, SDS = Sheehan Disability Scale.
*Pairwise comparison of LS means statistically significant ($p<.05$); p=.029 (global score); p=.021 (family life/home responsibilities item); p=.029 (role limitations due to physical problems).
**Pairwise comparison of LS means statistically significant ($p<0.01$); p=.002 (mental health component summary); p=.003 (role limitations due to emotional problems); p=.001 (mental health).
Note: A higher SDS score indicates greater disability. For the SF-36, higher scores indicate better health status or functioning.

Regarding resource utilization, in the open-label acute therapy phase, there was a statistically significant increase in the number of visits to a psychiatrist (mean change of 0.03 visits; $p<.001$). In the open-label continuation therapy phase, there was a statistically significant decrease in the number of visits to a psychiatrist (mean change of

-0.03 visits; p<.001). In the double-blind maintenance therapy phase, there were no statistically significant differences between treatment groups in the resource utilization and hospitalization module (p>.200).

Safety:

One death occurred during this study (a completed suicide); the death occurred during the open-label acute therapy phase while the patient was receiving duloxetine 60 mg QD, and the death was not attributed to study drug.

The incidence of serious adverse events (SAEs) was 6/514 [1.2%] in the open-label acute therapy phase, 13/413 [3.1%] in the open-label continuation therapy phase, and 4/142 [2.8%] for placebo and 7/146 [4.8%] for duloxetine (p=.541) in the double-blind maintenance therapy phase of the study.

The incidence of discontinuations due to adverse events (AEs) was 34/514 [6.6%] in the open-label acute therapy phase, 25/413 [6.1%] in the open-label continuation therapy phase, and 3/142 [2.1%] for placebo and 6/142 [4.1%} for duloxetine (p=.501) in the double-blind maintenance therapy phase of the study.

The most frequently reported AEs reported as reasons for discontinuation were nausea (8/514 [1.6%] during the open-label acute therapy phase and 1/413 [0.2%] during the open-label continuation therapy phase) and vomiting (5/14 [1.0%] during the open-label acute therapy phase and 1/413 [0.2%] during the open-label continuation therapy phase).

An overview of AEs is provided in Table HMDI.6.

A summary of treatment-emergent AEs occurring in at least 5% of patients in any study phase for the open-label acute, open-label continuation, double-blind maintenance, and optional follow-up taper phases is provided in Table HMDI.7.

Table HMDI.6. Overview of Adverse Events
Number and Percentage of Patients[a]
All Enrolled/Randomized Patients

Adverse Event	Acute Phase	Continuation Phase	Maintenance Phase			Taper/DC Phase		
	Duloxetine (N=514) n (%)	Duloxetine (N=413) n (%)	Placebo (N=142) n (%)	Duloxetine (N=146) n (%)	p-value[b]	Placebo (N=48) n (%)	Duloxetine (N=61) n (%)	p-value[b]
Deaths	1 (0.2)	0	0	0	NA	0	0	NA
Serious adverse events	6 (1.2)	13 (3.1)	4 (2.8)	7 (4.8)	.541	0	0	NA
Discontinuations due to an adverse event	34 (6.6)	25 (6.1)	3 (2.1)	6 (4.1)	.501	0	1 (1.6)	NA
Treatment-emergent adverse events	349 (67.9)	244 (59.1)	89 (62.7)	89 (61.0)	.809	4 (8.3)	14 (23.0)	.067

Abbreviations: DC = discontinuation, N = number of enrolled patients in treatment phase, n = number of patients in this category; NA = not applicable

[a] Patients may be counted in more than one category.

[b] p-values for placebo vs duloxetine using Fisher's exact test.

Table HMDI.7. Treatment-Emergent Adverse Events Occurring in at Least 5% of Patients in any Study Phase by Preferred Term
Number and Percentage of Patients[a]
All Enrolled/Randomized Patients

Adverse Events	Acute Phase	Continuation Phase	Maintenance Phase			Taper/DC Phase		
	Duloxetine (N=514) n (%)	Duloxetine (N=413) n (%)	Placebo (N=142) n (%)	Duloxetine (N=146) n (%)	p-value[a]	Placebo (N=48) n (%)	Duloxetine (N=61) n (%)	p-value[a]
Patients with ≥ 1 AE	349 (67.9)	244 (59.1)	89 (62.7)	89 (61.0)	.809	4 (8.3)	14 (23.0)	.067
Nausea	150 (29.2)	5 (1.2)	7 (4.9)	6 (4.1)	.783	0	1 (1.6)	1.000
Headache	79 (15.4)	39 (9.4)	11 (7.7)	13 (8.9)	.832	0	0	NA
Dry mouth	76 (14.8)	11 (2.7)	1 (0.7)	4 (2.7)	.371	0	0	NA
Hyperhidrosis	76 (14.8)	25 (6.1)	2 (1.4)	7 (4.8)	.173	0	0	NA
Fatigue	60 (11.7)	10 (2.4)	4 (2.8)	8 (5.5)	.378	0	0	NA
Constipation	48 (9.3)	13 (3.1)	0	0	NA	0	0	NA
Dizziness	41 (8.0)	10 (2.4)	9 (6.3)	5 (3.4)	.284	0	1 (1.6)	1.000
Diarrhea	38 (7.4)	18 (4.4)	4 (2.8)	2 (1.4)	.443	1 (2.1)	0	.440
Vomiting	28 (5.4)	5 (1.2)	2 (1.4)	2 (1.4)	1.000	0	0	NA
Insomnia	27 (5.3)	14 (3.4)	9 (6.3)	7 (4.8)	.615	0	0	NA
Decreased appetite	26 (5.1)	1 (0.2)	0	0	NA	0	0	NA
Nasopharyngitis	16 (3.1)	26 (6.3)	11 (7.7)	9 (6.2)	.648	0	1 (1.6)	1.000
Back pain	10 (1.9)	19 (4.6)	7 (4.9)	13 (8.9)	.247	0	1 (1.6)	1.000
Influenza	6 (1.2)	13 (3.1)	11 (7.7)	5 (3.4)	.128	0	1 (1.6)	1.000

Abbreviations: AE = adverse event, DC = discontinuation, N = number of enrolled patients in treatment phase, n = number of patients in this category; NA = not applicable

[a] Patients may be counted in more than one category.

[b] p-values for placebo vs duloxetine using Fisher's exact test.

Clinical Laboratory:

The most frequently occurring abnormal laboratory values during the open-label acute therapy phase included high creatine phosphokinase (CPK; 31/432 [7.2%]), high alanine aminotransferase (ALT; 26/425 [6.1%]), and low cholesterol (25/437 [5.7%]). The most frequently occurring abnormal laboratory values during the open-label continuation therapy phase included high CPK (33/347 [9.5%]), high ALT (26/347 [7.5%]), high AST (25/369 [6.8%]), high fasting glucose (24//358 [7.2%]), high prolactin (3/43 [7.0%]), and low total bilirubin (27/382 [7.1%]). The most frequently occurring abnormal laboratory values during the double-blind maintenance therapy phase included high alanine aminotransferase (ALT; 14/107 [13.1%] placebo and 19/121 [15.7%] duloxetine; p=.707), high prolactin (5/128 [17.9%] placebo and 3/24 [12/5%] duloxetine), and high CPK (17/109 [15.6%] placebo and 15/110 [13.6%] duloxetine; p=.706). There was a statistically significant difference between treatment groups during the double-blind maintenance therapy phase for abnormal laboratory values for high total bilirubin (5/129 [3.9%] placebo and 0/1386 [0%] duloxetine; p=.025).

Vital Signs:

There were no statistically significant differences between treatment groups with respect to changes in vital signs during the double-blind maintenance therapy phase or during the optional follow-up phase of the study. There were statistically significant differences within the treatment group from baseline to endpoint for mean pulse and weight (increase of 1.42 bpm for pulse; p<.001 and decrease of 0.69 kg for weight; p<.001 during the open-label acute therapy phase and increase of 1.75 bpm for pulse; p<.001 and increase of 0.88 kg for weight during the open-label continuation therapy phase).

Electrocardiogram:

For ECG results, there were statistically significant differences for the change from baseline to endpoint during the open-label acute therapy phase for heart rate (increase of 3.26 bpm; p<.001), 1000X60/heart rate (decrease of 43.79; p<.001), PR interval (decrease of 2.52 milliseconds; p.002), QT interval (decrease of 7.22 milliseconds; p<.001); and QTcB (increase of 2.61 milliseconds; p=.007). For ECG results, there were statistically significant differences for the change from baseline to endpoint during the open-label continuation therapy phase for heart rate (increase of 3.04 bpm; p<.001), 1000X60/heart rate (decrease of 39.70; p<.001), QT interval (decrease of 3.98 milliseconds; p=.007), QTcB interval (increase of 5.39 milliseconds; p<.001); and QT/cubic root RR (increase of 2.11; p=.025). For ECG results, there were statistically significant differences between placebo and duloxetine treatment in the mean change from baseline to endpoint during the double-blind maintenance therapy phase for QT interval (mean change 11.57 millisecconds placebo and 2.57 milliseconds duloxetine; p=.004), heart rate (-5.24 bpm placebo and 0.42 bpm duloxetine; p<.001), 1000X60/heart rate (65.29 and -2.56 p<.001), and PR interval (3.55 milliseconds placebo and 0.12 milliseconds duloxetine; p=.030).

Sexual Functioning:

During the open-label acute therapy phase, there were statistically significant differences for the change from baseline to endpoint for Item 1 (sex drive; $p<.001$), Item 2 (arousal; $p=.003$), Item 3 (vaginal lubrication/penile erection; $p=.025$), and for the sum of Items 1-5 ($p<.001$) of the ASEX scale. During the open-label continuation therapy phase, there were statistically significant differences for the change from baseline to endpoint for Item 1 ($p<.001$), Item 2 ($p<.001$), Item 4 (orgasm; $p<.001$), and for the sum of Items 1-5 ($p<.001$) of the ASEX scale. During the double-blind maintenance therapy phase, there were no significant differences between treatment groups in mean change from baseline to endpoint for any individual ASEX scale items or ASEX total score.