Summary ID# 9548

Clinical Study Summary: Study F1J-XM-HMED

Open-Label Duloxetine Extension Phase in Patients Who Have Completed the HMDG Clinical Trial

Date summary approved by Lilly: 30 July 2007

Brief Summary of Results

F1J-XM-HMED was a Phase 3 multicenter, open-label, outpatient study of patients who completed a previous duloxetine study, protocol code: F1J-MC-HMDG (HMDG: CT#8604). The primary objective of this study was to provide duloxetine at a flexible dose of 60 mg to 120 mg daily during 6 months for the continuation phase of treatment for those patients with major depressive disorder (MDD) who had previously completed the HMDG clinical trial. The study assessed the safety of duloxetine and summarized spontaneously reported adverse events.

Results of the study are as follow:

- Ninety-nine patients were included in the study; ninety-eight patients received treatment and were considered for the statistical analysis.
- Thirty-two patients experienced at least one treatment-emergent adverse event (TEAE) during the study.
- Sixteen patients experienced at least one TEAE probably related to treatment.
- One patient experienced one TEAE that satisfied the criteria of a serious adverse event (SAE; metastatic neoplasm), which was reported by the investigator to be nonrelated to the study drug. This patient later died after being discontinued from the study.
- No statistically significant changes in vital signs (blood pressure and heart rate) were observed between baseline and the final visit.

Title of Study: Open-Label Duloxetine Extension Phase in Patients Who Have Completed the HMDG Clinical Trial	
Investigator(s): This multicenter study included 12 principal investigators.	
Study Center(s): This study was conducted at 12 study centers in one country.	
Length of Study: ~1 year 6 months Date of first patient enrolled: 03 March 2005 Date of last patient completed entire study: 25 August 2006	**Phase of Development:** 3
Objectives: To provide duloxetine at a flexible dose of 60 mg to 120 mg daily during 6 months for the continuation phase of their treatment for those patients who had previously completed the HMDG clinical trial. The study assessed the safety of duloxetine and summarized and spontaneously reported adverse events.	
Study Design: Phase 3, open-label, outpatient study, of up to 6 months. ▪ Study Period I (24 weeks): Patients received open-label flexible dosing of duloxetine at the same dose that the patient was taking at the last visit of the HMDG clinical trial. The dose of duloxetine may have been adjusted in 30 mg increments to as high as 120 mg/day or as low as 60 mg/day. ▪ Study Period II (2- to 3-weeks duration): During this optional taper period, the dose of duloxetine was gradually reduced over a 2- to 3-week period (depending on the dose of duloxetine at entry to this period).	
Number of Patients: Planned: There were no limitations to the sample size Randomized/Entered: 99 patients entered in the study. 98 patients received treatment. Completed: 85 completed Study Period I and 66 completed Study Period II	
Main Criteria for Inclusion: Male or female patients at least 18 years of age who had previously satisfactorily completed the Lilly-sponsored HMDG clinical trial, and who were clinically controlled with duloxetine, as judged by the investigator.	
Dose and Mode of Administration: Duloxetine 60 to 120 mg/day given orally once or twice daily in 30 mg capsules.	
Reference Therapy, Dose, and Mode of Administration: None	
Duration of Treatment: Up to 6 months	
Variables: Safety: Safety was measured via collection of spontaneously reported treatment-emergent adverse events and vital signs.	
Evaluation Methods: Statistical: Safety data was collected and analyzed qualitatively as well as quantitatively. Exploratory analyses were conducted as deemed appropriate. No efficacy data was collected or analyzed. Safety analyses were conducted on the full analysis set which included all data from all patients receiving at least one dose of the study drug.	

Results:

Patient Demographics

Table HMED.1 summarizes patient characteristics at baseline. Of the 99 patients who entered the study, 98 were included in the statistical analysis, as one did not receive treatment. Of the 98 patients included in the statistical analysis, 80 were female (81, 6%) and 18 male (18, 4%). Almost all patients were Caucasian (96, 100%); two patients did not report their origin. The mean (± standard deviation [SD]) age was 52.9 ± 12.6 years.

Table HMED.1. Patient Characteristics at Baseline

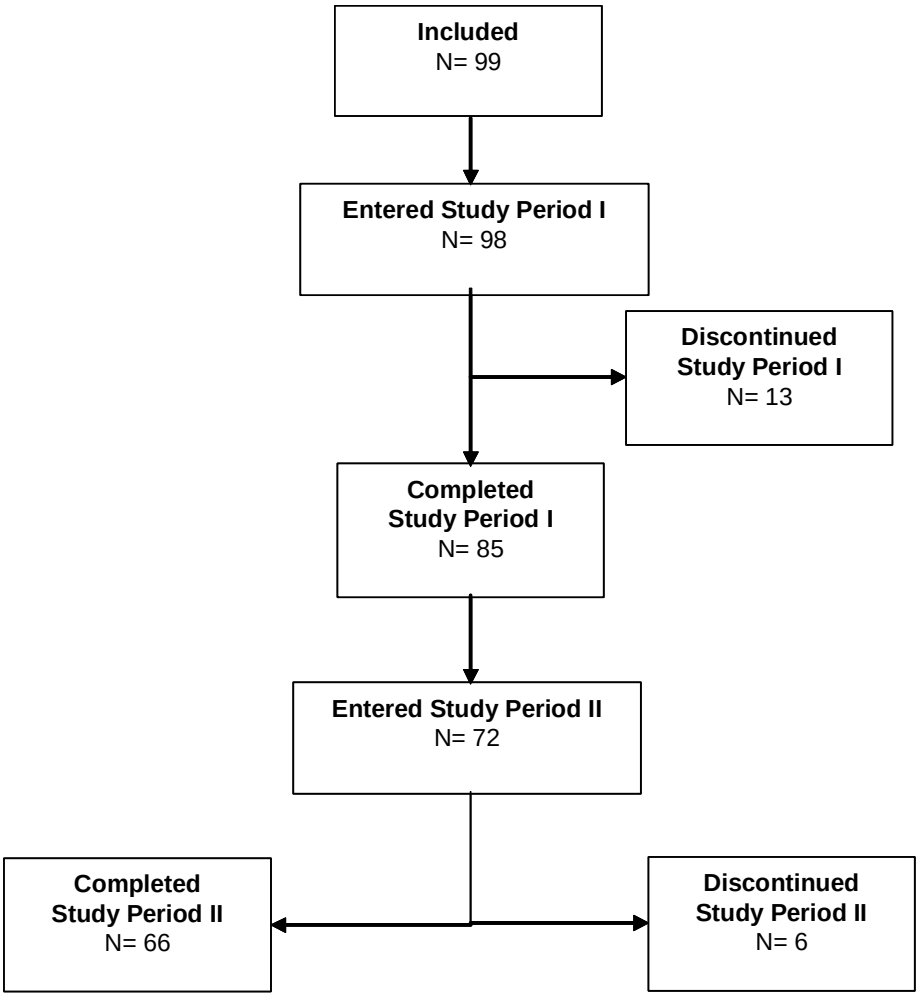
		N=98
Sex	Absent	0 (0.0%)
	Female	80 (81.6%)
	Male	18 (18.4%)
Origin	Absent	2 (%)
	Caucasian	96 (100.0%)
	African	0 (0.0%)
	Hispanic	0 (0.0%)
	South/East Asian	0 (0.0%)
	West Asian	0 (0.0%)
	Other	0 (0.0%)
Age(years)	N	98
	Range	21 - 80
	Q1	44
	Q3	61
	N absent	0
	Mean	52.9
	SD	12.6
	CI (mean) 95%	[50.3,55.4]
	Median	53

Abbreviations: CI = confidence interval; N = total number of patients; Q1 = 1st quartile (25th percentile); Q3 = 3rd quartile (75th percentile); SD = standard deviation.

Patient Disposition

A total of 99 patients were included in the study and 98 patients entered Study Period I. A total of 13 patients discontinued during Study Period I. Of the 85 completers of Study Period I, 72 patients entered into the optional Study Period II. A total of 6 patients discontinued during Study Period II and 66 patients completed.

Figure HMED.1 summarizes patient disposition during the study and Tables HMED.2 and HMED.3 summarize the discontinuation reasons during Study Period I and Period II, respectively.



Abbreviation: N = total number of patients.

Figure HMED.1. Overview of patient disposition.

Table HMED.2. Discontinuation Reasons During Study Period I

	N=98
Unknown	0 (0.0%)
Period I completed	85 (86.8%)
Lack of efficacy	2 (2.0%)
Adverse event	4 (4.1%)
Death	0 (0.0%)
Lost to follow up	0 (0.0%)
Entry criteria not met	1 (1.0%)
Protocol violation	2 (2.0%)
Patient decision	4 (4.1%)
Physician decision	0 (0.0%)
Sponsor decision	0 (0.0%)

Abbreviation: N = total number of patients.

Table HMED.3. Discontinuation Reasons During Study Period II

	N=72
Unknown	0 (0.0%)
Protocol Completed	66 (91.7%)
Lack of Efficacy	0 (0.0%)
Adverse Event	2 (2.8%)
Death	0 (0.0%)
Lost to follow up	0 (0.0%)
Entry Criteria not meet	0 (0.0%)
Protocol Violation	1 (1.4%)
Patient Decision	1 (1.4%)
Physician Decision	2 (2.8%)
Sponsor Decision	0 (0.0%)

Abbreviation: N = total number of patients.

Table HMED.4 summarizes baseline psychiatric characteristics from Study HMDG (CT#8604). The mean age of the first episode of MDD was 44.2 years (SD=13.1). The median duration of the current episode was 28 weeks.

Table HMED.4. Description of Previous MDD

		N=98
Age (years) with first MDD	N	98
	Range	10 - 79
	Q1	36
	Q3	51
	N absent	0
	Mean	44.2
	SD	13.1
	CI(mean) 95%	[41.6,46.9]
	Median	43
Time (weeks) since actual MDD	N	97
	Range	4 - 200
	Q1	18
	Q3	38
	N absent	1
	Mean	31.7
	SD	23.7
	CI(mean) 95%	[26.9,36.4]
	Median	28

Abbreviations: CI = confidence interval; MDD = major depressive disorder; N = total number of patients; Q1 = 1st quartile (25th percentile); Q3 = 3rd quartile (75th percentile); SD = standard deviation.

Of the 98 patients, 71 (72.4%) presented with one previous episode of MDD and the median number of previous episodes was 2 (Table HMED.5).

Table HMED.5. Description of Previous MDD Episodes

		N= 98
Previous MDD		
	No	27 (27.6%)
	Yes	71 (72.4%)
Number of Previous Episodes	N	70
	Range	1 - 35
	Q1	1
	Q3	4
	N absent	28
	Mean	3.4
	Standard Dev.	4.6
	CI(mean) 95%	[2.3,4.5]
	Median	2

Abbreviations: CI = confidence interval; MDD = major depressive disorder; N = total number of patients; Q1 = 1st quartile (25th percentile); Q3 = 3rd quartile (75th percentile); Standard Dev = standard deviation.

The median duration of previous episode was 24 weeks. The median time interval, between start of current episode and remission of previous one, was 56 weeks (Table HMED.6).

Table HMED.6. Description of Previous MDD Duration

		N=98
Duration (weeks) of Last episode	N	67
	Range	6 - 1086
	Q1	20
	Q3	36
	N absents	31
	Mean	44.7
	SD	130.2
	IC(mean) 95%	[12.9,76.4]
	Median	24
Time (weeks) since remission of last MDD	N	68
	Range	10 - 2052
	Q1	24
	Q3	175
	N absents	30
	Mean	161.5
	SD	297.2
	IC(media) 95%	[89.5,233.4]
	Median	58
If there have been 3 o more ¿was there a seasonal pattern?	Absents	28 (%)
	No	21 (30.0%)
	Yes	9 (12.9%)
	Not apply	40 (57,1%)

Abbreviations: CI = confidence interval; IC = major depressive disorder (MDD); N = total number of patients; Q1 = 1st quartile (25th percentile); Q3 = 3rd quartile (75th percentile); SD = standard deviation.

Safety

Table HMED.7 describes the occurrence of TEAEs. During the study 32 patients (32.7%) showed at least one TEAE. In 16 patients (16.3%), these TEAEs were classified as probably related to study drug. A total of 6 (6.1%) adverse events led to withdrawal of the patients and 1 (1.0%) TEAE satisfied the criteria to be classified as a SAE.

Table HMED.7. Summary of Treatment Emergent Adverse Events During the Study

	N=98
Patients with at least one TEAE	32 (32.7%)
Initiated at baseline visit	6 (6.1%)
Initiated at visit 2	15 (15.3%)
Initiated at visit 3	8 (8.2%)
Initiated at visit 4	4 (4.1%)
Patients with at least one probably related to treatment TEAE	16 (16.3%)
Patients with at least one serious TEAE	1 (1.0%)
Patients with at least one TEAE leading to withdrawal	6 (6.1%)

Abbreviation: N = total number of patients.

The most common TEAEs during the study are listed in Table HMED.8.

Table HMED.8. Treatment-Emergent Adverse Events During the Study

SYSTEM ORGAN CLASS	PREFERRED TERM	N=98
Gastrointestinal disorders	Diarrhoea	3 (3.1%)
	Nausea	6 (6.1%)
Infections and infestations	Nasopharyngitis	3 (3.1%)
Metabolism and nutrition disorders	Hyperglycaemia	4 (4.1%)
Nervous system disorders	Dizziness	7 (7.1%)
	Headache	7 (7.1%)
Psychiatric disorders	Anorgasmia	3 (3.1%)
	Anxiety	6 (6.1%)
	Insomnia	4 (4.1%)
Skin and subcutaneous tissue disorders	Hyperhidrosis	5 (5.1%)

Abbreviation: N = total number of patients.

Table HMED.9 summarizes the TEAEs probably related to study drug by organ system and preferred term. The most common related TEAEs reported by patients were dizziness, anxiety, nausea, headache, and hyperhidrosis.

Table HMED.9. List of Treatment-Emergent Adverse Events Probably Related to Study Drug

SYSTEM ORGAN CLASS	PREFERRED TERM	N=98
Ear and labyrinth disorders	AT LEAST ONE	1 (1.0%)
	Tinnitus	1 (1.0%)
Gastrointestinal disorders	AT LEAST ONE	6 (6.1%)
	Abdominal pain upper	1 (1.0%)
	Diarrhoea	2 (2.0%)
	Nausea	5 (5.1%)
General disorders and administration site conditions	AT LEAST ONE	2 (2.0%)
	Fatigue	2 (2.0%)
	Pain	1 (1.0%)
Investigations	AT LEAST ONE	3 (3.1%)
	Alanine aminotransferase increased	1 (1.0%)
	Blood creatine phosphokinase increased	1 (1.0%)
	Gamma-glutamyltransferase increased	1 (1.0%)
	Transaminases increased	1 (1.0%)
Metabolism and nutrition disorders	AT LEAST ONE	4 (4.1%)
	Anorexia	1 (1.0%)
	Hyperglycaemia	3 (3.1%)
Musculoskeletal and connective tissue disorders	AT LEAST ONE	2 (2.0%)
	Back pain	1 (1.0%)
	Muscle spasms	1 (1.0%)
Nervous system disorders	AT LEAST ONE	10 (10.2%)
	Dizziness	7 (7.1%)
	Headache	5 (5.1%)
	Paraesthesia	1 (1.0%)
	Tremor	2 (2.0%)
Psychiatric disorders	AT LEAST ONE	8 (8.2%)
	Affective disorder	1 (1.0%)
	Anorgasmia	3 (3.1%)
	Anxiety	6 (6.1%)
	Insomnia	4 (4.1%)
	Libido decreased	2 (2.0%)
	Orgasm abnormal	1 (1.0%)
Skin and subcutaneous tissue disorders	AT LEAST ONE	5 (5.1%)
	Hyperhidrosis	5 (5.1%)
Vascular disorders	AT LEAST ONE	1 (1.0%)
	Hypertension	1 (1.0%)

Abbreviation: N = total number of patients.

During the study 1 patient (1, 0%) suffered a SAE. The patient presented with "metastatic neoplasm" with the outcome of death after the patient was discontinued from the study. This SAE was reported by the investigator to be nonrelated to the study drug.

Change in vital signs (blood pressure and heart rate) was measured from baseline to the final visit. No statistically significant change was observed in heart rate (p=.200; Table HMED.10), systolic blood pressure (p=.212; Table 11), or diastolic blood pressure (p=.212; Table 12).

Table HMED.10. Heart Rate

		N=98	
Baseline	N	98	
	Range	56 - 120	
	Q1	72	
	Q3	87	
	N absent	0	
	Mean	80.1	
	SD .	11.8	
	CI(mean) 95%	[77.7,82.4]	
	Median	79	
Final	N	65	
	Range	59 - 131	
	Q1	70	
	Q3	81	
	N absent	33	
	Mean	77	
	SD .	10.6	
	CI(mean) 95%	[74.4,79.6]	
	Median	75	
Change (Final visit - Baseline visit)	N	65	T-Student p-value=0.200
	Range	-28 - 48	
	Q1	-7	
	Q3	2	
	N absent	33	
	Mean	-1.8	
	SD .	11.3	
	CI(mea) 95%	[-4.6,1]	
	Median	-2	

Abbreviations: CI = confidence interval; N = total number of patients; Q1 = 1st quartile (25th percentile); Q3 = 3rd quartile (75th percentile); SD = standard deviation.

Table HMED.11. Systolic Blood Pressure

		N=98	
Baseline	N	98	
	Range	86 - 171	
	Q1	120	
	Q3	140	
	N absent	0	
	Mean	129.2	
	SD .	17	
	CI (mean) 95%	[125.8,132.6]	
	Median	129.5	
Final	N	66	
	Range	75 - 176	
	Q1	120	
	Q3	140	
	N absent	32	
	Mean	127.6	
	SD .	17.8	
	CI (mean) 95%	[123.2,132]	
	Median	127.5	
Change (Final visit-Baseline visit)	N	66	T-Student p-value=0.212
	Range	-46 - 30	
	Q1	-10	
	Q3	5	
	N absent	32	
	Mean	-2.4	
	SD .	15.6	
	CI (mean) 95%	[-6.3,1.4]	
	Median	0	

Abbreviations: CI = confidence interval; N = total number of patients; Q1 = 1st quartile (25th percentile); Q3 = 3rd quartile (75th percentile); SD = standard deviation.

Table HMED.12. Diastolic Blood Pressure

		N=98	
Baseline	N	98	
	Range	53 - 110	
	Q1	70	
	Q3	86	
	N absent	0	
	Mean	78.9	
	SD .	10.5	
	CI (mean) 95%	[76.8,81]	
	Median	80	
Final	N	65	
	Range	58 - 114	
	Q1	70	
	Q3	85	
	N absent	33	
	Mean	77.3	
	SD .	10	
	IC(mean) 95%	[74.8,79.7]	
	Median	76	
Change (Final visit-Baseline visit)	N	65	T-Student p-value=0.212
	Range	-20 - 20	
	Q1	-5	
	Q3	3	
	N absent	33	
	Mean	-1.4	
	SD .	8.7	
	CI(mean) 95%	[-3.5,0.8]	
	Median	0	

Abbreviations: CI = confidence interval; N = total number of patients; Q1 = 1st quartile (25th percentile); Q3 = 3rd quartile (75th percentile); SD = standard deviation.