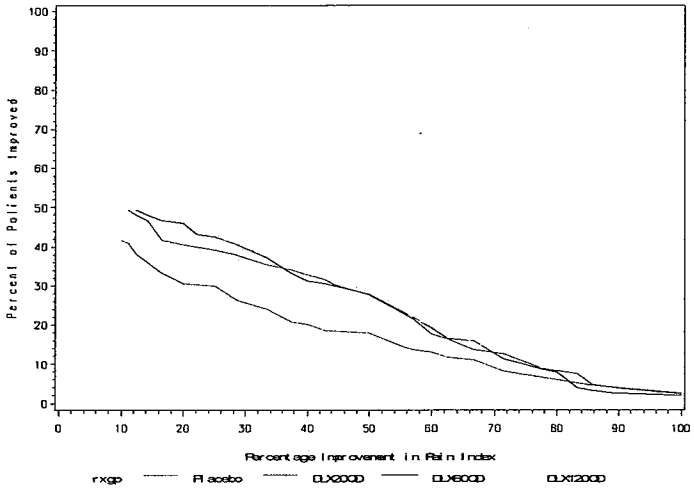
reduction or greater. In the curve below, we see evidence of response for duloxetine at doses of 20 mg QD, 60 mg QD, and 120 mg QD when compared to placebo.



The table below illustrates how duloxetine 60 mg QD and 120 mg QD are superior to placebo in terms of improvement of pain. Duloxetine 20 mg QD appears ineffective.

Responder Analysis of Brief Pain Inventory Average Pain Score at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Study HMCJ						
		≥ 30% Improvement in Pain			≥ 50% Improvement in Pain	
Study	Treatment Group	N	n(%)	p-value	n(%)	p-value
HMCJ	Placebo	144	37 (26%)		26 (18%)	
	Duloxetine 20 mg QD	79	28 (35%)	0.126	22 (28%)	0.089
	Duloxetine 60 mg QD	150	56 (37%)	0.032	42 (28%)	0.043
	Duloxetine 120 mg QD	147	57 (39%)	0.017	44 (30%)	0.018
Dr. Buenconsejo's Table.						

Appears This Way
On Original

Another secondary endpoint in HMCJ was the Fibromyalgia Impact Questionnaire. Although multiplicity adjustments were not made, in the table below we see that there appears to be improvement.

Fibromyalgia Impact Questionnaire Total Score Change from Baseline to Endpoint*: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Study HMCJ

		FIQ Total Score (BOCF)			FIQ Total Score (LOCF/BOCF)	
Study	Treatment Group	Baseline	LSMean Change	p-value†	LSMean Change	p-value†
HMCJ	Placebo	53.0	-8.0		-9.1	
	Duloxetine 20 mg QD	54.0	-11.1	0.130	-13.3	0.053
	Duloxetine 60 mg QD	51.7	-12.1	0.017	-12.9	0.032
	Duloxetine 120 mg QD	51.7	-11.7	0.030	-12.7	0.048

*negative implies improvement
†unadjusted p-value
Dr. Buenconsejo's Table.

The table below shows yet another secondary endpoint of CGI-Severity. This table suggests that duloxetine 60 mg QD and 120 mg QD are effective.

Change in CGI-Severity at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Study HMCJ

			CGI Improvement Score (LOCF)		CGI Improvement Score (WOCF)		CGI Improvement Score (BOCF)	
Study	Treatment Group	N	LSMean Change	p-value	LSMean Change	p-value	LSMean Change	p-value
HMCJ	Placebo	144	-0.6		-0.5		-0.6	
	Duloxetine 20 mg QD	79	-0.9	0.059	-0.8	0.063	-0.8	0.068
	Duloxetine 60 mg QD	150	-0.9	0.021	-0.8	0.033	-0.8	0.054
	Duloxetine 120 mg QD	147	-1.0	<0.001	-0.9	0.002	-0.9	0.005

* negative implies improvement
Dr. Buenconsejo's Table.

Analysis by Subgroups

The table below from Dr. Buenconsejo's review, shows mean BPI average pain score when subdivided by gender. We do not see a negative effect of duloxetine in men with respect to BPI

Endpoint Mean Brief Pain Inventory Average Pain Score: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Study by Gender: HMCJ							
		Women			Men		
Study	Treatment Group	N	Baseline	Endpoint Mean	N	Baseline	Endpoint Mean
BOCF							
HMCJ	Placebo	137	6.6	5.5	7	6.1	5.6
	Duloxetine 20 mg QD	76	6.8	5.1	3	6.3	6.3
	Duloxetine 60 mg QD	136	6.5	5.0	14	6.2	4.9
	Duloxetine 120 mg QD	143	6.4	4.8	4	7.0	4.5
LOCF/BOCF							
HMCJ	Placebo	137	6.6	5.4	7	6.1	5.7
	Duloxetine 20 mg QD	76	6.8	4.8	3	6.3	6.3
	Duloxetine 60 mg QD	136	6.5	4.9	14	6.2	4.3
	Duloxetine 120 mg QD	143	6.4	4.7	4	7.0	4.5

Endpoint mean BPI average pain score subdivided by race does not show treatment differences when subdivided by race.

Endpoint Mean Brief Pain Inventory Average Pain Score: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Study: HMCJ							
		White			Non-white		
Study	Treatment Group	N	Baseline	Endpoint Mean	N	Baseline	Endpoint Mean
BOCF							
HMCJ	Placebo	119	6.3	5.3	25	7.9	6.4
	Duloxetine 20 mg QD	66	6.6	5.0	13	7.8	5.8
	Duloxetine 60 mg QD	127	6.4	4.8	23	7.0	6.0
	Duloxetine 120 mg QD	126	6.3	4.6	21	7.1	5.9
LOCF/BOCF							
HMCJ	Placebo	119	6.3	5.2	25	7.9	6.4
	Duloxetine 20 mg QD	66	6.6	4.7	13	7.8	5.5
	Duloxetine 60 mg QD	127	6.4	4.6	23	7.0	5.7
	Duloxetine 120 mg QD	126	6.3	4.6	21	7.1	5.7
Dr. Buenconsejo's Table.							

Likewise, the table below indicates that endpoint mean BPI does not show treatment differences when subdivided by age.

Endpoint Mean Brief Pain Inventory Average Pain Score: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Study by Age: HMCJ							
		Age < 65			Age ≥ 65		
Study	Treatment Group	N	Baseline	Endpoint Mean	N	Baseline	Endpoint Mean
BOCF							
HMCJ	Placebo	136	6.6	5.4	8	6.9	6.3
	Duloxetine 20 mg QD	70	6.8	5.3	9	6.2	4.2
	Duloxetine 60 mg QD	135	6.5	4.9	15	6.3	5.2
	Duloxetine 120 mg QD	133	6.3	4.7	14	6.9	6.1
LOCF/BOCF							
HMCJ	Placebo	136	6.6	5.3	8	6.9	6.4
	Duloxetine 20 mg QD	70	6.8	4.9	9	6.2	4.3
	Duloxetine 60 mg QD	135	6.5	4.8	15	6.3	4.9
	Duloxetine 120 mg QD	133	6.3	4.6	14	6.9	6.0
Dr. Buenconsejo's Table.							

Endpoint mean BPI average pain score subdivided by presence or absence of major depressive disorder does not demonstrate major differences in treatment effect.

Endpoint Mean Brief Pain Inventory Average Pain Score: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Study HMCJ by Major Depressive Disorder Status

		No MDD			With MDD		
Study	Treatment Group	N	Baseline	Endpoint Mean	N	Baseline	Endpoint Mean
BOCF							
HMCJ	Placebo	109	6.4	5.3	35	7.0	6.0
	Duloxetine 20 mg QD	57	6.6	5.1	22	7.2	5.4
	Duloxetine 60 mg QD	115	6.4	4.9	35	6.7	5.1
	Duloxetine 120 mg QD	113	6.3	4.7	34	6.6	5.1
LOCF/BOCF							
HMCJ	Placebo	109	6.4	5.2	35	7.0	6.0
	Duloxetine 20 mg QD	57	6.6	4.8	22	7.2	5.0
	Duloxetine 60 mg QD	115	6.4	4.8	35	6.7	4.9
	Duloxetine 120 mg QD	113	6.3	4.7	34	6.6	4.9

Dr. Buenconsejo's Table.

10.1.2.8 Conclusions Regarding Efficacy Data in Study

This study provides evidence that duloxetine at doses of 60 mg QD and 120 mg QD is effective for [redacted] of fibromyalgia. No treatment by subgroup differences were seen for gender, race, age, or presence or absence of major depressive disorder. Duloxetine at a dose of 20 mg QD may be effective.

10.1.2.9 Safety Results

The table below shows the common adverse events observed in this study, as reported by Lilly in the final study report. Adverse events (MedDRA preferred terms) that occurred in more than 2% of subjects and at a frequency greater than placebo in the duloxetine treatment groups are summarized below. Among duloxetine-treated subjects, the most frequently reported adverse events were nausea, headache, constipation, dry mouth, and somnolence.

Treatment-Emergent Adverse Events Preferred Term by Decreasing Frequency All Randomized Patients 3-Month Therapy Phase				
Preferred Term	**Treatment**	**N**	**n**	**Percent**
PATIENTS WITH ≥ 1 TREATMENT-EMERGENT EVENT	1) PLACEBO	144	111	77.1
	2) DLX20QD	79	66	83.5
	3) DLX60QD	150	124	82.7
	4) DLX120QD	147	131	89.1
Nausea	1) PLACEBO	144	16	11.1
	2) DLX20QD	79	18	22.8
	3) DLX60QD	150	32	21.3
	4) DLX120QD	147	46	31.3
Headache	1) PLACEBO	144	12	8.3
	2) DLX20QD	79	10	12.7
	3) DLX60QD	150	23	15.3
	4) DLX120QD	147	22	15.0
Constipation	1) PLACEBO	144	6	4.2
	2) DLX20QD	79	9	11.4
	3) DLX60QD	150	15	10.0
	4) DLX120QD	147	31	21.1
Dry mouth	1) PLACEBO	144	7	4.9
	2) DLX20QD	79	7	8.9
	3) DLX60QD	150	19	12.7
	4) DLX120QD	147	27	18.4
Somnolence	1) PLACEBO	144	5	3.5
	2) DLX20QD	79	7	8.9
	3) DLX60QD	150	11	7.3
	4) DLX120QD	147	22	15.0
Diarrhoea	1) PLACEBO	144	11	7.6
	2) DLX20QD	79	5	6.3
	3) DLX60QD	150	13	8.7
	4) DLX120QD	147	15	10.2
Fatigue	1) PLACEBO	144	6	4.2
	2) DLX20QD	79	8	10.1
	3) DLX60QD	150	18	12.0
	4) DLX120QD	147	11	7.5
Upper respiratory tract infection	1) PLACEBO	144	9	6.3
	2) DLX20QD	79	8	10.1
	3) DLX60QD	150	14	9.3
	4) DLX120QD	147	12	8.2
Dizziness	1) PLACEBO	144	7	4.9
	2) DLX20QD	79	5	6.3
	3) DLX60QD	150	13	8.7
	4) DLX120QD	147	16	10.9
Insomnia	1) PLACEBO	144	5	3.5
	2) DLX20QD	79	5	6.3
	3) DLX60QD	150	10	6.7
	4) DLX120QD	147	18	12.2
Decreased appetite	1) PLACEBO	144	1	0.7
	2) DLX20QD	79	4	5.1
	3) DLX60QD	150	11	7.3
	4) DLX120QD	147	12	8.2
Hyperhidrosis	1) PLACEBO	144	0	0.0
	2) DLX20QD	79	4	5.1
	3) DLX60QD	150	8	5.3
	4) DLX120QD	147	11	7.5
Tremor	1) PLACEBO	144	0	0.0
	2) DLX20QD	79	1	1.3

	3) DLX60QD	150	5	3.3
	4) DLX120QD	147	14	9.5
Anorexia	1) PLACEBO	144	4	2.8
	2) DLX20QD	79	1	1.3
	3) DLX60QD	150	5	3.3
	4) DLX120QD	147	8	5.4
Pharyngolaryngeal pain	1) PLACEBO	144	3	2.1
	2) DLX20QD	79	3	3.8
	3) DLX60QD	150	3	2.0
	4) DLX120QD	147	9	6.1
Cough	1) PLACEBO	144	2	1.4
	2) DLX20QD	79	6	7.6
	3) DLX60QD	150	4	2.7
	4) DLX120QD	147	5	3.4
Urinary tract infection	1) PLACEBO	144	6	4.2
	2) DLX20QD	79	0	0.0
	3) DLX60QD	150	4	2.7
	4) DLX120QD	147	7	4.8
Arthralgia	1) PLACEBO	144	5	3.5
	2) DLX20QD	79	2	2.5
	3) DLX60QD	150	6	4.0
	4) DLX120QD	147	2	1.4
Anxiety	1) PLACEBO	144	3	2.1
	2) DLX20QD	79	2	2.5
	3) DLX60QD	150	3	2.0
	4) DLX120QD	147	6	4.1
Dysgeusia	1) PLACEBO	144	2	1.4
	2) DLX20QD	79	3	3.8
	3) DLX60QD	150	2	1.3
	4) DLX120QD	147	7	4.8
Muscle spasms	1) PLACEBO	144	2	1.4
	2) DLX20QD	79	3	3.8
	3) DLX60QD	150	5	3.3
	4) DLX120QD	147	4	2.7
Pain	1) PLACEBO	144	2	1.4
	2) DLX20QD	79	2	2.5
	3) DLX60QD	150	4	2.7
	4) DLX120QD	147	5	3.4
Pruritus	1) PLACEBO	144	4	2.8
	2) DLX20QD	79	2	2.5
	3) DLX60QD	150	4	2.7
	4) DLX120QD	147	3	2.0
Vomiting	1) PLACEBO	144	5	3.5
	2) DLX20QD	79	1	1.3
	3) DLX60QD	150	5	3.3
	4) DLX120QD	147	2	1.4
Anorgasmia	1) PLACEBO	144	1	0.7
	2) DLX20QD	79	2	2.5
	3) DLX60QD	150	2	1.3
	4) DLX120QD	147	7	4.8
Bruxism	1) PLACEBO	144	1	0.7
	2) DLX20QD	79	3	3.8
	3) DLX60QD	150	3	2.0
	4) DLX120QD	147	5	3.4
Dyspepsia	1) PLACEBO	144	3	2.1
	2) DLX20QD	79	1	1.3
	3) DLX60QD	150	6	4.0
	4) DLX120QD	147	2	1.4
Myalgia	1) PLACEBO	144	1	0.7
	2) DLX20QD	79	2	2.5
	3) DLX60QD	150	4	2.7
	4) DLX120QD	147	5	3.4

Migraine	1) PLACEBO	144	1	0.7
	2) DLX20QD	79	2	2.5
	3) DLX60QD	150	3	2.0
	4) DLX120QD	147	5	3.4
Pain in extremity	1) PLACEBO	144	2	1.4
	2) DLX20QD	79	2	2.5
	3) DLX60QD	150	4	2.7
	4) DLX120QD	147	3	2.0
Sinus headache	1) PLACEBO	144	3	2.1
	2) DLX20QD	79	1	1.3
	3) DLX60QD	150	2	1.3
	4) DLX120QD	147	5	3.4
Vision blurred	1) PLACEBO	144	3	2.1
	2) DLX20QD	79	2	2.5
	3) DLX60QD	150	1	0.7
	4) DLX120QD	147	5	3.4
Musculoskeletal pain	1) PLACEBO	144	3	2.1
	2) DLX20QD	79	1	1.3
	3) DLX60QD	150	2	1.3
	4) DLX120QD	147	4	2.7
Palpitations	1) PLACEBO	144	1	0.7
	2) DLX20QD	79	2	2.5
	3) DLX60QD	150	4	2.7
	4) DLX120QD	147	3	2.0
Pollakiuria	1) PLACEBO	144	1	0.7
	2) DLX20QD	79	3	3.8
	3) DLX60QD	150	2	1.3
	4) DLX120QD	147	4	2.7
Rash	1) PLACEBO	144	1	0.7
	2) DLX20QD	79	2	2.5
	3) DLX60QD	150	1	0.7
	4) DLX120QD	147	6	4.1

10.1.3 Protocol F1J-MC-HMEH

A 1-Year Safety Study of Duloxetine in Patients with Fibromyalgia

10.1.3.1 Objective/Rationale

The primary objective was to assess the safety and tolerability of duloxetine at doses up to 120 mg once daily (QD) for up to 60 weeks in patients diagnosed with fibromyalgia, as assessed by the American College of Rheumatology (ACR) criteria.

Secondary objectives included evaluating the persistence of efficacy of duloxetine for up to 1 year, evaluating the long-term differences in efficacy between duloxetine 60 mg/day and 120 mg/day, and evaluating the gain in efficacy in nonresponders associated with increasing duloxetine dosage from 60 to 120 mg/day.

10.1.3.2 Overall Design

This was a Phase 3, outpatient 62-week safety study, which included an 8-week open-label period, followed by a 52-week double-blind, randomized period, and concluding with a 2-week taper period. The study was designed to evaluate the safety and tolerability of duloxetine 60 mg and 120 mg once daily (QD) in patients diagnosed with fibromyalgia. Patients were assigned to duloxetine 30 mg QD for 1 week, duloxetine 60 mg QD for 7 weeks, and then were randomized 2:1 to 120 mg QD and 60 mg QD within response status (defined as $\geq$ 50% reduction from baseline to Week 8 in the Brief Pain Inventory (BPI) average pain score) for 52 weeks. Patients then entered a 2 week taper phase.

10.1.3.3 Population and Procedures

10.1.3.3.1 Inclusion/Exclusion Criteria

Planned enrollment was approximately 320 subjects randomized 1:1 to each of two treatment arms:

- duloxetine 60 mg QD
- duloxetine 120 mg QD

To be eligible, subjects were required to meet the following criteria:

- Male and female outpatients ≥18 years of age.
- Primary FMS as defined by the ACR: widespread aching pain in all four quadrants of the body and axial skeleton for >3 months duration and ≥11 of 18 tender points under digital palpitation examination with an approximate force of 4 kg/cm2.

- Score of ≥4 on the average pain item of the Brief Pain Inventory (BPI-Modified Short Form) at Visit 1 and Visit 2.

Subjects were to be excluded for:

- Any current primary Axis I diagnosis other than major depressive disorder (MDD), as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)
- Any current or previous DSM-IV Axis I diagnosis of psychosis, bipolar disorder, or schizoaffective disorder.
- Primary DSM-IV Axis I diagnosis of anxiety disorder within the past year (including panic disorder, agoraphobia without a history of panic disorder, obsessive compulsive disorder [OCD], post-traumatic stress disorder [PTSD], generalized anxiety disorder [GAD], and social phobia). Note: Patients with specific phobias were permitted to participate in the study.
- DSM-IV Axis II disorder, which, in the judgment of the investigator, would interfere with compliance with the study protocol.
- Suicidal risk as judged by the clinical investigator or as defined by a score of 2 or greater on question 9 of the Beck Depression Inventory-II (BDI-II).
- Past-year history of substance abuse or dependence, excluding nicotine and caffeine.
- Positive urine drug screen for any substance of abuse or excluded medication. Note: If the patient had a positive drug screen at Visit 1 for an excluded prescribed medication that may not have had an adequate wash-out period, a retest could be performed prior to Visit 2. If the retest was positive for the parent compound, the patient was to be excluded.
- Pregnancy/nursing
- Pain symptoms related to traumatic injury, structural rheumatic disease, or regional rheumatic disease (such as osteoarthritis, bursitis, tendonitis) that would interfere with interpretation of outcome measures.
- Regional pain syndrome, multiple surgeries or failed back syndrome.
- Confirmed current or previous diagnosis of rheumatoid arthritis, inflammatory arthritis, or infectious arthritis, or an autoimmune disease (for example, systemic lupus erythematosus).
- Any of the following laboratory values at Visit 1:
- An abnormal C-Reactive Protein level (>12) that is indicative of autoimmune disease
- Antinuclear antibody (ANA) with a dilution of >1:320
- Rheumatoid factor of ≥15 IU/ml.
- Alanine transaminase (ALT) >1.5 times the upper limit of normal (ULN), based on performing laboratory reference ranges.
- Abnormal thyroid-stimulating hormone (TSH) concentrations. Note: Patients previously diagnosed with hypothyroidism who had been treated on a stable dose of thyroid supplement for at least the past 3 months, with normal TSH concentrations and clinically euthyroid were permitted to participate in the study.
- Serious or unstable cardiovascular, hepatic, renal, respiratory, or hematologic illness, symptomatic peripheral vascular disease, or other medical condition (including unstable hypertension or not clinically ethyroid) or psychiatric conditions that, in the opinion of

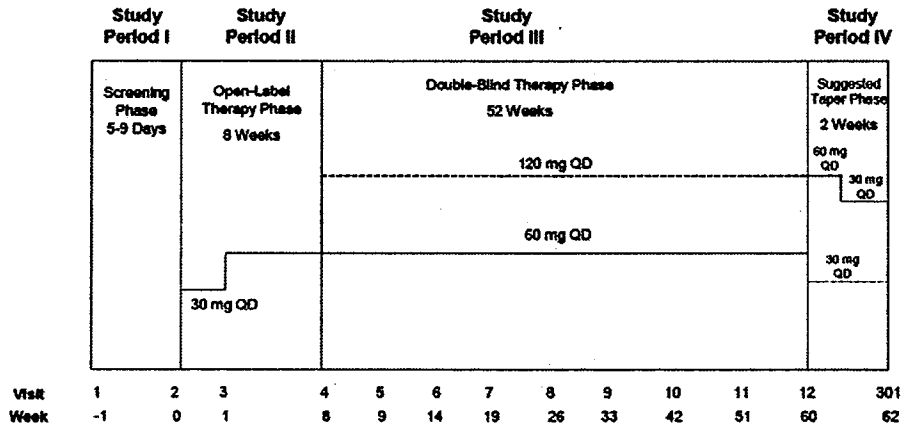
the investigator, would compromise participation or be likely to lead to hospitalization during the course of the study.

- Acute liver injury (such as hepatitis) or severe cirrhosis (Child- Pugh Class C).
- Uncontrolled seizures.
- Uncontrolled narrow-angle glaucoma.
- Any excluded medications that could not be discontinued at Visit 1.
- Recent (past 14 days) monoamine oxidase inhibitor (MAOI) or anticipated need to take within 5 days after discontinuing the study.
- Current or past treatment with duloxetine
- Previous participation in a duloxetine study
- Past 30 days investigational drug use
- Known hypersensitivity to duloxetine or any of the inactive ingredients history of frequent or severe allergic reactions to multiple medications.
- Patients could also be excluded if they were deemed by the investigator to be "treatment-refractory" or to have disability compensation issues that might compromise their responses.
- Employees of Lilly, Boehringer-Ingelheim, or investigator sites were also not eligible to participate.
- Disallowed concomitant medications included but were not limited to: monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), in addition to illicit drugs.

10.1.3.3.2 Procedures

The protocol described four study phases: a screening phase, an open-label phase, a double-blind phase, and a taper/discontinuation phase.

A schematic diagram illustrates these phases:



Abbreviations: QD = once daily.

Screening phase: Study Period I was a 1-week screening phase; during this period, no study drug was dispensed and patients were screened for study entry eligibility. After signing the informed consent form (ICD), each patient was assigned a patient number. At Visit 1, patients underwent screening tests and an electrocardiogram (ECG). All criteria for enrollment, including the ECG and safety and laboratory analyses (clinical chemistry, hematology, urinalysis, urine drug screen, and pregnancy test for all females) were verified prior to enrollment at Visit 2. Patients who did not meet inclusion criteria or who met exclusion criteria were discontinued from the study.

Open-label phase: Study Period II (Visit 2 to Visit 4) was an open-label therapy phase of approximately 8 weeks. Patients who met entry criteria were assigned to duloxetine 30 mg QD for 1 week, followed by duloxetine 60 mg QD for 7 weeks. Patients who did not tolerate duloxetine 60 mg QD during the open-label treatment period were discontinued from the study and entered the taper phase.

Double-blind phase: Study Period III (Visit 4 to Visit 12) was a double-blind therapy phase of approximately 52 weeks. Patients were randomly assigned in a 2:1 fashion at Visit 4 (Week 8) to receive either duloxetine 120 mg (60 mg x 2) QD or duloxetine 60 mg QD. Patients who did not tolerate duloxetine 60 mg QD or duloxetine 120 mg QD during the double-blind treatment period were discontinued from the study and entered the taper phase.

Taper/Discontinuation phase: Study Period IV (Visit 301) was a 2-week taper phase designed to minimize discontinuation-emergent adverse events (DEAEs). Patients who were taking duloxetine 120 mg QD at their point of discontinuation were provided duloxetine 60 mg QD for 1 week, followed by duloxetine 30 mg QD for 1 week. Patients who were taking duloxetine 60 mg QD at their point of discontinuation received duloxetine 30 mg QD for 2 weeks.

10.1.3.3.2.1 Dosing

As described above, eligible subjects were to be randomized to treatment with duloxetine 60 mg once daily (QD) for eight weeks, then to duloxetine 60 mg QD or duloxetine 120 mg QD in the ratio of 2:1.

Randomization was to occur at Visit 2, with assignment to treatment groups determined by a computer-generated random sequence using an Interactive Voice Response System (IVRS). Patients were to be stratified for presence or absence of MDD, with each stratum (depressed and non-depressed) randomly assigned within sites to achieve a relative balance across treatments.

Study drug treatments included:
- 30-mg capsules of duloxetine enteric-coated pellets,
- 60-mg capsules of duloxetine enteric-coated pellets,
- Placebo capsules identical in appearance to duloxetine capsules.

Study medication was packaged as indicated and dispensed to the patient at the principal investigator's study site. Study drug packaging was labeled with a unique identifier for drug accountability. Study drug bottles and blister packs contained additional capsules to allow for

sufficient study medication. Clinical trial materials were labeled according to the country's regulatory requirements.

Each patient was assigned a patient number after signing and dating the ICD. Enrollment and patient progress were tracked using an Interactive Voice Response System (IVRS). At Visit 2, all patients who met enrollment criteria received duloxetine 30 mg QD for 1 week, followed by duloxetine 60 mg QD for 7 weeks.

At Visit 4 (Week 8), patients were randomly assigned in a 2:1 fashion to receive either duloxetine 120 mg QD or 60 mg QD. Randomization was carried out at Visit 4 using IVRS within site and patient response status (response defined as a ≥ 50% reduction from Visit 2 [Week 0] baseline to Visit 4 [Week 8] in the Brief Pain Inventory [BPI] 24-hour average pain score).

To maintain blinding in Study Phase III, patients assigned to duloxetine 60 mg received 1 duloxetine 60 mg capsule and 1 placebo capsule QD while patients assigned duloxetine 120 mg received 2 duloxetine 60 mg capsules QD. Similarly for the Taper Phase, each patient was assigned 1 duloxetine (either 30 mg or 60 mg) capsule and 1 placebo capsule QD.

The dosing regimen for each treatment arm is illustrated in the table below:

Study Phase	Treatment	Dosage Form and Frequency	Dose Duration	Packaging
Screening	None	N/A	N/A	N/A
Open-Label	Duloxetine	30 mg QD 60 mg QD	8 weeks	Blister Packs, Bottles
Double-Blind	Duloxetine	60 mg QD (plus 1 placebo capsule) 120 mg (60 mg X 2 capsules) QD	52 Weeks	Bottles
Taper/ Discontinuation	Duloxetine	60 mg QD 30 mg QD Placebo QD (1 capsule per treatment group)	2 weeks	Blister Packs
Abbreviations: N/A = not applicable; QD = once daily.				

10.1.3.3.2.2 Schedule of Visits and Assessments

The overall study schematic is illustrated in the figure below.

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Visit	1	2	3	4	5	6	7	8	9	10	11	12	301	ET
Week	-1	0	1	8	9	14	19	26	33	42	51	60	62	>W1
Description														
Informed Consent	X													
Demographics	X													
Medical History	X													
Physical Exam	X													
Historical Illness	X													
ACR Criteria for Fibromyalgia	X													
Habits	X													
Alcohol Consumption		X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X												
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X													
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events/ Pre-existing conditions	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Drug		X	X	X	X	X	X	X	X	X	X	X		X[a]
Return Drug/ accountability			X	X	X	X	X	X	X	X	X	X	X	X
FIQ		X		X		X		X		X		X		X
Tender-point pain threshold		X		X		X		X		X		X		X
BPI-Modified Short Form	X	X		X		X		X		X		X		X
PGI-Improvement				X		X		X		X		X		X
PGI-Severity		X												
CGI-Severity		X		X		X		X		X		X		X
SDS		X		X		X		X		X		X		X
BDI-II	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X		X	X		X		X		X	X	X		X

Visit	1	2	3	4	5	6	7	8	9	10	11	12	301	ET
Week	-1	0	1	8	9	14	19	26	33	42	51	60	62	>W1
Blood Chemistry	X		X	X		X		X		X	X	X		X
Urine Drug Screen	X													
Pregnancy Test (females only)	X													
Urinalysis	X		X	X		X		X		X	X	X		X
Patient Summary													X	X

[a] If ET visit is followed by taper, drug will be dispensed.

10.1.3.4 Evaluations/Endpoints

The following efficacy measures were collected on CRFs at the times shown in the study schedule.

- The Brief Pain Inventory-Modified Short Form (BPI) (Severity and Interference items) is a self-reported Likert scale that measures the severity of pain and the interference of pain on function. The severity scores range from 0 (no pain) to 10 (pain as bad as you can imagine). There are 4 questions assessing the severity for worst pain, least pain, average pain in the past 24 hours, and pain right now. The interference scores range from 0 (does not interfere) to 10 (completely interferes). There are 7 questions assessing the interference of pain in the past 24 hours for general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life.
- The Fibromyalgia Impact Questionnaire (FIQ) is a self-administered questionnaire that measures fibromyalgia patient status, progress, and outcomes over the past week. This questionnaire is designed to measure the components of health status that are believed to be most affected by fibromyalgia. The FIQ is composed of a total of 20 items; the first 11 items measure physical functioning, and each item is rated on a 4-point Likert scale. Items 12 and 13 measure the number of days the patient felt well and the number of days the patient felt unable to work due to their fibromyalgia symptoms. Items 14 through 20 are numerical 11-point Likert scales (marked in 10-mm increments) on which the patient rates work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression. Because some patients do not do some of the tasks listed, they are given the opportunity to delete items from scoring. The total score ranges from 0 to 80, where higher scores indicate a more negative impact.
- The Patient's Global Impression of Severity (PGI-Severity) scale is completed by the patient and measures the degree of severity at baseline. The score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients)
- The Patient Global Impressions of Improvement (PGI-Improvement) scale is completed by the patient and measures the degree of improvement at the time of assessment. The score ranges from 1 (very much better) to 7 (very much worse).
- The Clinical Global Impressions of Severity (CGI-Severity) scale evaluates the severity of illness at the time of assessment. The score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). The CGI-Severity is administered by a study physician in the presence of the patient or after having been in the presence of the patient.
- The Tender Point Pain Threshold is assessed for all 18 tender points by a study physician or qualified study personnel, as defined in Lilly training materials. A dolorimeter (algometer) is used to exert the pressure at each point and to measure the threshold reading; when the patient first indicated pain, the threshold is recorded in kg/cm2.
- The patient-rated Sheehan Disability Scale (SDS) is used to assess the patient's general level of disability. The scale measures a patient's evaluation of the degree to which his or her symptoms disrupt work, social, and/or home life.

The following safety measurements were collected at the times shown in the study schedule.

- Adverse Events: During the study, AEs were collected at every visit, regardless of relationship to study drug. Investigators were responsible for monitoring the safety of patients who entered this study and for alerting Lilly or its designee to any event that seemed unusual. In addition, the investigator was instructed to record his or her assessment of the potential relatedness of each AE to study drug or drug delivery system. Adverse events were captured as actual terms and coded to Medical Dictionary for Regulatory Activities (MedDRA) terms by blinded Lilly clinical personnel.
- Concomitant Therapies: Concomitant therapies taken during the study were recorded. All medications currently taken or stated at the time of ICD signing were considered concomitant.
- Laboratory Data: During the study, laboratory tests, including chemistry, hematology, and urinalysis panels, were collected at regular intervals. A urine drug screen, and pregnancy test (if applicable) were completed at screening.
- Vital Signs: During the study, vital signs, including sitting blood pressure (systolic and diastolic), sitting pulse rate, weight, and height, were collected as indicated in the Study Schedule.
- Electrocardiograms (ECGs): An ECG was collected only at baseline to determine eligibility of the patient for entry into the study.
- The patient-rated Beck Depression Inventory-II (BDI-II) questionnaire was used to measure severity of depression at each study visit. The scores can range from 0 to 63 where higher scores indicate more severe depressive symptoms.

10.1.3.5 Statistical Plan

Efficacy Analyses
Descriptive statistics (including mean, median, standard deviation [SD], minimum, and maximum) were provided for the change from baseline to endpoint for each of the efficacy variables. Within-group change was evaluated by a Student's t-test to test the null hypothesis of no significant change from baseline within the open-label study phase. Between-group differences during the double-blind phase were assessed using 2 separate models. The primary model was a fixed-effects ANCOVA model assessing mean change from baseline to endpoint. Main effects for treatment group and investigative site were included, along with the baseline value of the respective measure as a covariate. Treatment-by-investigator interactions also were reported. A likelihood-based, MMRM analysis was used for confirmatory purposes that included the main effects of treatment group, site and visit, baseline value for the respective measure as a covariate, and the baseline-by-visit and treatment-by-visit interactions.

To evaluate the persistence of the efficacy of duloxetine 60 mg, additional analysis for BPI average pain score was conducted on the patients who had at least a 50% reduction on BPI average pain score at the entry of the double-blind study phase (Visit 4, Week 8) and remained on duloxetine 60 mg in the double-blind study phase. In the analysis, the change from baseline to endpoint on BPI average pain was summarized along with a 90% two-sided confidence interval (CI). When the upper bound of the 90% CI was less than 0.5, the null hypothesis that duloxetine

treatment effect on pain reduction on the fibromyalgia patients was not maintained in the 1-year double-blind study phase was rejected at the significance level of 0.05.

10.1.3.6 Results

10.1.3.6.1 Study Conduct/Outcome

10.1.3.6.1.1 Subject Characteristics

The Applicant planned to enroll a total of 345 patients who met entry criteria. In the double-blind phase, a total of 104 were assigned to duloxetine 60 mg QD and 203 to duloxetine 120 mg QD.

10.1.3.6.1.2 Enrollment by Center

Enrollment was distributed among centers as listed in the table below:

Patient Allocation by Investigator **All Enrolled Patients**	
Investigator	**All Enrolled Patients** **(N=350)** **n (%)**
100	16(4.57)
101	11(3.14)
102	22(6.29)
103	21(6.00)
200	10(2.86)
201	18(5.14)
202	17(4.86)
203	8(2.29)
300	10(2.86)
301	7(2.00)
302	10(2.86)
303	8(2.29)
304	12(3.43)
305	11(3.14)
307	14(4.00)
400	6(1.71)
401	9(2.57)
402	9(2.57)
403	17(4.86)
500	11(3.14)
501	2(0.57)
502	13(3.71)
503	12(3.43)
504	15(4.29)
600	6(1.71)
601	4(1.14)
602	2(0.57)
603	7(2.00)
700	3(0.86)
701	10(2.86)
702	4(1.14)
703	8(2.29)
704	17(4.86)

10.1.3.6.1.3 Subject Disposition

A total of 350 patients were enrolled in the open-label phase. 307 entered the double-blind and were randomized in a 2:1 ratio.

Reasons for discontinuation during the open-label phase are shown in the table below (Lilly's table HMEH.10.2)

Primary Reasons For Discontinuation	DLX60QD (N = 350) n (%)
DC due to ANY reason	43 (12.3)
Adverse Event	26 (7.4)
Subject Decision	9 (2.6)
Lost to follow up	4 (1.1)
Protocol Violation	3 (0.9)
Lack of Efficacy	1 (0.3)
Patients Continuing	307 (87.7)

Patient disposition for the double-blind phase are shown in the table below:

HMEH: Patient Disposition (At study completion; 1 year)		
	DLX 60 QD N = 104	DLX 120 QD N = 203
Completed acute phase	71 (68%)	124 (61%)
Discontinued		
Adverse Event	14 (13%)	34 (17%)
Physician decision	5 (5%)	19 (9%)
Lost to follow-up	2 (2%)	3 (1%)
Protocol Violation	4 (4%)	2 (1%)
Lack of Efficacy	8 (8%)	20 (10%)
Sponsor Decision		1 (1%)

At study completion, across all treatment groups, the most frequent reasons for withdrawal were adverse event (n=48), lack of efficacy (n=28), physician decision (n=24), protocol violation (n=6), lost to follow-up (n=5), and sponsor decision (n=1).

10.1.3.6.2 Demographics

The table below illustrates demographic and baseline characteristics of the 2 treatment groups. Overall, most patients were female Caucasians, with a median age of 50 years, a median weight of 70 kilograms, and a median height of 160 cm.

Patient Demographic Characteristics at Baseline
All Enrolled Patients

Variable	All Enrolled Patients (N = 350)
Sex	
No. of Patients	350
Female	335 (95.7)
Male	15 (4.3)
Age in Years at Consent	
No. of Patients	350
Mean	48.97
Median	49.55
Standard Dev.	11.07
Minimum	18.41
Maximum	83.82
Race	
No. of Patients	350
African	3 (0.9)
Caucasian	214 (61.1)
East Asian	46 (13.1)
Hispanic	82 (23.4)
Native American	1 (0.3)
West Asian	4 (1.1)

Patient Demographic Characteristics at Baseline
All Enrolled Patients (Concluded)

Variable	All Enrolled Patients (N = 350)
Weight in Kg at Baseline	
No. of Patients	350
Mean	69.95
Median	67.00
Standard Dev.	14.74
Minimum	41.00
Maximum	125.00
Height in Cm at Baseline	
No. of Patients	349
Mean	159.44
Median	160.00
Standard Dev.	7.09
Minimum	142.00
Maximum	189.00

10.1.3.6.3 Dosing Information

The table below illustrates exposure duration and compliance with medication across treatment groups during the study. Groups were similar with respect to mean duration of exposure.

Table HMEH.12.3. Exposure to Study Drug
All Enrolled Patients
Overall Study Phase

Variable	All Enrolled Patients (N = 350)
Duration of Exposure (Days)	
No. Patients	349
Mean	298.3
Median	416.0
Standard Deviation	161.2
Minimum	1.0
Maximum	491.0
Patient Years	285.1
Duration of Exposure (Days) - n(%)	
No. Patients	349
=0	0 (0.0)
>0	349 (100.0)
>=7	332 (95.1)
>=14	326 (93.4)
>=30	319 (91.4)
>=60	303 (86.8)
>=90	283 (81.1)
>=120	269 (77.1)
>=183	241 (69.1)
>=365	205 (58.7)

N = Number of enrolled patients, n = Number of patients within each time interval.
Patient years are calculated as total exposure days / 365.25.

Report: RMP.F1JO.HMEHSTAT.FINAL(SMEXPO12)
Program: RMP.F1JSHMEH.SASPGM(SMEXPO1)
Data: RMP.SAS.F1JS.L.MCHMEH.ADS.DBF

10.1.3.6.4 Protocol Violations

Protocol deviations were identified programmatically by searching the database for randomized subjects who had screening or baseline values falling outside of the ranges specified by inclusion or exclusion criteria (eg, values for age, weight, medical history, smoking history, laboratory parameters, etc). The database was also searched for subjects who used prohibited medications during the study and subjects who were withdrawn from the study due to protocol deviations. In addition, lists of protocol deviations were compiled by site monitors during routine center visits or during remote review of electronic data. All deviations identified by the methods described above were reviewed by Lilly for clinical significance. Those considered potentially significant are summarized in the table below.

Significant Protocol Violations
All Enrolled Patients
PLY-MC-HOKN

Violation Type	Inv/Patient	Violation Details
Exclusionary Con. Med. Taken	103/1326	SERTRALINE
	200/2004	AMITRIPTYLINE
	200/2007	VALPROATE SODIUM
	202/2203	SINEMET
	203/2303	AMITRIPTYLINE
	303/3303	CYCLOBENZAPRINE
	303/3310	CYCLOBENZAPRINE
	303/3310	ORPHENADRINE
	305/3509	RISPERIDONE
	305/3514	AMITRIPTYLINE
	307/3705	PROMETHAZINE
	307/3706	PROMETHAZINE
	307/3710	PROMETHAZINE
	307/3711	CYCLOBENZAPRINE
	400/4004	PREGABALIN
	401/4104	CYCLOBENZAPRINE
	402/4205	CYCLOBENZAPRINE
	402/4206	FLUOXETINE
	403/4306	CYCLOBENZAPRINE
	403/4310	PAROXETINE
	403/4314	AMITRIPTYLINE
	403/4317	MIRTAZAPINE
	504/5410	PREGABALIN
	701/7100	MEDICON A
	701/7105	MEDICON A
	702/7200	MEDICON A
	704/7407	GABAPENTIN
	704/7407	PROCHLORPERAZINE
	704/7410	DROPERIDOL
Inclusion/Exclusion	102/1215	Excl criteria #17 violated: Pt randomized with acute liver injury(such as hepatitis) or severe cirrhosis.
	102/1219	Excl criteria #17 violated: Pt randomized with acute liver injury(such as hepatitis) or severe cirrhosis.
Inclusion/Exclusion	103/1303	Excl criteria #17 violated: Pt randomized with acute liver injury(such as hepatitis) or severe cirrhosis.
	301/3104	Excl criteria #17 violated: Pt randomized with acute liver injury(such as hepatitis) or severe cirrhosis.
	703/7302	Pt did not receive > = 7 day washout from an antidepressant, antipsychotic, or anticonvulsant medication.
	704/7402	Excl criteria #17 violated: Pt randomized with acute liver injury(such as hepatitis) or severe cirrhosis.
Restricted Con. Med. Overused	102/1200	DEXAMETHASONE
	102/1211	BUDESONIDE
	102/1211	MELOXICAM
	103/1322	EXPECTORAN CODEIN
	200/2000	PANADEINE CO
	200/2002	MERSYNDOL
	201/2103	IBUPROFEN
	201/2116	MEDI FLU
	202/2212	DICLOFENAC
	202/2212	OXYCODONE
	202/2213	CODRAL COLD & FLU
	202/2217	PANADEINE CO
	302/3201	ETORICOXIB
	302/3210	DIPROSPAN
	303/3303	CYCLOBENZAPRINE
	305/3506	METAMIZOLE
	307/3703	CELECOXIB
	307/3708	BUDESONIDE
	307/3709	DICLOFENAC
	402/4205	CYCLOBENZAPRINE
	402/4205	FENTANYL
	402/4205	HYDROMORPHONE
	402/4205	NAPROXEN
	402/4206	OXYCOCET
	402/4206	PANADEINE CO
	402/4208	HYDROCORTISONE
Restricted Con. Med. Overused	403/4300	IBUPROFEN
	403/4313	TYLENOL SINUS MEDICATION
	403/4315	CORTISONE
	403/4315	INDOMETACIN
	502/5203	DICLOFENAC
	502/5203	NAPROXEN
	502/5205	ACECLOFENAC
	502/5205	TOMOPAN /SPA/
	502/5207	DICLOFENAC SODIUM
	502/5207	PREDNISOLONE
	502/5212	CELECOXIB
	503/5309	TIZANIDINE
	603/6307	BACLOFEN
	603/6307	FENTANYL
	700/7001	FLURBIPROFEN
	701/7100	MEDICON A
	701/7104	BROWN MIXTURE
	701/7105	MEDICON A
	702/7200	METHOCARBAMOL
	702/7200	TRIAMCINOLONE
	702/7202	HYDROCORTISONE
	702/7202	METHOCARBAMOL
	703/7101	BROWN MIXTURE
	703/7302	FLURBIPROFEN
	703/7304	PIROXICAM
	703/7311	CHLORZOXAZONE
	704/7403	BACLOFEN
	704/7403	SULINDAC
	704/7406	DICLOFENAC
	704/7408	CO-DAFALGAN
	704/7416	CHLORZOXAZONE

Protocol violations included subjects who did not meet inclusion/exclusion criteria, generally with no implications for interpretation of efficacy results, as well as several subjects who took contraindicated medications during the treatment phase and overused restricted contraindicated medications during the treatment phase.

10.1.3.7 Efficacy Results

Applicant's Analysis

The primary objective of this study was to assess long-term safety and tolerability of duloxetine at doses up to 120 mg/day.

The table below summarized the mean change in BPI average pain score by treatment group for all randomized patients with a baseline and at least 1 post-baseline BPI measure during the double-blind study phase. The Applicant states that there was no significant difference in mean change in average pain scores between treatment groups.

**Table HMEH.11.13. Brief Pain Inventory Average Pain Score
Mean Change from Baseline to Endpoint
All Randomized Patients
Double-Blind Study Phase**

BPI Average Pain Score

	Baseline						Endpoint						Change					
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max		Mean	SD	Median	Min	Max	
1) DLX60QD	102	4.31	2.43	4.00	0.00	9.00	4.26	2.72	5.00	0.00	10.00		-0.05	2.76	0.00	-9.00	8.00	
2) DLX120QD	202	4.59	2.37	5.00	0.00	9.00	4.53	2.77	5.00	0.00	10.00		-0.05	2.81	0.00	-8.00	9.00	

Interaction (Type II SS) Raw Data Treatment-by-Investigator F = 1.06 df = 14.273 p = .394

Main Effects (Type II SS) Raw Data
Treatment F = 0.47 df = 1,287 p = .495
Pooled Investigator F = 2.50 df = 14,287 p = .002

Least Squares Means for Change from Baseline
1) DLX60QD -0.37 (SE = 0.26)
2) DLX120QD -0.16 (SE = 0.19)

Pairwise Comparison of LS Means
DLX60QD-DLX120QD diff = -0.20 Two-sided 95% CI : (-0.78, 0.38) t = -0.68 p = 0.495

N = Number of patients with a baseline and at least one non-missing post-baseline value.
Type II sums of squares from ANCOVA Model = Treatment, Pooled Investigator and Baseline for main effects p-values. Model = Treatment
, Pooled Investigator, Baseline, and Treatment*Pooled Investigator for the interaction p-value.

Report: RMP.FLJO.HMEHSTAT.FINAL(LOSPI311)
Program: RMP.FLJSHMEH.SASPGM(LOSPI31)
Data: RMP.SAS.FLJS.L.NCHMEH.ADS.DBF

The Applicant states that for persistence of efficacy analysis, the mean change in BPI average pain score from baseline to endpoint did not reach significance in the initial responders on duloxetine 60 mg QD. However, initial responders began and ended the double-blind study phase with mean BPI average pain scores in the mild range that were well below the mean baseline pain scores at baseline. In addition improvements in mean average pain score were observed for non-responders within both treatment groups.

The table below presents the PGI-Improvement score for all randomized patients during the double-blind study phase. The Applicant states that a significantly lower (improvement) mean PGI-I score at endpoint was observed with duloxetine 60 mg QD when compared with duloxetine 120 mg QD.

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**Table HMEH.11.21. Patient's Global Impressions of Improvement Score
Mean at Endpoint
All Randomized Patients
Double-Blind Study Phase**

PGI-Improvement

	Endpoint				
	N	Mean	SD	Median	Min	Max
1) DLX60QD	102	2.40	1.25	2.00	1.00	7.00
2) DLX120QD	200	2.83	1.54	3.00	1.00	7.00

Interaction (Type II SS) Raw Data Treatment-by-Investigator F = 0.54 df = 14,271 p = .907

Main Effects (Type II SS) Raw Data
Treatment F = 6.91 df = 1,285 p = .009
Pooled Investigator F = 1.99 df = 14,285 p = .018

Least Squares Means at Endpoint
1) DLX60QD 2.19 (SE = 0.15)
2) DLX120QD 2.65 (SE = 0.11)

Pairwise Comparison of LS Means
DLX60QD-DLX120QD diff = -0.46 Two-sided 95% CI : (-0.80, -0.11) t = -2.63 p = 0.009

N = Number of patients with baseline PGI-S and at least one non-missing post-baseline PGI-I value.
Type II sums of squares from ANCOVA Model = Treatment, Pooled Investigator, and Baseline PGI-S for main effects p-values.
Model = Treatment, Pooled Investigator, Baseline and Treatment*Pooled Investigator for interaction p-value.

Report: RMP.FLJO.HMEHSTAT.FINAL(LOPGI311)
Program: RMP.FLJSHMEH.SASPGM(LOPGI31)
Data: RMP.SAS.FLJS.L.MCHMEH.ADS.DSF

Reviewer's Analysis

Statistically significant persistence of efficacy was not demonstrated in patients who had at least a 50% reduction in BPI average pain score at Week 8 (end of open-label phase) and had remained on duloxetine 60 mg QD in the 52-week double-blind phase. Dr. Buenconsejo applied imputation strategies to assign bad scores to dropouts and found that less than 50% of patients responded at the end of the 1-year double-blind phase. This means that approximately 20% of the patients who completed the study were not able to maintain their responder status at study end. At the end of the 1-year period, patients who were non-responders at week 8 did even worse, with only a 25% response.

Approximately 20% of the patients who did not respond at the end of week 8 and were administered duloxetine at 120 mg QD during the double-blind phase responded at the end of the study, implying that dose raising the dose from 60 mg QD to 120 mg QD does not improve pain response in fibromyalgia.

In her statistical review, Dr. Buenconsejo reanalyzed Study HMEH and found that:

> Applying BOCF to patients who dropped out of the study in the responder group (i.e. 39% of the patients in the duloxetine 60 mg QD group and 27% in the 120 mg QD group), less than 50% responded at the end of the study. This implies that close to 20% of the patients who completed the study were not able to maintain their response at the end of the study. However, this is still a bit better compared to patients in the non-responder group in which only less than 25% of patients responded at the end of the study. Another important finding from this analysis is that only 20% of the patients who did not respond at Week 8 and were given 120 mg QD during double-blind phase responded at the end of the study. This implies that increasing the dose did not improve their pain response.
>
> Applying LOCF/BOCF to patients who dropped out of the study in the responder group yield somewhat similar result to the BOCF strategy except that almost 50% responded at the end of the study. Patients who are responder at Week 8 appear to still be a bit better in terms of responding at the end of the study compared to the non-responder group. However, there is no evidence that there is persistence of effect among those initial responders who remained in the duloxetine 60 mg QD.

The following table is a responder analysis of BPI Average Pain Score at endpoint:

Responder Analysis (> 50% reduction from Week 0) of Brief Pain Inventory Average Pain Score at Endpoint					
		Responder at end of Visit 4		Non-responder at end of Visit 4	
Study	Treatment Group	N	n(%)	N	n(%)
LOCF	Duloxetine 60 mg QD	37	23 (62%)	67	19 (28%)
	Duloxetine 120 mg QD	75	43 (57%)	128	37 (29%)
BOCF	Duloxetine 60 mg QD	37	14 (38%)	67	17 (25%)
	Duloxetine 120 mg QD	75	34 (45%)	128	26 (20%)
LOCF/BOCF	Duloxetine 60 mg QD	37	19 (51%)	67	19 (28%)
	Duloxetine 120 mg QD	75	37 (49%)	128	32 (25%)
Dr. Buenconsejo's Table.					

10.1.3.8 Conclusions Regarding Efficacy Data in Study

Study HMEH did not demonstrate that duloxetine at doses of either 60 mg QD or 120 mg QD is effective for up to 1-year. This may be due to the sample size. Also, although clinical pharmacology data suggests that higher plasma levels may improve PGI-Improvement scores; this is not supported by clinical response as measured by BPI. In non-responders, increasing from a dose of duloxetine 60 mg QD to a dose of 120 mg QD does not appear to increase efficacy. Using some imputation strategies, non-responders at 8 weeks were more likely to become responders if maintained on 60 mg than if switched to 120 mg.

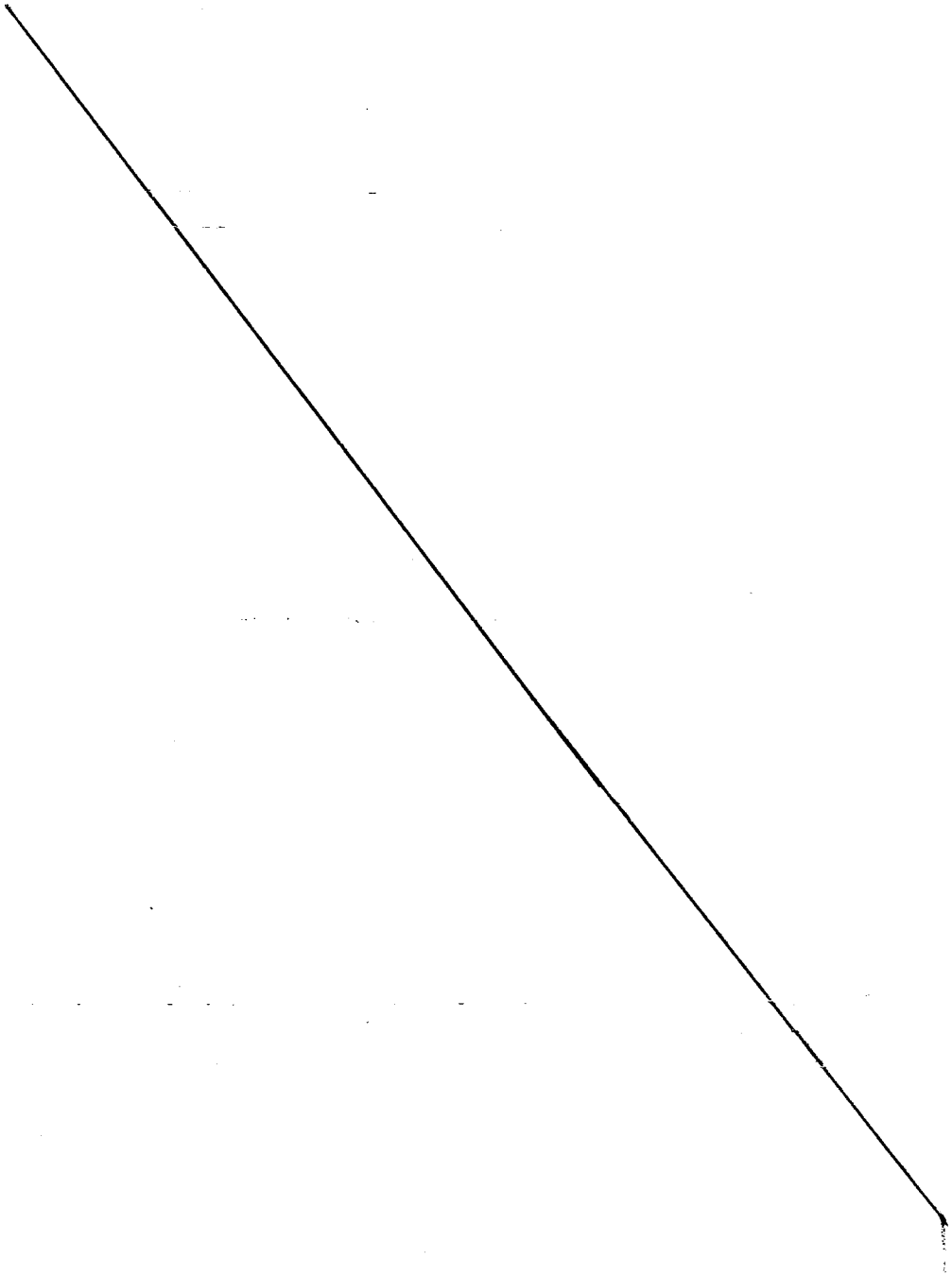
10.1.3.9 Safety Results

The table below shows the common adverse events observed in this study, as reported by Lilly in the final study report. Adverse events (MedDRA preferred terms) that occurred in more than 2% of subjects. The most frequently reported adverse events were nausea, headache, insomnia, dizziness, and constipation.

Treatment-Emergent Adverse Events Preferred Term by Decreasing Frequency All Enrolled Patients Overall Study Phase		
Preferred Term	**All Enrolled Patients n(%)**	
Patients with >= 1 Treatment-Emergent Event	**326**	**(93.1)**
Nausea	142	(40.6)
Headache	103	(29.4)
Insomnia	69	(19.7)
Dizziness	66	(18.9)
Constipation	61	(17.4)
Dry mouth	60	(17.1)
Somnolence	49	(14.0)
Diarrhoea	45	(12.9)
Hyperhidrosis	40	(11.4)
Fatigue	39	(11.1)
Abdominal pain upper	37	(10.6)
Anorexia	31	(8.9)
Back pain	31	(8.9)
Vomiting	30	(8.6)
Anxiety	28	(8.0)
Arthralgia	26	(7.4)
Upper respiratory tract infection	25	(7.1)
Hypertension	22	(6.3)
Therapeutic response unexpected	22	(6.3)
Urinary tract infection	22	(6.3)
Influenza	21	(6.0)
Dysgeusia	17	(4.9)
Dyspepsia	17	(4.9)
Nasopharyngitis	17	(4.9)
Pain	17	(4.9)
Decreased appetite	16	(4.6)
Tremor	16	(4.6)
Asthenia	15	(4.3)
Cough	15	(4.3)
Increased appetite	15	(4.3)
Migraine	15	(4.3)
Pain in extremity	15	(4.3)
Palpitations	15	(4.3)
Pharyngitis	15	(4.3)
Pruritus	15	(4.3)
Abdominal pain	14	(4.0)
Neck pain	14	(4.0)
Sinusitis	14	(4.0)
Abdominal distension	13	(3.7)
Muscle spasms	13	(3.7)
Weight increased	13	(3.7)
Hot flush	12	(3.4)
Vision blurred	12	(3.4)
Flatulence	11	(3.1)
Paraesthesia	11	(3.1)
Rash	11	(3.1)
Sedation	11	(3.1)
Carpal tunnel syndrome	10	(2.9)
Chest pain	10	(2.9)
Vertigo	10	(2.9)
Bronchitis	9	(2.6)
Gastritis	9	(2.6)
Gastroenteritis	9	(2.6)
Hypoaesthesia	9	(2.6)
Myalgia	9	(2.6)

Fall	8	(2.3)
Irritable bowel syndrome	8	(2.3)
Lethargy	8	(2.3)
Malaise	8	(2.3)
Musculoskeletal pain	8	(2.3)
Osteoarthritis	8	(2.3)
Pharyngolaryngeal pain	8	(2.3)
Pollakiuria	8	(2.3)
Tendonitis	8	(2.3)
Tinnitus	8	(2.3)

10.2 Line-by-Line Labeling Review



10.3 Additional Efficacy Review Tables and Figures

Table 6.1
Schedule of Events: Study HMBO

Table HMBO.9.1. Schedule of Events for Study Periods I and II Study F1J-MC-HMBO

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase								
Visit	1	2	3	4	5	6	7	8	9	10	ED <V10
Week	-5 to -2	-1	0	1	2	4	6	8	10	12	
Clinic Assessments											
Informed consent	x										
Demographics	x										
Medical history	x										
Complete physical exam	x									x	x
Consumptive habits	x										
Historical illness and previous medications	x										
ACR criteria for fibromyalgia	x										
MINI[a] (MDD diagnosis and others)	x										
Height	x										
Weight	x									x	x
ECG	x									x	x
Patient summary										x	x
Blood pressure (sitting), heart rate	x	x	x	x	x	x	x	x	x	x	x
Preexisting conditions and adverse events	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x
Study Drug											
Dispense drug		x	x	x	x	x	x	x	x		
Return drug/accountability			x	x	x	x	x	x	x	x	x
Efficacy Measurements											
FIQ	x	x	x	x	x	x	x	x	x	x	x
Mean tender point pain threshold[a]			x			x		x		x	x
CGI-Severity[b]			x			x		x		x	x
PGI-Improvement			x			x		x		x	x
Brief Pain Inventory			x	x	x	x	x	x	x	x	x
BDI-II			x			x		x		x	x
BAI			x			x		x		x	x
Exploratory Measures											
SSI			x								
Amplification Scale			x								

	Study Period I Screening Phase		Study Period II Acute Therapy Phase								
Visit	1	2	3	4	5	6	7	8	9	10	ED <V10
Week	-5 to -2	-1	0	1	2	4	6	8	10	12	
Health Outcomes Assessment											
SF-36			x							x	x
QLDS			x							x	x
SDS			x							x	x
Laboratory Assessments											
Hematology	x		x							x	x
Clinical chemistry and electrolyte group	x		x			x		x		x	x
Urine drug screen	x										
Serum pregnancy test	x										
Urinalysis	x										
Thyroid function test	x										
Antinuclear Antibody	x										
C-reactive protein	x										
Rheumatoid factor	x										

Appears This Way On Original

Table 6.2
Schedule of Events: Study HMCA

Table HMCA.9.2. Study Schedule

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase							Study Period III Discontinuation Phase	
Visit	1	2	3	4	5	6	7	8	9	10	ED <V10
Week	-5 to -1	0	1	2	4	6	8	10	12	13	
Clinical Assessments											
Informed consent	x										
Demographics	x										
Medical history	x										
Complete physical exam	x									x	x
Consumptive habits		x									
Historical illness and previous medications	x[a]										
ACR Criteria for Fibromyalgia	x										
Mini[b] (MDD diagnosis and others)	x										
Height		x									
Weight		x							x		x
ECG	x										
Patient summary										x	x
Blood pressure (sitting), heart rate	x	x	x	x	x	x	x	x	x	x	x
Preexisting conditions and adverse events	x[a]	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x[a]	x	x	x	x	x	x	x	x	x	x
Study Drug											
Dispense drug		x	x	x	x	x	x	x	x		
Return drug/accountability			x	x	x	x	x	x	x	x	x

(continued)

Table HMCA.9.2. Study Schedule (concluded)

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase							Study Period III Discontinuation Phase	
Visit	1	2	3	4	5	6	7	8	9	10	ED <V10
Week	-5 to -1	0	1	2	4	6	8	10	12	13	
Efficacy Measurements											
FIQ		x	x	x	x	x	x	x	x		x
Tender point pain threshold[b]		x			x		x		x		x
CGI-Severity[c]		x			x		x		x		x
PGI-Improvement					x		x		x		x
Brief Pain Inventory		x	x	x	x	x	x	x	x		x
$HAMD_{17}$[b]		x			x		x		x		x
Health Outcomes Assessment											
SF-36		x							x		x
QLDS		x							x		x
SDS		x							x		x
Laboratory Assessments											
Hematology	x										
Clinical chemistry and electrolyte group	x	x			x		x		x		x
Urine drug screen	x										
Serum pregnancy test	x										
Urinalysis	x										
Thyroid function test	x										
Antinuclear antibody	x										
C-reactive protein	x								x		x
Rheumatoid factor	x										

Table HMCA.9.2. Study Schedule (concluded)

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase							Study Period III Discontinuation Phase	
Visit	1	2	3	4	5	6	7	8	9	10	ED <V10
Week	-5 to -1	0	1	2	4	6	8	10	12	13	
Efficacy Measurements											
FIQ		x	x	x	x	x	x	x	x		x
Tender point pain threshold[b]		x			x		x		x		x
CGI-Severity[c]		x			x		x		x		x
PGI-Improvement					x		x		x		x
Brief Pain Inventory		x	x	x	x	x	x	x	x		x
$HAMD_{17}$[b]		x			x		x		x		x
Health Outcomes Assessment											
SF-36		x							x		x
QLDS		x							x		x
SDS		x							x		x
Laboratory Assessments											
Hematology	x										
Clinical chemistry and electrolyte group	x	x			x		x		x		x
Urine drug screen	x										
Serum pregnancy test	x										
Urinalysis	x										
Thyroid function test	x										
Antinuclear antibody	x										
C-reactive protein	x								x		x
Rheumatoid factor	x										

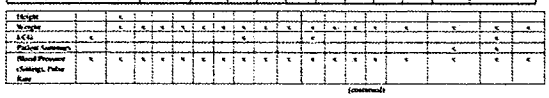


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Table 6.3
Schedule of Events: Study HMCJ

Study Schedule, Protocol F1J-MC-HMCJ

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase						Study Period III Continuation Phase			Study Period IV Extension Phase				Study Period V Taper Phase		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	301	ED 1 (Visits 3-11)	ED 2 (Visits 12-15)
Week	-1	0	1	2	4	6	11	15	19	23	28	32	40	48	56	58		
Preexisting Conditions and Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug																		
Dispense Drug		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Return Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Measurements																		
Brief Pain Inventory	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X
PGI-Improvement			X	X	X	X	X	X	X	X	X		X		X		X	X
PGI-Severity		X																
Tender Point Pain threshold[a]		X			X		X	X	X	X	X		X		X		X	X
CGI-Severity[b]		X			X		X	X	X	X	X						X	
FIQ		X			X		X	X	X	X	X						X	
MFI		X			X		X	X	X	X	X						X	
BDI-II	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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$HAMD_{17}$[c]		X						X			X				X		X	X

Study Schedule, Protocol F1J-MC-HMCJ

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase						Study Period III Continuation Phase			Study Period IV Extension Phase				Study Period V Taper Phase		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	301	ED 1 (Visits 3-11)	ED 2 (Visits 12-15)
Week	-1	0	1	2	4	6	11	15	19	23	28	32	40	48	56	58		
Health Outcomes Assessment																		
SDS		X						X			X		X		X		X	X
EQ-5D		X						X			X						X	
SF-36		X						X			X				X		X	X
Laboratory Assessments																		
Hematology	X							X			X				X		X	X
Clinical Chemistry	X				X		X	X	X	X	X				X		X	X
Fasting Lipid Profile	X							X			X				X		X	X
Urine Drug Screen	X																	
Pregnancy Test	X																	
Urinalysis	X																	
Thyroid Function Test	X																	
Antinuclear Antibody	X																	
C-Reactive Protein	X																	
Rheumatoid Factor	X																	

Study Schedule, Protocol F1J-MC-HMCJ

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase						Study Period III Continuation Phase			Study Period IV Extension Phase				Study Period V Taper Phase		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	301	ED 1 (Visits 3-11)	ED 2 (Visits 12-15)
Week	-1	0	1	2	4	6	11	15	19	23	28	32	40	48	56	58		
Health Outcomes Assessment																		
SDS		X						X			X		X		X		X	X
EQ-5D		X						X			X						X	
SF-36		X						X			X				X		X	X
Laboratory Assessments																		
Hematology	X							X			X				X		X	X
Clinical Chemistry	X				X		X	X	X	X	X				X		X	X
Fasting Lipid Profile	X							X			X				X		X	X
Urine Drug Screen	X																	
Pregnancy Test	X																	
Urinalysis	X																	
Thyroid Function Test	X																	
Antinuclear Antibody	X																	
C-Reactive Protein	X																	
Rheumatoid Factor	X																	

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Table 6.4
Schedule of Events: Study HMEF

Study Schedule, Protocol F1J-MC-HMEF

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase									Study Period III Extension Phase				Study Period IV Taper Phase		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	301	ED (Visits 3-11)	ED (Visits 12-15)
Week	-1	0	1	2	4	6	8	13	18	23	27	33	39	47	56	58		
Preexisting Conditions and Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug																		
Dispense Drug		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[c]	X[c]
Return Drug/Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Measurements																		
Brief Pain Inventory	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X
PGI-Improvement			X	X	X	X	X	X	X	X	X		X		X		X	X
PGI-Severity		X																
Tender Point Pain Threshold[a]		X			X		X	X	X	X	X		X		X		X	X
CGI-Severity[b]		X			X		X	X	X	X	X						X	
FIQ		X			X		X	X	X	X	X						X	
MFI		X			X		X	X	X	X	X						X	
BDI-II	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
$HAMD_{17}$[d]		X						X			X				X		X	X

Study Schedule, Protocol F1J-MC-HMEF

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase									Study Period III Extension Phase				Study Period IV Taper Phase		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	301	ED (Visits 3-11)	ED (Visits 12-15)
Week	-1	0	1	2	4	6	8	13	18	23	27	33	39	47	56	58		
Health Outcomes Assessment																		
SDS		X						X			X		X		X		X	X
EQ-5D		X						X			X						X	
SF-36		X						X			X				X		X	X
Laboratory Assessments																		
PK Sampling					X		X										X	
Hematology	X							X			X				X		X	X
Clinical Chemistry	X				X		X	X	X	X	X				X		X	X
Fasting Lipid profile	X							X			X				X		X	X
Urine Drug Screen	X																	
Pregnancy Test	X																	
Urinalysis	X																	
Thyroid Function Test	X																	
Antinuclear Antibody	X																	
C-Reactive Protein	X																	
Rheumatoid Factor	X																	

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Table 6.5
Schedule of Events: Study HMEH

F1J-MC-HMEH Study Report **Page 5938**

Visit	1	2	3	4	5	6	7	8	9	10	11	12	301	ET
Week	-1	0	1	8	9	14	19	26	33	42	51	60	62	>W1
Description														
Informed Consent	X													
Demographics	X													
Medical History	X													
Physical Exam	X													
Historical Illness	X													
ACR Criteria for Fibromyalgia	X													
Habits	X													
Alcohol Consumption		X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X												
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X													
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events/ Pre-existing conditions	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Drug		X	X	X	X	X	X	X	X	X	X	X		Xa
Return Drug/ accountability			X	X	X	X	X	X	X	X	X	X	X	X
FIQ		X		X		X		X		X		X		X
Tender-point pain threshold		X		X		X		X		X		X		X
BPI-Modified Short Form	X	X		X		X		X		X		X		X
PGI-Improvement				X		X		X		X		X		X
PGI-Severity		X												
CGI-Severity		X		X		X		X		X		X		X
SDS		X		X		X		X		X		X		X
BDI-II	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X		X	X		X		X		X	X	X		X

Visit	1	2	3	4	5	6	7	8	9	10	11	12	301	ET
Week	-1	0	1	8	9	14	19	26	33	42	51	60	62	>W1
Blood Chemistry	X		X	X		X		X		X	X	X		X
Urine Drug Screen	X													
Pregnancy Test (females only)	X													
Urinalysis	X		X	X		X		X		X	X	X		X
Patient Summary													X	X

[a] If ET visit is followed by taper, drug will be dispensed.

Table 6.6
Study HMBO - Reasons For Discontinuation
All Randomized Patients
Acute Therapy Phase

	PLACEBO (N=103)	DLX60BID (N=104)	Total (N=207)
Primary Reason for Discontinuation	n (%)	n (%)	n (%)
Protocol completed	66 (64.1)	58 (55.8)	124 (59.9)
AE	11 (10.7)	18 (17.3)	29 (14.0)
Unable to contact patient (lost to follow-up)	3 (2.9)	6 (5.8)	9 (4.3)
Personal conflict or other patient decision	9 (8.7)	10 (9.6)	19 (9.2)
Physician decision	0	1 (1.0)	1 (0.5)
Protocol Violation	1 (1.0)	2 (1.9)	3 (1.4)
Lack of Efficacy	13 (12.6)	9 (8.7)	22 (10.6)

Applicant's Table, Page 59, HMBO Clinical Report.

Table 6.7
Study HMBO – Reasons for Discontinuation by Visit

	Placebo (N=103)				DLX60BID (N=104)			
	Total	AE	LOE	Others	Total	AE	LOE	Others
Visit 4	7%	3%	2%	2%	11%	4%	3%	4%
Visit 5	6%	0%	3%	3%	9%	5%	1%	3%
Visit 6	8%	2%	4%	2%	13%	7%	2%	4%
Visit 7	6%	4%	1%	1%	5%	1%	1%	3%
Visit 8	9%	2%	3%	4%	4%	1%	0%	3%
Visit 9	1%	0%	0%	1%	4%	0%	2%	2%

Dr. Joan Buenconsejo's Table.

Table 6.8
Study HMCA - Reasons for Discontinuation
Comparison of Treatment Groups
All Randomized Patients

	PLACEBO (N=120)	DLX60QD (N=118)	DLX60BID (N=116)	TOTAL (N=354)
Events	n(%)	n(%)	n(%)	n(%)
AE	14(11.7)	25(21.2)	27(23.3)	66(18.6)
Unable to contact pat(lost to follow-up)	4(3.3)	1(0.8)	5(4.3)	10(2.8)
Personal conflict or other pat decision	1(0.8)	3(2.5)	4(3.4)	8(2.3)
Physician decision	0(0.0)	1(0.8)	0(0.0)	1(0.3)
Noncompl	1(0.8)	3(2.5)	1(0.9)	5(1.4)
Protocol Violation	1(0.8)	0(0.0)	0(0.0)	1(0.3)
Lack of Efficacy	18(15.0)	7(5.9)	4(3.4)	29(8.2)
Withdrawal of informed consent	13(10.8)	1(0.8)	4(3.4)	18(5.1)

Applicant's Table, Page 65, HMCA Clinical Report

Table 6.9
Study HMCA – Reasons for Discontinuation by Visit

	Placebo (N=120)				DLX60QD (N=118)				DLX60BID (N=116)			
	Total	AE	LOE	Others	Total	AE	LOE	Others	Total	AE	LOE	Others
Visit 3/Baseline	5%	3%	0%	3%	15%	14%	1%	1%	15%	12%	1%	2%
Visit 4	8%	2%	4%	3%	2%	1%	1%	0%	5%	4%	0%	1%
Visit 5	13%	3%	6%	4%	8%	5%	1%	2%	9%	4%	2%	3%
Visit 6	6%	1%	3%	2%	4%	0%	1%	3%	2%	0%	1%	1%
Visit 7	9%	3%	1%	5%	1%	0%	0%	1%	3%	2%	0%	1%
Visit 8	1%	0%	1%	0%	3%	2%	2%	0%	4%	1%	0%	3%
Visit 9	1%	0%	0%	1%	2%	0%	1%	1%	1%	0%	0%	1%
Visit 10	0%	0%	0%	0%	1%	1%	0%	0%	0%	0%	0%	0%

Dr. Joan Buenconsejo's Table.

Table 6.10
Study HMCJ - Reasons for Study Discontinuation
All Randomized Patients
3-Month Therapy Phase

Primary Reason for Discontinuation	Treatment	N	n	Percent
DC due to ANY reason	1) PLACEBO	144	60	41.67
	2) DLX20QD	79	30	37.97
	3) DLX60QD	150	53	35.33
	4) DLX120QD	147	52	35.37
Adverse Event	1) PLACEBO	144	17	11.81
	2) DLX20QD	79	8	10.13
	3) DLX60QD	150	22	14.67
	4) DLX120QD	147	32	21.77
Lack of Efficacy	1) PLACEBO	144	14	9.72
	2) DLX20QD	79	8	10.13
	3) DLX60QD	150	11	7.33
	4) DLX120QD	147	6	4.08
Subject Decision	1) PLACEBO	144	10	6.94
	2) DLX20QD	79	8	10.13
	3) DLX60QD	150	9	6.00
	4) DLX120QD	147	5	3.40
Lost to follow up	1) PLACEBO	144	13	9.03
	2) DLX20QD	79	3	3.80
	3) DLX60QD	150	7	4.67
	4) DLX120QD	147	7	4.76

Applicant's Table, Page 80, HMCA Clinical Report.

Table 6.11
Study HMCJ – Reasons for Discontinuation by Visit

	Placebo (N=144)				DLX 20/60 QD (N=79)				DLX60QD (N=150)				DLX120QD (N=147)			
	Total	AE	LOE	Others	Total	AE	LOE	Others	Total	AE	LOE	Others	Total	AE	LOE	Others
Visit 2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	1%	0%	0%	1%
Visit 3	6%	1%	1%	4%	6%	0%	1%	5%	9%	5%	1%	3%	9%	5%	0%	3%
Visit 4	5%	1%	1%	3%	4%	3%	1%	0%	7%	4%	1%	2%	3%	3%	0%	0%
Visit 5	9%	5%	2%	2%	3%	1%	0%	1%	5%	1%	0%	3%	4%	3%	0%	1%
Visit 6	9%	2%	3%	3%	4%	1%	1%	1%	6%	2%	1%	3%	3%	2%	1%	1%
Visit 7	10%	3%	1%	6%	8%	0%	4%	4%	7%	2%	3%	1%	8%	5%	3%	0%
Visit 8	3%	1%	1%	1%	13%	5%	1%	6%	3%	1%	2%	0%	7%	3%	1%	3%

Dr. Joan Buenconsejo's Table.

Table 6.12
Study HMCJ - Reasons for Study Discontinuation
All Randomized Patients
6-Month Therapy Phase

Primary Reason for Discontinuation	Treatment	N	n	Percent
DC due to ANY reason	1) PLACEBO	144	72	50.00
	2) DLX60QD	150	68	45.33
	3) DLX120QD	147	68	46.26
	4) DLX20/60QD	79	35	44.30
Adverse Event	1) PLACEBO	144	19	13.19
	2) DLX60QD	150	23	15.33
	3) DLX120QD	147	39	26.53
	4) DLX20/60QD	79	9	11.39
Lack of Efficacy	1) PLACEBO	144	16	11.11
	2) DLX60QD	150	15	10.00
	3) DLX120QD	147	7	4.76
	4) DLX20/60QD	79	8	10.13
Subject Decision	1) PLACEBO	144	12	8.33
	2) DLX60QD	150	12	8.00
	3) DLX120QD	147	10	6.80
	4) DLX20/60QD	79	10	12.66
Lost to follow up	1) PLACEBO	144	18	12.50
	2) DLX60QD	150	10	6.67
	3) DLX120QD	147	8	5.44
	4) DLX20/60QD	79	4	5.06

Applicant's Table, Page 91, HMCJ Clinical Report.

Table 6.13
Study HMEF - Reasons for Discontinuation
All Randomized Patients
6-month Therapy Phase

	PLACEBO (N=168)		DLX60/120QD (N=162)		Total (N=330)	
Primary Reason for Discontinuation	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
DC due to ANY reason	65	(38.7)	61	(37.7)	126	(38.2)
Adverse Event	19	(11.3)	30	(18.5)	49	(14.8)
Lack of Efficacy	25	(14.9)	12	(7.4)	37	(11.2)
Subject Decision	9	(5.4)	5	(3.1)	14	(4.2)
Protocol Violation	5	(3.0)	8	(4.9)	13	(3.9)
Lost to follow up	6	(3.6)	4	(2.5)	10	(3.0)
Physician Decision	1	(0.6)	1	(0.6)	2	(0.6)
Sponsor Decision	0	(0.0)	1	(0.6)	1	(0.3)
Patients Continuing	103	(61.3)	101	(62.3)	204	(61.8)

Applicant's Table, Page 69, HMEF Clinical Report.

Table 6.14
Study HMEH - Reasons for Study Discontinuation
All Enrolled Patients in Open-Label Study Phase

Primary Reasons For Discontinuation	DLX60QD (N = 350) n (%)
DC due to ANY reason	43 (12.3)
Adverse Event	26 (7.4)
Subject Decision	9 (2.6)
Lost to follow up	4 (1.1)
Protocol Violation	3 (0.9)
Lack of Efficacy	1 (0.3)
Patients Continuing	307 (87.7)

Applicant's Table, Page 77, HMEH Clinical Report

Table 6.15
Study HMCJ – Mean BPI Average Pain Score at Endpoint by Gender
All Randomized Patients in the 3-Month Placebo-Controlled Study

		Women			Men		
Study	**Treatment Group**	**N**	**Baseline**	**Endpoint Mean**	**N**	**Baseline**	**Endpoint Mean**
				BOCF			
HMCJ	Placebo	137	6.6	5.5	7	6.1	5.6
	DLX 20 mg QD	76	6.8	5.1	3	6.3	6.3
	DLX 60 mg QD	136	6.5	5.0	14	6.2	4.9
	DLX 120 mg QD	143	6.4	4.8	4	7.0	4.5
				LOCF/BOCF			
HMCJ	Placebo	137	6.6	5.4	7	6.1	5.7
	DLX 20 mg QD	76	6.8	4.8	3	6.3	6.3
	DLX 60 mg QD	136	6.5	4.9	14	6.2	4.3
	DLX 120 mg QD	143	6.4	4.7	4	7.0	4.5

DLX = duloxetine
Dr. Buenconsejo's Table

Table 6.16
Study HMCJ – PGI-Improvement at Endpoint by Gender
All Randomized Patients in the 3-Month Placebo Controlled Studies

		Women		Men	
Study	**Treatment Group**	**N**	**Endpoint Mean**	**N**	**Endpoint Mean**
		LOCF			
HMCJ	Placebo	138	3.0	4	2.5
	DLX 20 mg QD	75	2.9	2	4.0
	DLX 60 mg QD	130	3.1	13	3.2
	DLX 120 mg QD	132	3.5	7	3.7
		WOCF			
HMCJ	Placebo	138	3.1	4	2.5
	DLX 20 mg QD	75	3.1	2	4.5
	DLX 60 mg QD	129	3.2	13	3.3
	DLX 120 mg QD	132	3.7	6	3.8

DLX = duloxetine
Dr. Buenconsejo's Table.

Table 6.17
Studies HMCA and HMCJ –Mean Brief Average Pain Score at Endpoint by Race
All Randomized Patients in the 3-Month Placebo-Controlled Studies

		White			Non-white		
Study	**Treatment Group**	**N**	**Baseline**	**Endpoint Mean**	**N**	**Baseline**	**Endpoint Mean**
				BOCF			
HMCA	Placebo	107	6.4	5.5	13	7.8	6.2
	DLX 60 mg QD	106	6.3	4.2	12	7.0	5.8
	DLX 60 mg BID	104	6.2	4.3	12	7.8	6.8
HMCJ	Placebo	119	6.3	5.3	25	7.9	6.4
	DLX 20 mg QD	66	6.6	5.0	13	7.8	5.8
	DLX 60 mg QD	127	6.4	4.8	23	7.0	6.0
	DLX 120 mg QD	126	6.3	4.6	21	7.1	5.9
				LOCF/BOCF			
HMCA	Placebo	107	6.4	5.3	13	7.8	6.2
	DLX 60 mg QD	106	6.3	4.1	12	7.0	5.7
	DLX 60 mg BID	104	6.2	4.0	12	7.8	6.3
HMCJ	Placebo	119	6.3	5.2	25	7.9	6.4
	DLX 20 mg QD	66	6.6	4.7	13	7.8	5.5
	DLX 60 mg QD	127	6.4	4.6	23	7.0	5.7
	DLX 120 mg QD	126	6.3	4.6	21	7.1	5.7

DLX = duloxetine
Dr. Buenconsejo's Table.

Table 6.18
Studies HMCA and HMCJ – PGI-Improvement at Endpoint by Race
All Randomized Patients in the 3-Month Placebo Controlled Studies

		White		Non-White	
Study	**Treatment Group**	**N**	**Endpoint Mean**	**N**	**Endpoint Mean**
		LOCF			
HMCA	Placebo	100	3.7	11	3.5
	DLX 60 mg QD	103	3.1	11	3.6
	DLX 60 mg BID	99	3.0	12	3.3
HMCJ	Placebo	121	2.9	21	3.3
	DLX 20 mg QD	64	2.9	13	3.2
	DLX 60 mg QD	120	3.1	23	3.3
	DLX 120 mg QD	115	3.6	24	2.7
		WOCF			
HMCA	Placebo	100	3.8	11	3.5
	DLX 60 mg QD	103	3.1	11	3.6
	DLX 60 mg BID	99	3.1	12	3.4
HMCJ	Placebo	121	3.1	21	3.4
	DLX 20 mg QD	64	3.1	13	3.3
	DLX 60 mg QD	119	3.2	23	3.4
	DLX 120 mg QD	114	3.8	24	3.0

DLX = duloxetine
Dr. Buenconsejo's Table.

Table 6.19
Studies HMCA and HMCJ – Mean BPI Average Pain Score at Endpoint by Age
All Randomized Patients in the 3-Month Placebo Controlled Studies

		Age < 65			Age ≥ 65		
Study	**Treatment Group**	**N**	**Baseline**	**Endpoint Mean**	**N**	**Baseline**	**Endpoint Mean**
				BOCF			
HMCA	Placebo	109	6.6	5.7	11	5.5	3.6
	DLX 60 mg QD	113	6.4	4.4	5	6.6	1.6
	DLX 60 mg BID	105	6.3	4.4	11	6.6	5.7
HMCJ	Placebo	136	6.6	5.4	8	6.9	6.3
	DLX 20 mg QD	70	6.8	5.3	9	6.2	4.2
	DLX 60 mg QD	135	6.5	4.9	15	6.3	5.2
	DLX 120 mg QD	133	6.3	4.7	14	6.9	6.1
				LOCF/BOCF			
HMCA	Placebo	109	6.6	5.6	11	5.5	3.6
	DLX 60 mg QD	113	6.4	4.3	5	6.6	1.6
	DLX 60 mg BID	105	6.3	4.1	11	6.6	6.0
HMCJ	Placebo	136	6.6	5.3	8	6.9	6.4
	DLX 20 mg QD	70	6.8	4.9	9	6.2	4.3
	DLX 60 mg QD	135	6.5	4.8	15	6.3	4.9
	DLX 120 mg QD	133	6.3	4.6	14	6.9	6.0

DLX = duloxetine
Dr. Buenconsejo's Table.

Table 6.20
Studies HMCA and HMCJ – PGI-Improvement at Endpoint by Age
All Randomized Patients in the 3-Month Placebo-Controlled Studies

		Age < 65		Age ≥ 65	
Study	**Treatment Group**	**N**	**Endpoint Mean**	**N**	**Endpoint Mean**
		LOCF			
HMCA	Placebo	100	3.8	11	2.7
	DLX 60 mg QD	109	3.2	5	1.6
	DLX 60 mg BID	100	3.0	11	3.7
HMCJ	Placebo	129	2.9	13	3.5
	DLX 20 mg QD	68	2.9	9	3.2
	DLX 60 mg QD	128	3.1	15	3.6
	DLX 120 mg QD	131	3.5	8	3.8
		WOCF			
HMCA	Placebo	100	3.9	11	2.7
	DLX 60 mg QD	109	3.2	5	1.6
	DLX 60 mg BID	100	3.0	11	3.7
HMCJ	Placebo	129	3.1	13	3.7
	DLX 20 mg QD	68	3.1	9	3.2
	DLX 60 mg QD	127	3.2	15	3.7
	DLX 120 mg QD	130	3.6	8	4.4

DLX = duloxetine
Dr. Buenconsejo's Table.

10.4 Additional Safety Review Tables and Figures

Table 7.1
SAEs Reported in All Fibromyalgia Studies Which Appear Unrelated to Study Medication

	Study	Subject ID	Treatment	Age	Race	Sex	MedDRA Preffered Term/Comment
1	HMBO	HMBO-102-1230	DLX60BID	39	Caucasian	M	FEMUR FRACTURE
Unrelated to study medication.							
2	HMCA	HMCA-109-1928	DLX60BID	32	Caucasian	F	APPENDICITIS
Unrelated to study medication.							
3	HMCA	HMCA-113-2302	DLX60QD	35	Caucasian	F	BLOOD CREATINE PHOSPHOKINASE INCREASED
							HEPATIC ENZYME INCREASED
Patient was not taking study medication; unrelated to study medication.							
4	HMCJ	HMCJ-100-1005	DLX60QD	56	Caucasian	F	HIATUS HERNIA
Unrelated to study medication.							
5	HMCJ	HMCJ-114-2418	DLX120QD	56	Caucasian	F	CARDIAC FAILURE CONGESTIVE
Obese female with arrhythmia & COPD, blood pressure was controlled; Unrelated to study medication.							
6	HMCJ	HMCJ-115-2509	DLX120QD	52	Hispanic	F	BRONCHITIS BACTERIAL
Unrelated to study medication.							
7	HMCJ	HMCJ-120-3025	DLX60QD	68	Caucasian	F	MALIGNANT MELANOMA
Unrelated to study medication.							
8	HMCJ	HMCJ-123-3304	DLX120QD	42	Caucasian	F	LOCAL SWELLING
							PAIN IN EXTERMITY
Underwent surgery to remove old scar tissue from previous car accident; Unrelated to study medication							
9	HMCJ	HMCJ-126-3631	DLX120QD	45	Hispanic	F	HYPERGLICEMIA
							UPPER RESPIRATORY TRACT INFECTION
							URINARY TRACT INFECTION
Hyperglycemia present at baseline and exacerbation was associated with infection; Unrelated to study medication.							
10	HMCJ	HMCJ-128-3806	DLX120QD	51	Hispanic	F	NEPHROLITHIASIS
Unrelated to study medication.							
11	HMCJ	HMCJ-130-4017	DLX30QD	45	Caucasian	F	ASTHMA
Unrelated to study medication.							
12	HMCJ	HMCJ-130-4020	DLX120QD	67	Caucasian	F	COLON NEOPLASM
Unrelated to study medication.							
13	HMEF	HMEF-606-6453	DLX120QD	63	Caucasian	F	ARTHRALGIA
Unrelated to study medication.							
14	HMEF	HMEF-606-6466	DLX60QD	56	Caucasian	F	LUNG INFECTION PSEUDOMONAL
Unrelated to study medication.							
15	HMEH	HMEH-103-1319	DLX120QD	53	Hispanic	F	VENOUS INSUFFICIENCY
Unrelated to study medication.							
16	HMEH	HMEH-202-2215	DLX60QD	18	Caucasian	F	ABSCESS INTESTINAL
							APPENDICITIS
Unrelated to study medication.							
17	HMEH	HMEH-203-2302	DLX60QD	52	Caucasian	F	ANGINA UNSTABLE
Patient had several risk factors for CAD and was found to have CAD, BP normal during trial; Unrelated to study medication.							
18	HMEH	HMEH-303-3310	DLX120QD	50	Hispanic	F	THERMAL BURN

Unrelated to study medication.							
19	HMEH	HMEH-403-4304	DLX60QD	47	Caucasian	M	TRANSIENT ISCHEMIC ATTACK
Patient had classic TIA with multiple. Elevated SBP at baseline, which was untreated and undiagnosed. BP remained stable on DLX. Elevated cholesterol which was diagnosed, but untreated. Unrelated to study medication.							
20	HMEH	HMEH-603-6307	DLX60QD	57	Caucasian	F	LUMBAR VERTEBRAL FRACTURE
Unrelated to study medication.							
21	HMEH	HMEH-700-7001	DLX120QD	49	Asian	F	DROWSINESS
Patient experienced drowsiness and fainted had full neuron workup which was negative. Discontinued benzodiazepine, but continued DLX and symptom resolved. Unrelated to study medication.							
22	HMEH	HMEH-701-7100	DLX120QD	40	Asian	F	CARPAL TUNNEL SYNDROME
Unrelated to study medication.							
23	HMEH	HMEH-703-7301	DLX60QD	59	Asian	F	HYPERPARATHYROIDISM PRIMARY
Unrelated to study medication.							
24	HMEH	HMEH-704-7410	DLX120QD	42	Asian	F	UTERINE LEIOMYOMA
Unrelated to study medication.							
25	HMEH	HMEH-704-7417	DLX60QD	36	Asian	F	NEPHROLITHIASIS
Unrelated to study medication.							
DLX= duloxetine							

Table 7.2
Transaminase Abnormalities Reported as Reasons for Discontinuation – MedDRA Preferred Terms
All Patient Who Received Duloxetine For All Indications

Event	Duloxetine N=27229 n(%)
OVERALL	82(0.3%)
Hepatic enzyme increased	35(0.1%)
Alanine aminotransferase increased	26(0.1%)
Gamma-glutamyltransferase increased	12(0.0%)
Aspartate aminotransferase increased	5(0.0%)
Transaminases increased	2(0.0%)
Alanine aminotransferase abnormal	1(0.0%)
Hepatic enzyme abnormal	1(0.0%)

N = Number of duloxetine patients, n = Number of patients with adverse event as reason for study discontinuation
Applicant's Table, Page 4399, 5.3.5.3 Multistudy Analyses

Table 7.3
Hepatic-Related Treatment-Emergent Adverse Events – MedDRA Preferred Terms
Fibromyalgia Placebo-Controlled and Open-Label Studies

	Fibromyalgia Placebo-Controlled Trials		All Fibromyalgia Patient – Placebo-Controlled and Open-Label
Event	**PLACEBO (N=535) n(%)**	**DULOXETINE (N=876) n(%)**	**DULOXETINE (N=1236) n(%)**
PATIENTS WITH >=1 TEAE	4(0.7%)	10(1.1%)	15(1.2%)
Hepatic enzyme increased	1(0.2%)	4(0.5%)	5(0.4%)
Alanine aminotransferase increased	0(0.0%)	3(0.3%)	3(0.2%)
Liver function test abnormal	1(0.2%)	2(0.2%)	1(0.1%)
Gamma-glutamyltransferase increased	1(0.2%)	1(0.1%)	1(0.1%)
Hepatic cyst	1(0.2%)	1(0.1%)	1(0.1%)
Aspartate aminotransferase increased	0(0.0%)	1(0.1%)	1(0.1%)
Blood alkaline phosphatase increased	1(0.2%)	0(0.0%)	1(0.1%)

N = Number of randomized patients, n = Number of patients with treatment-emergent adverse events
Applicant's Table, Page 4401, 5.3.5.3 Multistudy Analyses

Table 7.4
Treatment-Emergent Adverse Events Occuring in ≥ 5% of Patients by Decreasing Frequency MedDRA Preferred Term For All Fibromyalgia Patients Treated With Duloxetine

MedDra Preferred Term	Duloxetine (N=1236) n (%)
Patients with ≥ 1 Treatment-Emergent Adverse Event	1115 (90.2)
Nausea	410 (33.2)
Headache	280 (22.7)
Dry mouth	223 (18.0)
Insomnia	202 (16.3)
Constipation	193 (15.6)
Dizziness	165 (13.3)
Fatigue	164 (13.3)
Diarrhoea	151 (12.2)
Somnolence	134 (10.8)
Hyperhidrosis	104 (8.4)
Upper respiratory tract infection	89 (7.2)
Anorexia	74 (6.0)
Decreased appetite	74 (6.0)
Nasopharyngitis	68 (5.5)
Back pain	67 (5.4)
Anxiety	59 (4.8)
Arthralgia	59 (4.8)
Abdominal pain upper	58 (4.7)
Vomiting	57 (4.6)
Dyspepsia	54 (4.4)
Tremor	54 (4.4)
Muscle spasms	53 (4.3)
Urinary tract infection	49 (4.0)
Sinusitis	48 (3.9)
Hot flush	47 (3.8)
Cough	46 (3.7)
Migraine	45 (3.6)
Pain	45 (3.6)
Pain in extremity	43 (3.5)
Myalgia	42 (3.4)
Dysgeusia	41 (3.3)
Influenza	41 (3.3)

Therapeutic response unexpected	41 (3.3)
Hypertension	38 (3.1)
Pharyngolaryngeal pain	38 (3.1)
Pruritus	37 (3.0)
Palpitations	36 (2.9)
Rash	35 (2.8)
Musculoskeletal pain	34 (2.8)
Paraesthesia	34 (2.8)
Weight increased	34 (2.8)
Abdominal pain	33 (2.7)
Bronchitis	33 (2.7)
Sleep disorder	32 (2.6)
Vision blurred	32 (2.6)
Asthenia	29 (2.3)
Flatulence	29 (2.3)
Depression	28 (2.3)
Neck pain	27 (2.2)
Hypoaesthesia	26 (2.1)
Seasonal allergy	26 (2.1)
Increased appetite	25 (2.0)
Night sweats	25 (2.0)
Pollakiuria	25 (2.0)
Abdominal distension	23 (1.9)
Gastroenteritis viral	23 (1.9)
Irritable bowel syndrome	23 (1.9)
Lethargy	23 (1.9)
Sedation	23 (1.9)
Chest pain	22 (1.8)
Contusion	22 (1.8)
Disturbance in attention	22 (1.8)
Fibromyalgia	22 (1.8)
Chills	21 (1.7)
Libido decreased	21 (1.7)
Feeling jittery	20 (1.6)
Pharyngitis	20 (1.6)
Sinus headache	20 (1.6)
Fall	19 (1.5)
Nervousness	19 (1.5)
Muscle twitching	18 (1.5)
Vertigo	18 (1.5)
Weight decreased	18 (1.5)
Pyrexia	17 (1.4)
Abnormal dreams	16 (1.3)
Nightmare	16 (1.3)
Sinus congestion	16 (1.3)
Stomach discomfort	16 (1.3)
Tinnitus	16 (1.3)

Anorgasmia	15 (1.2)
Oedema peripheral	15 (1.2)
Restlessness	15 (1.2)
Dry eye	14 (1.1)
Gastritis	14 (1.1)
Gastrooesophageal reflux disease	14 (1.1)
Osteoarthritis	14 (1.1)
Bruxism	13 (1.1)
Gastroenteritis	13 (1.1)
Irritability	13 (1.1)
Musculoskeletal stiffness	13 (1.1)
Restless legs syndrome	13 (1.1)
Thirst	13 (1.1)
Joint sprain	12 (1.0)
Tendonitis	12 (1.0)
Urinary hesitation	12 (1.0)
Urticaria	12 (1.0)
Modified from Applicant's Table, Page 173, Clinical Safety Summary Appendix.	

Table 7.5
Laboratory Values – Chemistry Analytes Change from Baseline to Maximum
All Randomized Patients in Fibromyalgia Placebo-Controlled Trials

				Baseline		Change to Maximum	
Lab Test	**Unit**	**Therapy**	**N**	**Mean**	**SD**	**Mean**	**SD**
ALKALINE PHOSPHATASE	U/L	Placebo Duloxetine	505 819	74.95 76.20	23.22 23.55	3.63 7.07	9.71 12.57
ALT/SGPT	U/L	Placebo Duloxetine	504 818	20.73 21.53	9.89 10.36	3.60 8.49	11.87 38.27
AST/SGOT	U/L	Placebo Duloxetine	503 810	20.75 21.17	6.13 6.77	2.87 5.83	7.36 21.74
BICARBONATE, HCO3	mmol/L	Placebo Duloxetine	503 819	23.99 23.91	2.41 2.58	1.38 1.94	2.67 2.70
BILIRUBIN, TOTAL	umol/L	Placebo Duloxetine	504 820	7.29 7.60	3.90 3.79	1.24 1.01	3.02 2.72
CALCIUM	mmol/L	Placebo Duloxetine	505 820	2.45 2.46	0.10 0.10	0.04 0.03	0.10 0.09
CHLORIDE	mmol/L	Placebo Duloxetine	505 818	104.64 104.79	2.55 2.88	1.37 0.76	2.32 2.73
CHOLESTEROL	mmol/L	Placebo Duloxetine	505 820	5.50 5.52	1.08 1.03	0.17 0.29	0.66 0.70
CREATINE PHOSPHOKINASE	U/L	Placebo Duloxetine	504 819	84.00 90.09	48.32 68.68	23.80 56.59	80.70 600.17
CREATININE	umol/L	Placebo Duloxetine	505 820	95.90 96.44	12.74 13.08	4.88 5.45	9.77 9.14
GGT (GGPT/SGGT/YGGT)	U/L	Placebo Duloxetine	505 818	24.01 26.02	28.52 21.94	3.01 3.94	18.54 21.28
INORGANIC PHOSPHORUS	mmol/L	Placebo Duloxetine	505 820	1.15 1.18	0.17 0.17	0.09 0.07	0.17 0.18
POTASSIUM	mmol/L	Placebo Duloxetine	505 817	4.30 4.30	0.40 0.41	0.19 0.21	0.40 0.41
SODIUM	mmol/L	Placebo Duloxetine	504 817	141.38 141.46	2.39 2.69	1.07 0.82	2.71 3.27
TOTAL PROTEIN	g/L	Placebo Duloxetine	505 820	72.64 72.79	4.09 4.18	0.65 0.60	3.58 3.54
UREA NITROGEN	mmol/L	Placebo Duloxetine	505 820	5.19 5.21	1.44 1.47	0.64 0.66	1.27 1.26
URIC ACID	umol/L	Placebo Duloxetine	505 820	290.01 294.62	74.45 78.92	23.01 9.89	41.99 43.66

N = Number of patients with a baseline and at least one non-missing post-baseline measurement.
SD = standard deviation
Modified from Applicant's Table, Page 81-82, Clinical Safety Summary

Table 7.6
Laboratory Values – Hematology Analytes Change from Baseline to Maximum
All Randomized Patients in Fibromyalgia Placebo-Controlled Trials

				Baseline		Change to Maximum	
Lab Test	**Unit**	**Therapy**	**N**	**Mean**	**SD**	**Mean**	**SD**
BANDS	GI/L	Placebo Duloxetine	313 487	0.00 0.00	0.01 0.01	0.00 0.00	0.01 0.02
BASOPHILS	GI/L	Placebo Duloxetine	363 565	0.05 0.05	0.03 0.02	0.01 0.01	0.03 0.03
EOSINOPHILS	GI/L	Placebo Duloxetine	363 565	0.14 0.14	0.11 0.11	0.01 0.03	0.08 0.10
ERYTHROCYTE COUNT	TI/L	Placebo Duloxetine	363 565	4.72 4.74	0.39 0.38	-0.01 -0.00	0.24 0.24
HEMATOCRIT	Actual Count	Placebo Duloxetine	361 564	0.42 0.42	0.04 0.03	-0.00 0.00	0.03 0.02
HEMOGLOBIN	mml/L	Placebo Duloxetine	363 565	8.49 8.48	0.72 0.68	-0.06 -0.02	0.43 0.46
LEUKOCYTE COUNT	GI/L	Placebo Duloxetine	363 565	6.74 6.64	1.79 1.69	0.24 0.29	1.39 1.43
LYMPHOCYTES	GI/L	Placebo Duloxetine	363 565	2.06 2.06	0.64 0.61	0.06 0.07	0.44 0.42
LYMPHOCYTES, ATYPICAL	GI/L	Placebo Duloxetine	225 387	0.00 0.00	0.01 0.00	-0.00 0.00	0.01 0.01
MEAN CELL HEMOGLOBIN (MCH)	fmol	Placebo Duloxetine	363 563	1.81 1.79	0.13 0.11	-0.00 0.01	0.06 0.06
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)	mml/L	Placebo Duloxetine	361 564	20.40 20.29	0.95 0.85	0.11 0.09	0.77 0.81
MEAN CELL VOLUME (MCV)	fL	Placebo Duloxetine	361 564	88.66 88.56	5.49 4.76	0.44 0.84	3.35 3.16
MONOCYTES	GI/L	Placebo Duloxetine	363 565	0.34 0.34	0.12 0.12	0.04 0.05	0.12 0.12
NEUTROPHILS, SEGMENTED	GI/L	Placebo Duloxetine	363 565	4.14 4.05	1.38 1.34	0.21 0.22	1.23 1.24
PLATELET COUNT	GI/L	Placebo Duloxetine	359 561	283.80 280.68	64.67 60.94	2.91 13.52	39.03 42.68

N = Number of patients with a baseline and at least one non-missing post-baseline measurement.
SD = standard deviation
Modified from Applicant's Table, Pages 96-97, Clinical Safety Summary

Table 7.7
Treatment-Emergent Laboratory Values at Any Time – Chemistry Analytes (Reference Ranges)
All Randomized Patients in Fibromyalgia Placebo-Controlled Trials

		Placebo			Duloxetine		
Lab Test	**Direction**	**N**	**n**	**%**	**N**	**n**	**%**
ALKALINE PHOSPHATASE	High	478	12	2.5	773	42	5.4
	Low	505	3	0.6	820	2	0.2
ALT/SGPT	High	450	36	8.0	729	111	15.2
	Low	506	1	0.2	820	3	0.4
AST/SGOT	High	482	25	5.2	781	79	10.1
	Low	503	3	0.6	816	0	0
BICARBONATE, HCO3	High	504	7	1.4	821	28	3.4
	Low	501	6	1.2	811	6	0.7
BILIRUBIN, TOTAL	High	499	6	1.2	812	4	0.5
	Low	478	54	11.3	772	75	9.7
CALCIUM	High	475	24	5.1	771	38	4.9
	Low	507	0	0	822	2	0.2
CHLORIDE	High	501	5	1.0	811	8	1.0
	Low	507	2	0.4	821	7	0.9
CHOLESTEROL	High	466	15	3.2	762	45	5.9
	Low	452	52	11.5	746	76	10.2
CREATINE PHOSPHOKINASE	High	465	35	7.5	761	93	12.2
	Low	506	0	0	822	0	0
CREATININE	High	503	10	2.0	810	19	2.3
	Low	506	3	0.6	821	2	0.2
GGT (GGPT/SGGT/YGGT)	High	475	17	3.6	736	39	5.3
	Low	506	4	0.8	821	5	0.6
INORGANIC PHOSPHORUS	High	504	3	0.6	816	7	0.9
	Low	504	11	2.2	820	22	2.7
POTASSIUM	High	500	12	2.4	810	23	2.8
	Low	506	7	1.4	814	20	2.5
SODIUM	High	481	20	4.2	775	32	4.1
	Low	505	1	0.2	819	11	1.3
TOTAL PROTEIN	High	500	3	0.6	813	3	0.4
	Low	506	0	0	819	3	0.4
UREA NITROGEN	High	492	15	3.0	807	40	5.0
	Low	507	0	0	822	0	0
URIC ACID	High	489	22	4.5	784	17	2.2
	Low	502	1	0.2	816	11	1.3

N = total number of at risk patients with the lab test, n = total number of at risk patients with specific lab result
Modified from Applicant's Table, Page 83-85, Clinical Safety Summary

Table 7.8
Treatment-Emergent Laboratory Values at Any Time – Hematology Analytes (Reference Ranges)
All Randomized Patients in Fibromyalgia Placebo-Controlled Trials

		Placebo			Duloxetine		
Lab Test	**Direction**	**N**	**n**	**%**	**N**	**n**	**%**
ANISOCYTOSIS	Abnormal	216	13	6.0	398	4	1.0
BANDS	High	313	0	0	487	0	0
	Low	313	0	0	487	0	0
BASOPHILS	High Low	365	1	0.3	567	2	0.4
		366	0	0	567	0	0
EOSINOPHILS	High	364	0	0	560	6	1.1
	Low	366	0	0	567	0	0
ERYTHROCYTE COUNT	High	363	1	0.3	561	4	0.7
	Low	350	6	1.7	538	15	2.8
HEMATOCRIT	High	352	7	2.0	558	5	0.9
	Low	359	2	0.6	562	8	1.4
HEMOGLOBIN	High	364	0	0	565	1	0.2
	Low	352	13	3.7	546	14	2.6
HYPOCHROMIA	Abnormal	72	1	1.4	203	0	0
LEUKOCYTE COUNT	High	353	13	3.7	554	15	2.7
	Low	360	7	1.9	555	12	2.2
LYMPHOCYTES	High	361	5	1.4	557	5	0.9
	Low	362	2	0.6	564	4	0.7
MACROCYTOSIS	Abnormal	195	4	2.1	324	3	0.9
MEAN CELL HEMOGLOBIN (MCH)	High	364	0	0	565	3	0.5
	Low	344	5	1.5	547	7	1.3
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)	High	364	0	0	567	0	0
	Low	344	25	7.3	543	36	6.6
MEAN CELL VOLUME (MCV)	High Low	351 354	10 12	2.8 3.4	562	11	2.0
					554	4	0.7
MICROCYTOSIS	Abnormal	209	6	2.9	388	2	0.5
MONOCYTES	High Low	366 363	2	0.5	566	7	1.2
			2	0.6	565	5	0.9
NEUTROPHILS, SEGMENTED	High	354	16	4.5	552	20	3.6
	Low	359	5	1.4	556	16	2.9
PLATELET COUNT	High Low	345	10	2.9	544	18	3.3
		360	4	1.1	562	0	0
POLYCHROMIA	Abnormal	207	8	3.9	376	2	0.5

N = total number of at risk patients with the lab test, n = total number of at risk patients with specific lab result
Modified from Applicant's Table, Page 98-100, Clinical Safety Summary

Table 7.9
Treatment-Emergent Potentially Clinically Significant Values at Any Time
All Randomized Patients in Fibromyalgia Placebo-Controlled Trials

		PLACEBO			DULOXETINE		
Vital Statistic	**Abnormality**	**N**	**n**	**Percent**	**N**	**n**	**Percent**
Pulse	High	527	1	0.2	855	4	0.5
	Low	519	2	0.4	846	3	0.4
Sitting Diastolic BP	High	522	1	0.2	847	6	0.7
	Low	523	3	0.6	852	3	0.4
Sitting Systolic BP	High	525	1	0.2	848	3	0.4
	Low	517	3	0.6	845	2	0.2
Weight (kg)	Gain	499	2	0.4	823	10	1.2
	Loss	499	6	1.2	823	18	2.2

N = Number of patients at risk of having PCS values at baseline.
n = Number of patients with a PCS postbaseline measurement.
Baseline values are lowest in baseline interval for PCS low and highest value in baseline interval for PCS high.
Criteria: SYS low (≤90 and decrease from baseline ≥20), SYS high(≥180 and increase from baseline≥20),
DIA low (≤50 and decrease from baseline≥15),DIA high (≥105 and increase from baseline≥15),
Pulse low(≤50 and decrease from baseline≥15), Pulse high (≥120 and increase from baseline≥15),
WGTKG low decrease from baseline>=10%, high increase from baseline>=10%.
Applicant's Table, Page 113, Clinical Safety Summary.

Table 7.10
Vital Signs and Weight - Treatment-Emergent Potentially Clinically Significant Values at Any Time
All Fibromyalgia Patients Treated With Duloxetine (Placebo-Controlled & Open-Label Studies)

		DULOXETINE		
Vital Statistic	**Abnormality**	**N**	**n**	**Percent**
Pulse	High	1202	6	0.5
	Low	1194	3	0.3
Sitting Diastolic BP	High	1189	14	1.2
	Low	1198	6	0.5
Sitting Systolic BP	High	1195	9	0.8
	Low	1185	13	1.1
Weight (kg)	Gain	1171	38	3.2
	Loss	1171	35	3.0

N = Number of patients at risk of having PCS values at baseline.
n = Number of patients with a PCS postbaseline measurement.
Applicant's Table, Page 804, Clinical Safety Summary Appendix.

Table 7.11
Electrocardiogram Intervals and Heart Rate
Treatment-Emergent Abnormal Values at Any Time
All Randomized Patients in Fibromyalgia Placebo-Controlled Trials

		PLACEBO			DULOXETINE		
ECG Parameters	Abnormality	N	n	Percent	N	n	Percent
HR	High	354	0	0	545	0	0
	Low	345	2	0.6	539	4	0.7
PR	Abnormal	341	7	2.1	533	7	1.3
QRS	Abnormal	234	47	20.1	364	95	26.1
QT	Abnormal	338	10	3.0	526	11	2.1
QTcB	Abnormal	349	9	2.6	536	11	2.1
QTcF	Abnormal	353	3	0.8	542	5	0.9

N = number of randomized patients with baseline and postbaseline measurements who were 'normal' at baseline.
n = Number of randomized patients with abnormal postbaseline measurement.
Modified from Applicant's Table, Page 121, Clinical Safety Summary

Table 7.12
Electrocardiogram Intervals and Heart Rate
Treatment-Emergent Potentially Clinically Significant Values at Any Time
All Randomized Patients in Fibromyalgia Placebo-Controlled Trials

		PLACEBO			DULOXETINE		
ECG Parameters	Abnormality	N	n	Percent	N	n	Percent
HR	High	354	0	0	545	0	0
	Low	345	2	0.6	539	4	0.7
PR	High	343	8	2.3	533	6	1.1
	Low	350	5	1.4	531	16	3.0
QRS	High	347	4	1.2	536	7	1.3
	Low	354	0	0	545	0	0
QTcF	Abnormal	354	1	0.3	545	2	0.4

N = Number of patients at risk of having PCS values at baseline.
n = Number of patients with a PCS postbaseline measurement.
Modified from Applicant's Table, Page 123, Clinical Safety Summary

Table 7.13
Patient Demographics and Baseline Characteristics
All Enrolled Patients
Primary Long-Term Analyses Set (Study HMEH)

	All Enrolled Patients
Variable	(N = 350)
Sex	
No. of Patients	350
Female	335 (95.7)
Male	15 (4.3)
Age in Years at Consent	
No. of Patients	350
Mean	48.97
Median	49.55
Standard Dev.	11.07
Minimum	18.41
Maximum	83.82
Race	
No. of Patients	350
African	3 (0.9)
Caucasian	214 (61.1)
East Asian	46 (13.1)
Hispanic	82 (23.4)
Native American	1 (0.3)
West Asian	4 (1.1)
Weight in Kg at Baseline	
No. of Patients	350
Mean	69.95
Median	67.00
Standard Dev.	14.74
Minimum	41.00
Maximum	125.00
Height in Cm at Baseline	
No. of Patients	349
Mean	159.44
Median	160.00
Standard Dev.	7.09
Minimum	142.00
Maximum	189.00
Applicant's Table, Page 55-56, Summary of Clinical Safety Appendix	

Table 7.14

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase								
Visit	1	2	3	4	5	6	7	8	9	10	ED <V10
Week	-5 to -2	-1	0	1	2	4	6	8	10	12	
Clinic Assessments											
Informed consent	x										
Demographics	x										
Medical history	x										
Complete physical exam	x									x	x
Consumptive habits	x										
Historical illness and previous medications	x										
ACR criteria for fibromyalgia	x										
MINI* (MDD diagnosis and others)	x										
Height	x										
Weight	x									x	x
ECG	x									x	x
Patient summary										x	x
Blood pressure (sitting), heart rate	x	x	x	x	x	x	x	x	x	x	x
Preexisting conditions and adverse events	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x
Study Drug											
Dispense drug		x	x	x	x	x	x	x	x		
Return drug/accountability			x	x	x	x	x	x	x	x	x
Efficacy Measurements											
FIQ	x	x	x	x	x	x	x	x	x	x	x
Mean tender point pain threshold[a]			x			x		x		x	x
CGI-Severity[b]			x			x		x		x	x
PGI-Improvement			x			x		x		x	x
Brief Pain Inventory			x	x	x	x	x	x	x	x	x
BDI-II			x			x		x		x	x
BAI			x			x		x		x	x
Exploratory Measures											
SSI			x								
Amplification Scale			x								

	Study Period I Screening Phase		Study Period II Acute Therapy Phase								
Visit	1	2	3	4	5	6	7	8	9	10	ED <V10
Week	-5 to -2	-1	0	1	2	4	6	8	10	12	
Health Outcomes Assessment											
SF-36			x							x	x
QLDS			x							x	x
SDS			x							x	x
Laboratory Assessments											
Hematology	x		x							x	x
Clinical chemistry and electrolyte group	x		x			x		x		x	x
Urine drug screen	x										
Serum pregnancy test	x										
Urinalysis	x										
Thyroid function test	x										
Antinuclear Antibody	x										
C-reactive protein	x										
Rheumatoid factor	x										

Abbreviations: BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory; CGI-Severity = Clinical Global Impressions of Severity; ECG = Electrocardiogram; ED = early discontinuation; FIQ = Fibromyalgia Impact Questionnaire; MINI = Mini International Neuropsychiatric Interview; PGI-Improvement = Patient Global Impressions of Improvement; QLDS = Quality of Life in Depression Scale; SDS = Sheehan Disability Scale; SF-36 = Medical Outcomes Study Short Form-36; SSI = Somatic Symptom Inventory.

[a] Qualified study personnel, as defined in Lilly training materials, performed these assessments.

[b] A study physician administered the CGI-Severity in the presence of the patient.

Applicant's Table, Pages 41-42, Clinical Study Report F1J-MC-HMBO.

Appears This Way On Original

Table 7.15

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase							Study Period III Discontinuation Phase	
Visit	1	2	3	4	5	6	7	8	9	10	ED <V10
Week	-5 to -1	0	1	2	4	6	8	10	12	13	
Clinical Assessments											
Informed consent	x										
Demographics	x										
Medical history	x										
Complete physical exam	x									x	x
Consumptive habits		x									
Historical illness and previous medications	x[a]										
ACR Criteria for Fibromyalgia	x										
Mini[b] (MDD diagnosis and others)	x										
Height		x									
Weight		x							x		x
ECG	x										
Patient summary										x	x
Blood pressure (sitting), heart rate	x	x	x	x	x	x	x	x	x	x	x
Preexisting conditions and adverse events	x[a]	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x[a]	x	x	x	x	x	x	x	x	x	x
Study Drug											
Dispense drug		x	x	x	x	x	x	x	x		
Return drug/accountability			x	x	x	x	x	x	x	x	x

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase							Study Period III Discontinuation Phase	
Visit	1	2	3	4	5	6	7	8	9	10	ED <V10
Week	-5 to -1	0	1	2	4	6	8	10	12	13	
Efficacy Measurements											
FIQ		x	x	x	x	x	x	x	x		x
Tender point pain threshold[b]		x			x		x		x		x
CGI-Severity[c]		x			x		x		x		x
PGI-Improvement					x		x		x		x
Brief Pain Inventory		x	x	x	x	x	x	x	x		x
$HAMD_{17}$[b]		x			x		x		x		x
Health Outcomes Assessment											
SF-36		x							x		x
QLDS		x							x		x
SDS		x							x		x
Laboratory Assessments											
Hematology	x										
Clinical chemistry and electrolyte group	x	x			x		x		x		x
Urine drug screen	x										
Serum pregnancy test	x										
Urinalysis	x										
Thyroid function test	x										
Antinuclear antibody	x										
C-reactive protein	x								x		x
Rheumatoid factor	x										

x = Performed at this visit.

Abbreviations: ACR = American College of Rheumatology; CGI-Severity = Clinical Global Impressions of Severity; ECG = Electrocardiogram; ED = early discontinuation; FIQ = Fibromyalgia Impact Questionnaire; $HAMD_{17}$ = Hamilton Depression 17-item scale; MDD = major depressive disorder; MINI = Mini International Neuropsychiatric Interview; PGI-Improvement = Patient Global Impressions of Improvement; QLDS = Quality of Life Depression Scale; SDS = Sheehan Disability Scale; SF-36 = Medical Outcomes Study Short Form-36; V = visit.

[a] Recorded on Source document at Visit 1 and entered on CRF at Visit 2.

[b] Qualified study personnel, as defined in Lilly training materials, must perform these assessments.

[c] A study physician must administer the CGI-Severity in the presence of the patient or after having been in the presence of the patient.

Applicant's Table, Pages 45-46, Clinical Study Report F1J-MC-HMCA.

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Table 7.16

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase						Study Period III Continuation Phase			Study Period IV Extension Phase				Study Period V Taper Phase		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	301	ED 1 (Visits 3-11)	ED 2 (Visits 12-15)
Week	-1	0	1	2	4	8	11	15	19	23	28	32	40	48	56	58		
Clinic Assessments																		
Informed Consent	X																	
Demographics	X																	
Medical History	X																	
Complete Physical Exam	X																	
Habits: Average Alcohol Consumption and Tobacco Consumption	X																	
Actual Alcohol Consumption		X						X			X				X		X	X
Historical Illness and Previous Medications	X																	
ACR Criteria for FMS	X																	
MINI[a] (MDD diagnosis and others)	X																	
Height		X																
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X							X			X						X	
Patient Summary																X	X	
Blood Pressure (Sitting), Pulse Rate	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase						Study Period III Continuation Phase			Study Period IV Extension Phase				Study Period V Taper Phase		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	301	ED 1 (Visits 3-11)	ED 2 (Visits 12-15)
Week	-1	0	1	2	4	8	11	15	19	23	28	32	40	48	56	58		
Preexisting Conditions and Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug																		
Dispense Drug		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[d]	X[d]
Return Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Measurements																		
Brief Pain Inventory	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X
PGI-Improvement			X	X	X	X	X	X	X	X	X		X		X		X	X
PGI-Severity		X																
Tender Point Pain threshold		X			X		X	X	X	X	X		X		X		X	X
CGI-Severity[b]		X			X		X	X	X	X	X						X	
FIQ		X			X		X	X	X	X	X						X	
MFI		X			X		X	X	X	X	X						X	
BDI-II	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
$HAMD_{17}$[c]		X						X			X				X		X	X

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase						Study Period III Continuation Phase			Study Period IV Extension Phase				Study Period V Taper Phase		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	301	ED 1 (Visits 3-11)	ED 2 (Visits 12-15)
Week	-1	0	1	2	4	8	11	15	19	23	28	32	40	48	56	58		
Health Outcomes Assessment																		
SDS		X						X			X		X		X		X	X
EQ-5D		X						X			X						X	
SF-36		X						X			X				X		X	X
Laboratory Assessments																		
Hematology	X							X			X				X		X	X
Clinical Chemistry	X				X			X	X	X	X				X		X	X
Fasting Lipid Profile	X							X			X				X		X	X
Urine Drug Screen	X																	
Pregnancy Test	X																	
Urinalysis	X																	
Thyroid Function Test	X																	
Antinuclear Antibody	X																	
C-Reactive Protein	X																	
Rheumatoid Factor	X																	

Abbreviations: ACR = American College of Rheumatology; BDI-II = Beck Depression Inventory -II; CGI-Severity = Clinical Global Impressions of Severity; Cont = continuation; ED = early discontinuation; ECG = electrocardiogram; EQ-5D = Euro-Qol Questionnaire - 5 Dimension; Ext = extension; FIQ = Fibromyalgia Impact Questionnaire; $HAMD_{17}$ = 17-item Hamilton Depression Rating Scale; MFI = Multidimensional Fatigue Inventory; MINI = Mini International Neuropsychiatric Interview; PGI-Improvement = Patient's Global Impressions of Improvement; SF-36 = 36-item Short-Form Health Survey; SDS = Sheehan Disability Scale.

a Qualified study personnel, as defined in Lilly training materials, must perform these assessments.

b A study physician must administer the CGI-Severity in the presence of the patient or after having been in the presence of the patient.

c If ED visit is being followed by the study drug tapering phase.

Applicant's Table, Pages 2455-2460, Clinical Study Report F1J-MC-HMCJ.

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Table 7.17

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase									Study Period III Extension Phase				Study Period IV Taper Phase		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	301	ED (Visits 3-11)	ED (Visits 12-15)
Week	-1	0	1	2	4	6	8	13	18	23	27	33	39	47	56	58		
Clinic Assessments																		
Informed Consent	x																	
Demographics	x																	
Medical History	x																	
Complete Physical Exam	x																	
Habits: Average Alcohol Consumption, Tobacco Consumption	x																	
Actual Alcohol Consumption		x						x			x				x	x	x	x
Historical Illness and Previous Medications	x																	
ACR Criteria for FMS	x																	
MINI+ (3-DD diagnosis and others)	x																	
Height		x																
Weight		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG	x							x			x						x	
Patient Summary																x	x	x
Blood Pressure (Sitting), Pulse Rate	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase									Study Period III Extension Phase				Study Period IV Taper Phase		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	301	ED (Visits 3-11)	ED (Visits 12-15)
Week	-1	0	1	2	4	6	8	13	18	23	27	33	39	47	56	58		
Precluding Conditions and Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study Drug																		
Dispense Drug		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Return Drug Accountability			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Efficacy Measurements																		
Brief Pain Inventory	x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
PGIc Improvement			x	x	x	x	x	x	x	x	x		x		x		x	x
PGI-Severity		x																
Tender Point Pain Thresholds[a]		x			x		x	x	x	x	x		x		x		x	x
CGI-Severity[b]		x			x		x	x	x	x	x						x	
FIQ		x			x		x	x	x	x	x						x	
MFI		x			x		x	x	x	x	x						x	
BDI-II	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
$HAMD_{17}$[c]		x			x		x		x		x						x	

Description	Study Period I Screening Phase		Study Period II Acute Therapy Phase									Study Period III Extension Phase				Study Period IV Taper Phase		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	301	ED (Visits 3-11)	ED (Visits 12-15)
Week	-1	0	1	2	4	6	8	13	18	23	27	33	39	47	56	58		
Health Outcomes Assessment																		
SDS		x						x			x		x		x		x	x
EQ-5D		x						x			x						x	
SF-36		x						x			x				x		x	x
Laboratory Assessments																		
PK Sampling					x		x										x	
Hematology	x							x			x				x		x	x
Clinical Chemistry	x				x		x	x	x	x	x				x		x	x
Fasting Lipid profile	x							x			x				x		x	x
Urine Drug Screen	x																	
Pregnancy Test	x																	
Urinalysis	x																	
Thyroid Function Test	x																	
Antinuclear Antibody	x																	
C-Reactive Protein	x																	
Rheumatoid Factor	x																	

Abbreviations: ACR = American College of Rheumatology; BDI-II = Beck Depression Inventory-II; CGI-Severity = Clinical Global Impressions of Severity; ED = early discontinuation; ECG = Electrocardiogram; EQ-5D = EuroQol Questionnaire - 5 Dimension; FIQ = Fibromyalgia Impact Questionnaire; $HAMD_{17}$ = 17-item Hamilton Depression Rating Scale; MFI = Multidimensional Fatigue Inventory; MINI = Mini International Neuropsychiatric Interview; PGI-Improvement = Patient's Global Impression of Improvement; SF-36 = 36-item Short-Form Health Survey; SDS = Sheehan Disability Scale.

a Qualified study personnel, as defined in Lilly training materials, must perform these assessments.

b A study physician must administer the CGI-Severity in the presence of the patient.

c If ED visit is being followed by the study drug tapering phase.

Applicant's Table, Pages 1288-1292, Clinical Study Report F1J-MC-HMEF.

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Table 7.18

Visit	1	2	3	4	5	6	7	8	9	10	11	12	301	ET
Week	-1	0	1	8	9	14	19	26	33	42	51	60	62	>W1
Description														
Informed Consent	X													
Demographics	X													
Medical History	X													
Physical Exam	X													
Historical Illness	X													
ACR Criteria for Fibromyalgia	X													
Habits	X													
Alcohol Consumption		X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X												
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X													
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events/ Pre-existing conditions	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Drug		X	X	X	X	X	X	X	X	X	X	X		X[a]
Return Drug/ accountability			X	X	X	X	X	X	X	X	X	X	X	X
FIQ		X		X		X		X		X		X		X
Tender-point pain threshold		X		X		X		X		X		X		X
BPI-Modified Short Form	X	X		X		X		X		X		X		X
PGI-Improvement				X		X		X		X		X		X
PGI-Severity		X												
CGI-Severity		X		X		X		X		X		X		X
SDS		X		X		X		X		X		X		X
BDI-II	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X		X	X		X		X		X	X	X		X

Visit	1	2	3	4	5	6	7	8	9	10	11	12	301	ET
Week	-1	0	1	8	9	14	19	26	33	42	51	60	62	>W1
Blood Chemistry	X		X	X		X		X		X	X	X		X
Urine Drug Screen	X													
Pregnancy Test (females only)	X													
Urinalysis	X		X	X		X		X		X	X	X		X
Patient Summary													X	X

[a] If ET visit is followed by taper, drug will be dispensed.

Applicant's Table, Pages 5938-5939, Clinical Study Report F1J-MC-HMEH.

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Table 7.19
Worldwide Regulatory Actions Through 5/2/2007

Issue	Country	Action Taken	Date
Pediatric suicidality	United States	Boxed warning: The FDA requested a boxed warning as well as updated Warnings and Precautions language and a Medication Guide concerning pediatric suicidality for all antidepressants in the US on October 14, 2004. These labeling updates and the Medication Guide were added to the Cymbalta US label and approved by FDA on 18 February 2005 .	October 15, 2004; actions completed on 18 February 2005
Hepatic safety	United States	On August 16, 2005, Lilly received a letter from FDA requesting that the hepatic section of Cymbalta USPI be updated, based upon information collected from spontaneous reporting, and that Lilly provide a "Dear Healthcare Provider" letter to healthcare providers informing them of the labeling change. The letter also requested that Lilly further study the safety of duloxetine in patients with mild-moderate hepatic dysfunction. After discussions with the FDA in teleconferences on September 15 and October 3, 2005, a revised USPI was submitted to the Division on October 11, 2005 as a CBE sNDA labeling change. The "Dear Healthcare Provider" letter was posted to the Cymbalta website the following day and then distributed via mailings. The FDA approved the CBE on 06 June 2006.	16 August 2005 to 06 June 2006
Serotonin syndrome	United States	On 09 May 2006, the FDA requested class labeling for all selective serotonin reuptake inhibitors (SSRI)/serotonin norepinephrine reuptake inhibitors (SNRI) and triptans regarding drug-drug interactions of these compounds and the potential development of serotonin syndrome. Following discussions with the FDA, Lilly submitted a CBE sNDA labeling change adding the class labeling on 30 August 2006.	May to September, 2006 The FDA approved this CBE on 20 September 2006.
Orthostatic hypotension, Syncope, Blood pressure	United States		
Hepatic safety	South Africa	Medicines Control Council requested that Lilly provide a "Dear Healthcare Professional" letter to healthcare providers informing them of the hepatic effects of duloxetine based upon information collected from spontaneous reporting. Lilly prepared a "Dear Healthcare Professional" that was approved by Medicines Control Council and was distributed to health care providers in February 2007.	Request from Medicines Control Council - January 2007

Pediatric suicidality	European Union	All duloxetine products (Cymbalta/Xeristar/Ariclaim/Yentreve): A Referral procedure (Articles 18 and 31) was initiated in January 2005 by the CHMP with regards pediatric suicidality for all SSRIs and SNRIs. A class-labeling warning regarding suicide-related behaviors in children and adolescents was requested (CHMP Opinion of 22 April).	Completed September 2005 The European Commission approved this label change in September 2005
SUI and suicidality	European Union	Duloxetine in SUI (Yentreve/Ariclaim): The Marketed Authorization Holder (MAH) was requested to provide a written answer to a list of question including all data available for duloxetine regarding suicide attempt in the indication of SUI and its potential impact on the risk-benefit balance. After reviewing this data the CHMP requested the MAH submit an application to amend the label accordingly on 5 August 2005.	Completed November 2005 The European Commission approved this label change in November 2005.
Hyponatremia, gastro-intestinal hemorrhage, Adverse drug reactions	European Union	All duloxetine products Following a request of the CHMP in its conclusion of the review of PSUR 01, a type II variation was submitted in August 2005 to update the SPC with: Section 4.4 - Precaution for patients at increased risks of hyponatremia, reported cases of GI hemorrhage. Section 4.8 -Adverse drug reactions.	Completed March 2006 The European Commission approved this label change in March 2006
Heart Rate, Blood pressure, Withdrawal symptoms, Akathisia, Psychomotor restlessness	European Union	All duloxetine products: Following a request of the CHMP in its conclusion of the review of PSUR 02, a type II variation was submitted in February 2006 to updated Section 4.4 of the SPC with: - A precaution for use in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure, - A class labeling warning on withdrawal symptoms, - A class labeling warning on akathisia and psychomotor restlessness.	Completed May 2006 The European Commission approved this label change in May 2006.
Hypertension, Hypertensive crisis. Renal impairment, Akathisia/psychomotor restlessness, Hepatic failure	European Union	All duloxetine products: Following a request of the CHMP in its conclusion of the review of PSUR 03, a type II variation was submitted in August 2006 to update the SPC with: Section 4.3: - A contraindication for the initiation of treatment in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis. - A contraindication for patients with severe renal impairment (Yentreve and Ariclaim only). Section 4.4: - Updated class labeling wording on Akathisia/psychomotor restlessness. - Reported cases of clinically significant hypertension and hypertensive crisis. Section 4.8: - The adverse event hepatic failure.	Completed November 2006 The European Commission approved this label change in November 2006.

Suicidality	United States	The FDA issued a press release and posted information on the FDA website, describing the revised class labeling language on suicidality and antidepressant use required for all antidepressants. The FDA sent manufacturers of all antidepressants revised class labeling for the use of antidepressants (including duloxetine) and the risk of suicidality for patients aged 18 to 24 years. The new class labeling also states that there is no demonstrated risk for patients beyond 24 years and that there is a decrease in risk of suicidality for patients greater than 65 years. This information was revised in both the boxed warning at the beginning of labeling as well as in the "Warnings" section of the labeling. The Medication Guide was also updated to contain this information. Manufacturers were given 30 days to implement this new labeling. Lilly	
Suicide related events, muscle spasm	European Union	All duloxetine products: Following a request of the CHMP in its conclusion of the review of PSUR 04, a type II variation was submitted in March 2007 to update the SPC with: Section 4.4: -Update of warning on suicide with increased risk of suicide-related events for patients having pre-existing suicidal ideation or young adults. Section 4.8: - The adverse event Muscle spasm This procedure is on-going.	Ongoing

Abbreviations: AEs = adverse events; ALT = alanine transaminase; CHMP = Committee for Medicinal Products for Human Use; DPN = diabetic peripheral neuropathy; DPNP = diabetic peripheral neuropathic pain; FDA = Food and Drug Administration; GI = gastrointestinal; HbA1c= glycosylated hemoglobin; Lilly = Eli Lilly and Company; MDD = major depressive disorder; PSUR = Periodic Safety Update Report; sNDA = Supplemental New Drug Application; SPC = Summary of Product Characteristics; US = United States; USPI = United States Package Insert.
Applicant's Table, Pages 35-38, Post-marketing Report.

Table 7.20 Common Adverse Events
Treatment-Emergent Adverse Events by Assigned Dose By System Organ Class and by High Level Group Term
All Randomized Patients in Fibromyalgia Placebo-Controlled Studies at 3 Months (HMBO, HMCA, HMCJ & HMEF)

EVENT (Patients with ≥ 1 TEAE)	PLACEBO (N=535) n(%)	DLX 20 QD (N=79) n(%)	DLX 60 QD (N=430) n(%)	DLX 60 BID (N=220) n(%)	DLX 120 QD (N=147) n(%)
ALL BODY SYSTEMS COMBINED	394(73.64%)	65(82.28%)	367(85.35%)	191(86.82%)	130(88.44%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2(0.37%)	1(1.27%)	0(0.00%)	1(0.45%)	1(0.68%)
Spleen, lymphatic and reticuloendothelial system disorders	1(0.19%)	1(1.27%)	0(0.00%)	1(0.45%)	0(0.00%)
Anaemias nonhaemolytic and marrow depression	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	1(0.68%)
Red blood cell disorders	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
CARDIAC DISORDERS	12(2.24%)	2(2.53%)	11(2.56%)	5(2.27%)	6(4.08%)
Cardiac disorder signs and symptoms	7(1.31%)	2(2.53%)	8(1.86%)	5(2.27%)	3(2.04%)
Cardiac arrhythmias	4(0.75%)	0(0.00%)	3(0.70%)	0(0.00%)	1(0.68%)
Cardiac valve disorders	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	1(0.68%)
Coronary artery disorders	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Heart failures	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	1(0.68%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	1(0.68%)
Neurological disorders congenital	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	1(0.68%)
EAR AND LABYRINTH DISORDERS	11(2.06%)	0(0.00%)	14(3.26%)	4(1.82%)	3(2.04%)
Inner ear and VIIIth cranial nerve disorders	4(0.75%)	0(0.00%)	11(2.56%)	1(0.45%)	2(1.36%)
Aural disorders NEC	5(0.93%)	0(0.00%)	3(0.70%)	3(1.36%)	1(0.68%)
Hearing disorders	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Middle ear disorders (excl congenital)	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
ENDOCRINE DISORDERS	1(0.19%)	0(0.00%)	1(0.23%)	0(0.00%)	1(0.68%)
Adrenal gland disorders	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Parathyroid gland disorders	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	1(0.68%)
Thyroid gland disorders	0(0.00%)	0(0.00%)	1(0.23%)	0(0.00%)	0(0.00%)
EYE DISORDERS	16(2.99%)	5(6.33%)	18(4.19%)	10(4.55%)	11(7.48%)
Vision disorders	3(0.56%)	2(2.53%)	8(1.86%)	3(1.36%)	4(2.72%)
Eye disorders NEC	5(0.93%)	1(1.27%)	4(0.93%)	2(0.91%)	2(1.36%)
Ocular infections, irritations and inflammation	6(1.12%)	1(1.27%)	2(0.47%)	0(0.00%)	3(2.04%)
Ocular neuromuscular disorders	1(0.19%)	1(1.27%)	2(0.47%)	4(1.82%)	0(0.00%)
Ocular sensory symptoms NEC	1(0.19%)	1(1.27%)	1(0.23%)	1(0.45%)	0(0.00%)
Ocular structural change, deposit and degeneration NEC	0(0.00%)	0(0.00%)	2(0.47%)	0(0.00%)	1(0.68%)
Ocular hemorrhages and vascular disorders NEC	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	1(0.68%)
GASTROINTESTINAL DISORDERS	147(27.48%)	34(43.04%)	227(52.79%)	115(52.27%)	78(53.06%)
Gastrointestinal signs and symptoms*	87(16.26%)	24(30.38%)	148(34.42%)	70(31.82%)	51(34.69%)
Gastrointestinal motility and defecation conditions	61(11.40%)	12(15.19%)	96(22.33%)	34(15.45%)	36(24.49%)
Salivary gland conditions	26(4.86%)	7(8.86%)	72(16.74%)	43(19.55%)	27(18.37%)
Dental and gingival conditions	4(0.75%)	0(0.00%)	6(1.40%)	2(0.91%)	1(0.68%)
Oral soft tissue conditions	1(0.19%)	1(1.27%)	3(0.70%)	3(1.36%)	0(0.00%)
Gastrointestinal inflammatory conditions	4(0.75%)	1(1.27%)	1(0.23%)	0(0.00%)	0(0.00%)
Gastrointestinal conditions NEC	1(0.19%)	1(1.27%)	1(0.23%)	1(0.45%)	1(0.68%)
Gastrointestinal vascular conditions	1(0.19%)	1(1.27%)	1(0.23%)	1(0.45%)	1(0.68%)
Tongue conditions	2(0.37%)	0(0.00%)	1(0.23%)	1(0.45%)	0(0.00%)
Anal and rectal conditions NEC	0(0.00%)	0(0.00%)	1(0.23%)	1(0.45%)	1(0.68%)
Gastrointestinal hemorrhages NEC	1(0.19%)	0(0.00%)	0(0.00%)	1(0.45%)	1(0.68%)
Abdominal hernias and other abdominal wall conditions	0(0.00%)	0(0.00%)	2(0.47%)	0(0.00%)	0(0.00%)
Gastrointestinal stenosis and obstruction	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	101(18.88%)	17(21.52%)	98(22.79%)	72(32.73%)	33(22.45%)
General system disorders NEC	90(16.82%)	15(18.99%)	82(19.07%)	63(28.64%)	27(18.37%)
Body temperature conditions	10(1.87%)	0(0.00%)	14(3.26%)	7(3.18%)	7(4.76%)
Therapeutic and nontherapeutic effects (excl toxicity)	5(0.93%)	1(1.27%)	9(2.09%)	8(3.64%)	0(0.00%)
Administration site reactions	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Tissue disorders NEC	0(0.00%)	1(1.27%)	0(0.00%)	0(0.00%)	0(0.00%)
HEPATOBILIARY DISORDERS	2(0.37%)	1(1.27%)	0(0.00%)	0(0.00%)	0(0.00%)
Hepatobiliary neoplasms	1(0.19%)	1(1.27%)	0(0.00%)	0(0.00%)	0(0.00%)

Gallbladder disorders	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
IMMUNE SYSTEM DISORDERS	12(2.24%)	1(1.27%)	6(1.40%)	8(3.64%)	4(2.72%)
Allergic conditions	12(2.24%)	1(1.27%)	6(1.40%)	8(3.64%)	4(2.72%)
INFECTIONS AND INFESTATIONS	142(26.54%)	21(26.58%)	96(22.33%)	41(18.64%)	38(25.85%)
Infections – pathogen class unspecified	110(20.56%)	15(18.99%)	75(17.44%)	34(15.45%)	34(23.13%)
Viral infectious disorders	25(4.67%)	6(7.59%)	21(4.88%)	9(4.09%)	5(3.40%)
Bacterial infectious disorders	8(1.50%)	2(2.53%)	7(1.63%)	0(0.00%)	2(1.36%)
Fungal infectious disorders	7(1.31%)	0(0.00%)	3(0.70%)	3(1.36%)	0(0.00%)
Ectoparasitic disorders	0(0.00%)	0(0.00%)	1(0.23%)	0(0.00%)	0(0.00%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	26(4.86%)	8(10.13%)	37(8.60%)	9(4.09%)	14(9.52%)
Injuries	19(3.55%)	5(6.33%)	26(6.05%)	7(3.18%)	7(4.76%)
Bone and joint injuries	7(1.31%)	2(2.53%)	10(2.33%)	2(0.91%)	5(3.40%)
Injuries by physical agents	1(0.19%)	2(2.53%)	3(0.70%)	0(0.00%)	0(0.00%)
Procedural and device related injuries and complications NEC	1(0.19%)	0(0.00%)	1(0.23%)	0(0.00%)	2(1.36%)
Chemical injury and poisoning	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
INVESTIGATIONS	15(2.80%)	1(1.27%)	24(5.58%)	13(5.91%)	16(10.88%)
Physical examination topics	2(0.37%)	1(1.27%)	6(1.40%)	7(3.18%)	9(6.12%)
Cardiac and vascular investigations (excl enzyme tests)	8(1.50%)	0(0.00%)	8(1.86%)	3(1.36%)	4(2.72%)
Hepatobiliary investigations	3(0.56%)	0(0.00%)	6(1.40%)	1(0.45%)	2(1.36%)
Enzyme investigations NEC	1(0.19%)	0(0.00%)	1(0.23%)	0(0.00%)	0(0.00%)
Gastrointestinal investigations	0(0.00%)	0(0.00%)	1(0.23%)	1(0.45%)	0(0.00%)
Investigations, imaging and histopathology procedures NEC	0(0.00%)	0(0.00%)	0(0.00%)	1(0.45%)	1(0.68%)
Metabolic , nutritional and blood gas investigations	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	1(0.68%)
Renal and urinary tract investigations and urinalyses	1(0.19%)	0(0.00%)	1(0.23%)	0(0.00%)	0(0.00%)
Hematology investigations (incl blood groups)	0(0.00%)	0(0.00%)	1(0.23%)	0(0.00%)	0(0.00%)
Lipid analyses	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Musculoskeletal and soft tissue investigations (excl enzyme tests)	0(0.00%)	0(0.00%)	1(0.23%)	0(0.00%)	0(0.00%)
Reproductive organ and breast investigations (excl hormone analyses)	0(0.00%)	0(0.00%)	0(0.00%)	1(0.45%)	0(0.00%)
Skin investigations	0(0.00%)	0(0.00%)	0(0.00%)	1(0.45%)	0(0.00%)
METABOLISM AND NUTRITION DISORDERS	28(5.23%)	9(11.39%)	50(11.63%)	30(13.64%)	22(14.97%)
Appetite and general nutritional disorders	20(3.74%)	7(8.86%)	44(10.23%)	27(12.27%)	19(12.93%)
Electrolyte and fluid balance conditions	3(0.56%)	1(1.27%)	1(0.23%)	1(0.45%)	1(0.68%)
Lipid metabolism disorders	4(0.75%)	0(0.00%)	2(0.47%)	1(0.45%)	0(0.00%)
Glucose metabolism disorders (incl diabetes mellitus)	1(0.19%)	1(1.27%)	2(0.47%)	0(0.00%)	2(1.36%)
Acid-base disorders	0(0.00%)	0(0.00%)	0(0.00%)	1(0.45%)	0(0.00%)
Protein and amino acid metabolism disorders NEC	0(0.00%)	1(1.27%)	0(0.00%)	0(0.00%)	0(0.00%)
Purine and pyrimidine metabolism disorders NEC	0(0.00%)	0(0.00%)	1(0.23%)	0(0.00%)	0(0.00%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	122(22.80%)	17(21.52%)	88(20.47%)	39(17.73%)	20(13.61%)
Musculoskeletal and connective tissue disorders NEC	62(11.59%)	9(11.39%)	36(8.37%)	23(10.45%)	6(4.08%)
Muscle disorders	29(5.42%)	6(7.59%)	32(7.44%)	17(7.73%)	13(8.84%)
Joint disorders	31(5.79%)	4(5.06%)	26(6.05%)	6(2.73%)	3(2.04%)
Bone disorders (excl congenital and fractures)	11(2.06%)	1(1.27%)	2(0.47%)	1(0.45%)	1(0.68%)
Tendon, ligament and cartilage disorders	7(1.31%)	1(1.27%)	3(0.70%)	0(0.00%)	0(0.00%)
Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders)	2(0.37%)	0(0.00%)	2(0.47%)	2(0.91%)	0(0.00%)
Synovial and bursal dirorders	3(0.56%)	0(0.00%)	0(0.00%)	1(0.45%)	0(0.00%)
NEOPLASMS BENIGN, MALIGNANT AND USPECIFIED (INCL CYSTS AND POLYPS)	1(0.19%)	0(0.00%)	1(0.23%)	0(0.00%)	0(0.00%)
Reproductive neoplasms female benign	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Skin neoplasms malignant and unspecified	0(0.00%)	0(0.00%)	1(0.23%)	0(0.00%)	0(0.00%)
NERVOUS SYSTEM DISORDERS	123(22.99%)	26(32.91%)	173(40.23%)	96(43.64%)	69(46.94%)
Neurological disorders NEC	62(11.59%)	15(18.99%)	89(20.70%)	57(25.91%)	45(30.61%)
Headaches	64(11.96%)	12(15.19%)	88(20.47%)	50(22.73%)	29(19.73%)
Movement disorders (incl Parkinsonism)	5(0.93%)	2(2.53%)	21(4.88%)	8(3.64%)	17(11.56%)
Mental impairment disorders	9(1.68%)	2(2.53%)	8(1.86%)	4(1.82%)	4(2.72%)

Sleep disturbances (incl subtypes)	4(0.75%)	1(1.27%)	6(1.40%)	3(1.36%)	0(0.00%)
Neuromuscular disorders	1(0.19%)	0(0.00%)	2(0.47%)	1(0.45%)	1(0.68%)
Peripheral neuropathies	4(0.75%)	0(0.00%)	0(0.00%)	0(0.00%)	1(0.68%)
Spinal cord and nerve root disorders	1(0.19%)	0(0.00%)	1(0.23%)	2(0.91%)	0(0.00%)
Cranial nerve disorders (excl neoplasms)	0(0.00%)	0(0.00%)	2(0.47%)	0(0.00%)	0(0.00%)
PSYCHIATRIC DISORDERS	119(22.24%)	12(15.19%)	100(23.26%)	86(39.09%)	47(31.97%)
Sleep disorders and disturbances	55(10.28%)	6(7.59%)	58(13.49%)	64(29.09%)	29(19.73%)
Anxiety disorders and symptoms	29(5.42%)	2(2.53%)	23(5.35%)	20(9.09%)	9(6.12%)
Depressed mood disorders and disturbances	32(5.98%)	1(1.27%)	11(2.56%)	8(3.64%)	5(3.40%)
Sexual dysfunctions, disturbances and gender identity disorders	3(0.56%)	4(5.06%)	12(2.79%)	7(3.18%)	12(8.16%)
Changes in physical activity	3(0.56%)	3(3.80%)	10(2.33%)	3(1.36%)	7(4.76%)
Mood disorders and disturbances NEC	11(2.06%)	1(1.27%)	7(1.63%)	2(0.91%)	2(1.36%)
Disturbances in thinking and perception	3(0.56%)	1(1.27%)	3(0.70%)	1(0.45%)	0(0.00%)
Deliria (incl confusion)	2(0.37%)	0(0.00%)	2(0.47%)	1(0.45%)	0(0.00%)
Personality disorders and disturbances in behavior	2(0.37%)	1(1.27%)	0(0.00%)	0(0.00%)	0(0.00%)
Suicidal and self-injurious behaviors NEC	2(0.37%)	0(0.00%)	0(0.00%)	0(0.00%)	1(0.68%)
Impulse control disorders NEC	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	1(0.68%)
Communication disorders and disturbances	0(0.00%)	0(0.00%)	0(0.00%)	1(0.45%)	0(0.00%)
Dissociative disorders	0(0.00%)	0(0.00%)	1(0.23%)	0(0.00%)	0(0.00%)
Schizophrenia and other psychotic disorders	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Somatoform and factitious disorders	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
RENAL AND URINARY DISORDERS	16(2.99%)	4(5.06%)	21(4.88%)	5(2.27%)	11(7.48%)
Urinary tract signs and symptoms	13(2.43%)	3(3.80%)	20(4.65%)	5(2.27%)	9(6.12%)
Renal disorders (excl nephrolithiasis)	2(0.37%)	1(1.27%)	1(0.23%)	0(0.00%)	0(0.00%)
Bladder and bladder neck disorders (excl calculi)	1(0.19%)	0(0.00%)	1(0.23%)	0(0.00%)	0(0.00%)
Urolithiasis	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	2(1.36%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	22(4.11%)	1(1.27%)	15(3.49%)	8(3.64%)	3(2.04%)
Menstrual cycle and uterine bleeding	7(1.31%)	0(0.00%)	10(2.33%)	3(1.36%)	1(0.68%)
Breast disorders	4(0.75%)	0(0.00%)	4(0.93%)	1(0.45%)	0(0.00%)
Sexual function and fertility disorders	2(0.37%)	1(1.27%)	1(0.23%)	3(1.36%)	1(0.68%)
Vulvovaginal disorders (excl infections and inflammations)	3(0.56%)	0(0.00%)	1(0.23%)	0(0.00%)	1(0.68%)
Uterine, pelvic and broad ligament disorders	2(0.37%)	0(0.00%)	1(0.23%)	1(0.45%)	0(0.00%)
Menopause and related conditions	2(0.37%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Ovarian and fallopian tube disorders	2(0.37%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Reproductive tract disorders NEC	2(0.37%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Male reproductive tract infections and inflammations	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	40(7.48%)	11(13.92%)	37(8.60%)	21(9.55%)	18(12.24%)
Respiratory disorders NEC	29(5.42%)	8(10.13%)	28(6.51%)	11(5.00%)	16(10.88%)
Upper respiratory tract disorders (excl infections)	11(2.06%)	5(6.33%)	10(2.33%)	9(4.09%)	4(2.72%)
Bronchial disorders (excl neoplasms)	3(0.56%)	1(1.27%)	3(0.70%)	2(0.91%)	2(1.36%)
Lower respiratory tract disorders (excl obstruction and infection)	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Pleural disorders	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	47(8.79%)	13(16.46%)	62(14.42%)	24(10.91%)	27(18.37%)
Skin appendage conditions	18(3.36%)	6(7.59%)	39(9.07%)	14(6.36%)	18(12.24%)
Epidermal and dermal conditions	25(4.67%)	6(7.59%)	22(5.12%)	8(3.64%)	9(6.12%)
Angioedema and urticaria	3(0.56%)	2(2.53%)	1(0.23%)	0(0.00%)	1(0.68%)
Skin vascular abnormalities	1(0.19%)	0(0.00%)	2(0.47%)	1(0.45%)	1(0.68%)
Cutaneous neoplasms benign	1(0.19%)	0(0.00%)	0(0.00%)	1(0.45%)	0(0.00%)
Skin and subcutaneous tissue disorders NEC	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
SOCIAL CIRCUMSTANCES	0(0.00%)	0(0.00%)	2(0.47%)	0(0.00%)	0(0.00%)
Age related factors	0(0.00%)	0(0.00%)	2(0.47%)	0(0.00%)	0(0.00%)
SURGICAL AND MEDICAL PROCEDURES	10(1.87%)	2(2.53%)	11(2.56%)	2(0.91%)	3(2.04%)
Head and neck therapeutic procedures	6(1.12%)	1(1.27%)	4(0.93%)	2(0.91%)	2(1.36%)
Bone and joint therapeutic procedures	0(0.00%)	0(0.00%)	3(0.70%)	0(0.00%)	0(0.00%)
Obstetric and gynecological therapeutic procedures	1(0.19%)	1(1.27%)	1(0.23%)	0(0.00%)	0(0.00%)
Dye therapeutic procedures	2(0.37%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Skin and subcutaneous tissue therapeutic procedures	0(0.00%)	0(0.00%)	2(0.47%)	0(0.00%)	0(0.00%)

Breast therapeutic procedures	0(0.00%)	0(0.00%)	1(0.23%)	0(0.00%)	0(0.00%)
Gastrointestinal therapeutic procedures	1(0.19%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Therapeutic procedures and supportive care NEC	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	1(0.68%)
VASCULAR DISORDERS	19(3.55%)	2(2.53%)	24(5.58%)	12(5.45%)	8(5.44%)
Vascular disorders NEC	12(2.24%)	2(2.53%)	17(3.95%)	9(4.09%)	6(4.08%)
Vascular hypertensive disorders	6(1.12%)	0(0.00%)	6(1.40%)	3(1.36%)	2(1.36%)
Decreased and nonspecific blood pressure disorders and shock	1(0.19%)	0(0.00%)	1(0.23%)	0(0.00%)	0(0.00%)
Arteriosclerosis, stenosis, vascular insufficiency and necrosis	0(0.00%)	0(0.00%)	1(0.23%)	0(0.00%)	0(0.00%)
Vascular hemorrhagic disorders	0(0.00%)	0(0.00%)	1(0.23%)	0(0.00%)	0(0.00%)

N = Number of randomized patients, n = Number of patients with treatment-emergent adverse event
For HMCJ and HMEF - visit 8 is last visit of comparator period.
Applicant's Table, Regulatory Response 4-March-2008 – Adverse Events by Dose, Pages 94- 104.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ricardo Dent
4/25/2008 04:45:37 PM
MEDICAL OFFICER

Celia Winchell
4/25/2008 04:47:42 PM
MEDICAL OFFICER
I concur with Dr. Dent's conclusions. See my memo.