European Medicines Agency

**REFUSAL ASSESSMENT REPORT
FOR
Xeristar**

**International non-proprietary name/Common name:
(duloxetine hydrochloride)**

Procedure No. EMEA/H/C/573/II/26

Variation Assessment Report as adopted by the CHMP with
All information of a commercially confidential nature deleted

SCIENTIFIC DISCUSSION

1. Introduction

Duloxetine is classified as a serotonin norepinephrine reuptake inhibitor (SNRI). It is a selective inhibitor of both serotonin (5-HT) and norepinephrine (NE) receptors. Both 5-HT and NE have been implicated in the mediation of endogenous pain inhibitory mechanisms via the descending inhibitory pain pathways in the brain and spinal cord.

Duloxetine is currently approved under the trade name Cymbalta/Xeristar for the treatment of major depressive disorder (MDD), treatment of diabetic peripheral neuropathic pain (DPNP) in adults and treatment of generalised anxiety disorder (GAD) and under the trade name Yentreve/Ariclaim for the diabetic peripheral neuropathic pain (DPNP) in adults and the treatment of stress urinary incontinence (SUI).

This variation concerns an application for extension of the approved indication for Xeristar to include the treatment of fibromyalgia with or without depression.

2. Non Clinical Aspects

Environmental risk assessment (ERA)
Based on the updated Environmental Risk Assessment and the study reports submitted by the Marketing Authorisation Holder (MAH), the CHMP asked the MAH to update the Predicted Environmental Concentration in surface water (PEC$_{surface water}$) refinement. Further to the data submitted by the MAH the CHMP considered this concern to have been addressed.

3. Clinical Aspects

3.1 GCP aspects
All studies referred to this application are stated to be Good Clinical Practice principles compliant. Statistical analyses and study reporting were conducted in compliance with the principles described in the relevant International Conference on Harmonisation (ICH) guidelines.
In addition, the MAH confirmed that the ethical requirements of the clinical trial directive 2001/20/EC were applied for clinical trials conducted outside the European Union (EU).

3.2 Scientific Advice
A CHMP scientific advice was requested by the MAH, on the clinical development program of duloxetine in fibromyalgia and the response was given on the 21 October 2004.
The key aspects of the CHMP recommendations were the following:
- Fibromyalgia is an ill defined and extremely heterogeneous condition without universal consensus on its characteristic and diagnostic features and no objective investigations to aid diagnosis, but the use of American College of Rheumatology (ACR) criteria is supported.
- To stratify for presence or absence of current major depressive disorder seems reasonable to establish whether the effect of duloxetine in patients with fibromyalgia is dependent of its antidepressant effect.
- With regard to study duration, for short-term treatment of fibromyalgia at least 12 weeks on stable dose is required but for long-term (maintenance of effect, tolerance), an open label extension of 12 months is required.
- If the co-primary endpoints (pain endpoint and patient global assessment) proposed by the MAH are met, then it is possible that an indication reflecting fibromyalgia syndrome might be granted. If the key secondary endpoints also show positive effects, this would greatly enhance the credibility of the "syndrome" indication.

- The full package (5 studies) could be sufficient to grant a marketing authorisation but the exact wording of the indication cannot be determined until the studies have been completed and data assessed.

3.3 Clinical pharmacology

No new clinical pharmacology studies have been completed to support the fibromyalgia indication. A population pharmacokinetic (Pop PK) analysis that included patients from a Phase 3 study in fibromyalgia (HMEF) is included to support this submission.

Pharmacokinetics

Pharmacokinetic data from patients with MDD, SUI, DPNP, or fibromyalgia were analyzed using the nonlinear mixed-effects modelling program (NONMEM), Version 5. A total of 2002 duloxetine plasma concentrations from 594 patients enrolled in Phase 2 or 3 clinical studies for MDD (Studies HMAQ and HMAU), SUI (Study SAAW), DNP (Study HMAVa), or fibromyalgia (Study HMEF) were included.

Duloxetine pharmacokinetics were adequately described using a one-compartment model, parameterized in terms of absorption rate constant (Ka), oral clearance (CL/F), and apparent volume of distribution (V/F).

Table APP.2.7.2.1. Summary of Population Pharmacokinetic Analyses

Study (F1J-)	Dosage Route	Dosage Form Information	Dose (mg)	Number of Observations from Number of Patients	Observed Conc. (ng/mL) Mean (Range)	K_a (hr^{-1}) Population Estimate (%SEE)	CL/F (L/hr) Population Estimate (%SEE)	V/F (L) Population Estimate (%SEE)	Comments
Analysis of, HMAQ, HMAU, HMAV(a), SAAW, and HMEF	Oral	Capsulated enteric-coated pellets	20 QD	204 from 47[a]	10.8 (0.5-98.1)	0.168 (14.8)	45.1 (3.26)	814 (13.3)	Population PK analysis in male and female patients with fibromyalgia, MDD, SUI, or DNP. Sex, smoking status, age, dose, and ethnic origin has a statistically significant effect on duloxetine pharmacokinetics but is not clinically important. Duloxetine PK did not differ between patients with MDD, SUI, DNP, or fibromyalgia.
			20 BID	362 from 206[a]	30.5 (0.5-106)				
			30 BID	18 from 18[a]	36.0 (0.6-140)				
			40 BID	520 from 223[a]	80.5 (2.5-406)				
			60 QD	380 from 187[a]	50 (0.5-203)				
			60 BID	518 from 224[a]	116 (0.6-445)				

Abbreviations: BID = twice daily; CL/F = oral clearance; Conc. = concentration; DNP = diabetic neuropathic pain; K_a = absorption rate; MDD = major depressive disorder; PK = pharmacokinetics; QD = once daily; SEE = standard error of the estimate; SUI = stress urinary incontinence; V/F = volume of distribution.
[a] Some patients took more than one dosage, therefore the sum of patients in each dosage group exceeds the number of patients included in the analysis.

Five covariates, smoking status, gender, dose, age, and ethnic origin, were identified as having a statistically significant influence on duloxetine pharmacokinetics. These covariates were identified in prior analyses to affect duloxetine's pharmacokinetics, except for ethnic origin (see Table 2.7.2.1 below).

Smoking status and sex had an effect on the bioavailability of duloxetine. Dose and age had an effect on CL/F, whereas ethnic origin had an effect on V/F. As disease condition was not identified as a statistically significant covariate, the pharmacokinetics of duloxetine are not dependent on the disease. Similarly, the pharmacokinetics of duloxetine are not dependent on body weight or dosing regimen.

Women had 64% higher average duloxetine concentrations at steady state ($C_{av,ss}$) than males receiving the same dose of duloxetine. Similarly, non-smokers had nearly 43% higher $C_{av,ss}$ than smokers receiving the same dose of duloxetine. Non-smoking female patients had a $C_{av,ss}$ nearly 2.3 times higher than smoking male patients receiving the same dose of duloxetine. The effect of sex and smoking status is likely related to the higher CYP1A2 activity or concentration in men and smokers.

Table 2.7.2.1. **Pharmacokinetic Parameters in Final Population Model**

	Units	Estimate	%SEE	95% CI
Pharmacokinetic model				
Effect of smoking on F[a]	-	-0.298	13.9	-0.373 – -0.213
Effect of sex on F[b]	-	-0.389	9.13	-0.453 – -0.319
Absorption rate constant, K_a	hr^{-1}	0.168	14.8	0.113 – 0.231
Oral Clearance (CL/F)	L/hr	45.1	3.26	42.4 – 48.0
Effect of age on CL/F[c]	-	-0.00725	31.7	-0.0113 – -0.003026
Effect of dose on CL/F[d]	-	-0.00446	20.3	-0.00610 – -0.00283
Oral Volume of Distribution (V/F)	L	814	13.3	587 – 1064
Effect of origin on V/F[e]	-	1.02	38.8	0.369 – 2.01
Interpatient variability				
CL/F	%	58.9	8.39	-
V/F	%	96.6	15.9	-
Residual Error				
Proportional	%	30.8	7.65	-
Additive	ng/mL	5.17	13.6	-

Abbreviations: CI = confidence interval; CL/F = oral clearance; F = bioavailability; K_a = absorption rate constant; SEE = standard error of the estimate; V/F = oral volume of distribution.

a F (smokers) = F (non-smokers) × [1 − 0.298], F (non-smokers) = 1

b F (males) = F (females) × [1 − 0.389], F (females) = 1

c CL/F = 45.1 × Exp[-0.00446 × Dose]

d CL/F = 45.1 × [1 - 0.00725 × (Age - 49)]

e V/F (Hispanics) = 814 × [1 + 1.02]

The effects of age, dose, and ethnic origin on $C_{av,ss}$ are minor and less than those noted with sex and smoking status. The effect of doubling the duloxetine dose (30 mg to 60 mg or 60 mg to 120 mg) resulted in 2.3 and 2.6 times the $C_{av,ss}$, respectively. Oral clearance (CL/F) decreased 25% in the age range of 29 years (5th percentile) to 69 years (95th percentile of this dataset). Ethnic origin had an effect on V/F, in Hispanic patients being 2 times higher than the value estimated for non-Hispanic patients. As ethnic origin did not have an effect on CL/F, the $C_{av,ss}$ at a dose is the same for all patients irrespective of their ethnic origin.

Overall, the combined effects of sex, smoking, age, dose, and ethnic origin explained only about 8% and 27% of the interpatient variability in CL/F and volume of distribution (V/F), respectively. There remains a high degree of interpatient variability (60 to 100%) unexplained in duloxetine pharmacokinetics.

As the magnitude of the effect of these covariates are small relative to the magnitude of interpatient variability, specific dose recommendations for duloxetine based upon sex, smoking status, age, dose, or ethnic origin are not warranted.

- *Concentration-response relationship*

In Study HMEF the relationship between duloxetine exposure and efficacy response was investigated. There is a duloxetine concentration dependent increase in BPI-average pain score reduction such that when duloxetine dose is doubled from 60 mg (typical average drug concentration at steady state [$C_{av,ss}$] = 72 ng/mL) to 120 mg ($C_{av,ss}$ = 189 ng/mL at 120 mg), there is a 49% increase in BPI-average pain score reduction (that is, from -1.08 to -1.62) and a 22% increase in area under the concentration curve to pain relief (AUCpain relief) (that is, from 224 to 272). There did not appear to be an effect of duloxetine $C_{av,ss}$ on 30% or 50% reduction in BPI-average pain score.

CHMP conclusions

A population pharmacokinetic analysis on patients with MDD, SUI, DPNP or fibromyalgia (594 patients) revealed a statistically significant effect of sex, smoking status, age, and ethnic origin on duloxetine pharmacokinetics. These findings fall into line with those already provided by previous analyses. The clinical impact of them appears to be at present limited. The interpatient variability is much superior to that attributed to those identified factors and makes unnecessary a specific dosage recommendation based on any of them.

3.4 *Clinical efficacy*

The clinical development plan for the efficacy of duloxetine in the treatment of fibromyalgia includes 4 placebo-controlled studies (**Study HMBO, Study HMCA, Study HMCJ, and Study HMEF**) with 876 duloxetine-treated patients and 535 placebo-treated patients, and one long-term uncontrolled study **(Study HMEH)** with 350 duloxetine-treated patients (double-blind comparison of 60 mg and 120 mg). These studies are summarised in the table below, and then dealt with individually further down in this report.

Study ID	Design/ Control type	Number of subjects by arm entered/ completed	Duration	Gender	Primary Endpoint(s)
HMBO	Parallel, double-blind, placebo-controlled	Randomized: 104 duloxetine, 103 placebo. Completed: 58 duloxetine, 66 placebo.	3 months	Male and female patients	Reduction in FIQ Pain Item and FIQ Total Score
HMCA	Parallel, double-blind, fixed dose, placebo-controlled study	Randomized: 234 duloxetine, 120 placebo. Completed: 148 duloxetine, 68 placebo.	3 months	Female patients	Reduction in average pain item of the BPI scale
HMCJ	Parallel, double-blind, fixed dose, placebo-controlled study	Randomized: 376 duloxetine, 144 placebo Completed 3-month therapy phase: 242 duloxetine, 84 placebo Completed 6-month therapy phase: 206 duloxetine, 72 placebo	3 month therapy phase, 3 month continuation phase	Male and female patients	Reduction in average pain item of the BPI scale and improvement in the PGI-I scale
HMEF	Parallel, double-blind, placebo-controlled study	Randomized: 162 duloxetine, 168 placebo Completed: 101 duloxetine, 103 placebo	6 months	Male and female patients	Reduction in average pain item of the BPI scale and improvement in the PGI-I scale
HMEH	open-label period, followed by a double-blind period.	Randomized: 307 duloxetine Completed: 195 duloxetine (duloxetine 60mg: 71 Duloxetine 120mg: 124)	2 months open label followed by 1 year double-blind	Male and female patients	Safety and tolerability Persistence of efficacy was also assessed

Abbreviations: BID = twice daily; BPI = Brief Pain Inventory; FIQ = Fibromyalgia Impact Questionnaire; HMBO = Study F1J-MC-HMBO; HMCA = Study F1J-MC-HMCA; HMCJ = Study F1J-MC-HMCJ; HMEF = Study F1J-MC-HMEF; HMEH = Study F1J-MC-HMEH; ID = identification; MDD = major depressive disorder; PGI-I = Patient's Global Impressions of Improvement.

Source: Clinical study reports for Study HMBO, Study HMCA, Study HMCJ, Study HMEF, and Study HMEH.

Methods

- *Population*

All studies enrolled patients 18 years of age or older who fulfilled the ACR criteria for fibromyalgia (widespread aching pain in all 4 quadrants of the body and axial skeleton for >3 months duration and ≥11 of 18 tender points). A cut-off of ≥4 on the Brief Pain Inventory (BPI) average pain score was required for study entry. Patients were stratified in the randomization based on their major depressive disease status at baseline in all 4 placebo-controlled studies. The MAH stated that entry criteria for these studies were chosen to ensure inclusion of moderately ill fibromyalgia patients with or without MDD but at the same time were broad enough to ensure generalizability for practical clinical use. Efforts were made to include patients of both genders.

- *Key exclusion Criteria*

● Any current primary Axis I diagnosis other than MDD (except in Study HMEH).
● Pain symptoms related to traumatic injury, structural rheumatic disease, or regional rheumatic disease (such as osteoarthritis, bursitis, and tendonitis).
● Rheumatoid arthritis, inflammatory arthritis, or infectious arthritis, or an autoimmune disease (eg. systemic lupus erythematosus).
● Use of any excluded medications that could not be discontinued at Visit 1 (e.g. narcotics, Non Steroidal Anti-Inflammatory Drugs (NSAIDs), tramadol, triptans, anticonvulsants, and antidepressants).

- *Objective*

The main objective of all four placebo-controlled studies was to assess the efficacy of duloxetine on the reduction of pain severity in patients with fibromyalgia with or without MDD (two of these, HMCJ and HMEF, included a functional measure as a co primary endpoint). Study HMEH, was conducted to assess longer-term safety and tolerability but a secondary objective was to evaluate the persistence of efficacy over 12 month's treatment.

- *Statistical methods*

In general, treatment group differences in continuous measures were based on comparisons of Least-Squares Mean (LSMean) change from baseline (or LSMeans at endpoint for the PGI-Improvement) derived from an analysis of covariance model. Mean change analyses were implemented using Last-Observation-Carried Forward (LOCF). Mixed-effects repeated measures modelling (MMRM analysis) was also implemented to provide visit wise comparisons between groups, but for the purpose of this overview the focus is on the LOCF analyses. Categorical measures were compared using Fisher's exact test and/or the Cochran-Mantel-Haenszel (CMH) test for general association adjusting for investigative sites. Study HMCJ and Study HMEF included gatekeeper strategies for selected secondary endpoints to adjust for multiplicity associated with multiple endpoints, doses and time points. To make side-by-side comparisons of findings from the 4 placebo-controlled studies uniform, the analysis of covariance (ANCOVA) were standardized to remove any inconsistencies in findings that may have been attributable to the use of slightly different analytic models between the earlier studies (Study HMBO and Study HMCA) and the more recent studies (Study HMCJ and Study HMEF). In all cases, the results from the standardized analyses were consistent with those presented in the individual clinical study reports (CSRs).

- *Efficacy Variables*

All five studies focused on pain as the primary endpoint measure. The Study HMBO utilized both the Fibromyalgia Impact Questionnaire (FIQ) total score and the FIQ pain severity item score as co primary endpoints. In the four subsequent studies, the Brief Pain Inventory (BPI) assessment scale (using the average pain severity) was employed as primary endpoint. The Patient's Global Impressions of Improvement (PGI-Improvement) scale was selected as a co primary measure in HMCJ and HMEF to deal with additional symptoms, such as tenderness, stiffness, fatigue, anxiety and sleep, mood and cognitive disturbances with a major impact in physical and emotional function of patients and ensure that changes seen in the BPI were clinically meaningful for the patient. The PGI-Improvement scale

was a secondary measure in HMBO and HMCA. Response rates were compared, defined as either a ≥50% or ≥30% reduction from baseline at endpoint only in the BPI average pain score. Persistence of effect was evaluated in patients who remained on 60 mg for 52 weeks after having at least a 50% reduction on the BPI average pain score during the 8 week open label phase (Study HMEH).

Primary Endpoint measures

- The Brief Pain Inventory (BPI) – Modified Short Form (Severity and Interference scores) is a self-reported scale that measures the severity of pain and the interference of pain on function. It was developed as a pain assessment tool for use with cancer patients. 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 the pain right now. The interference scores (used as secondary outcome measure) range from 0 (does not interfere) to 10 (completely interferes). The average interference score is the arithmetic mean of the 7 interference 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 Patient's Global Impressions of Improvement (PGI-Improvement) scale is self-administered scale that measures the degree of overall improvement at the time of assessment with respect to the patient's status at randomization. The score ranges from 1 (very much better) to 7 (very much worse).

- The Fibromyalgia Impact Questionnaire (FIQ) is a self-administered specific health questionnaire which evaluates current health status in patients with fibromyalgia. It is one of the most commonly used tool for clinical investigations in this condition. The total FIQ score assess physical function in 11 items rated on a 4-point Likert-type scale, two items measure the number of days the patient felt well and the number of days the patient felt unable to work due to his/her fibromyalgia symptoms, and the seven other components assess in 11-point Likert-type scales (marked in 10-mm increments) work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression. The total score ranges from 0 to 80 with a higher score indicative of more negative impact.

Secondary Endpoint measures

Besides the components of the BPI and FIQ scores not used as primary endpoint measures, the following variables are analyzed as secondary outcomes.

- 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 have disrupted work, social, and/or home life. The score ranges from 0 to 30 with a lower score indicating a lower level of disability.

- The Clinical Global Impressions of Severity (CGI-Severity) scale evaluates the severity of illness at the time of assessment from the clinician's perspective. The score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). It is robust, simple and sensitive to change, reproducing the clinical judgment in daily practice. However it is subjective in its nature and requires an in-depth knowledge of patient and patient history.

- The Multidimensional Fatigue Inventory (MFI) is a 20-item, self-reporting instrument designed to collect data on the following 5 dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. Each dimension score is derived by summing the scores of the 4 individual items that pertain to each dimension. Dimensional scores range from 4 to 20 with a higher score reflecting greater levels of fatigue.

- Tender Point Pain Thresholds are assessed for all 18 tender points by a study physician or qualified study personnel accordingly with training materials. A dolorimeter (algometer) was used to exert the pressure at each point and to measure the threshold reading; when the patient first indicates pain, the threshold is recorded in kg/cm^2.

- The self-administered 36-item Short-Form Health Survey (SF-36) consists of 36 questions covering 8 health domains: physical functioning, bodily pain, role limitations due to physical problems, role limitations due to emotional problems, general health perceptions, mental health, social function, and vitality.

- Each domain is scored by summing the individual items and transforming the scores into a 0 to 100 scale, with higher scores indicating better health status or functioning. The Physical and Mental Component scores are constructed based on the 8 SF-36 domains.

- The EuroQoL Questionnaire-5Dimension (EQ-5D) is a generic, multidimensional, health-related, quality-of-life instrument. The scale allows patients to rate their health state in 5 health domains: mobility, self-care, usual activities, pain/discomfort, and mood. A single score between 1 and 3 is generated for each domain. For each patient, the outcomes from the 5 domains are mapped to a single index (score) through an algorithm. The index ranges between -0.59 and 1 with the higher score indicating a better health state as perceived by the patient.

Results

Study HMBO

Study HMBO was a Phase 2, parallel-group, double-blind, fixed-dose, placebo-controlled study in male and female patients, designed to assess the efficacy of duloxetine 60 mg BID (twice daily) compared with placebo at the end of the 12-week therapy phase in reducing both the pain severity as measured by the FIQ Pain Item and the FIQ Total Score in patients with ACR defined primary fibromyalgia, with or without MDD.

Results

No statistically significant differences were observed between treatment groups in terms of age, gender, origin, weight, presence of MDD, or presence of secondary anxiety disorder. A significantly greater percentage of placebo-treated patients took antidepressants before entering the study compared with duloxetine-treated patients [51 (49.51%) vs. 35 (33.65%), p=0.024]. Antidepressants were reported as taken either for mood or pain control. The difference in the percentage of patients who previously took antidepressants was not statistically significantly different between MDD patients (48.1%) and non-MDD patients (37.5%). A statistically significant treatment group difference was observed in patients who received at least one previous medication for insomnia [29 (28.2%) vs. 16 (15.4%) in placebo and duloxetine groups, respectively, p=0.029]. No statistically significant treatment group differences were observed in study drug compliance at any visit or overall.

Primary outcome measures

- The mean change analysis (from baseline to endpoint) for the FIQ Total Score and FIQ Pain Item Score showed that duloxetine treatment group had numerically greater improvement than the placebo treatment groups in both endpoint measures, but differences were non-statistically significant (p= 0.080 for FIQ total and p=0.090 for FIQ Pain).

- Repeated measures analysis for the FIQ Total Score demonstrated statistically significant superiority of duloxetine over placebo only at 4th and 12th weeks (last visit) of treatment. No statistically significant superiority of duloxetine at the last visit (12th week) was observed in repeated measures analysis for the FIQ Pain Item Score (duloxetine only was statistically significantly superior to placebo at 1st, 2nd and 4th week).

Table HMBO.11.9.   FIQ Total Score
                     Repeated Measures Analysis
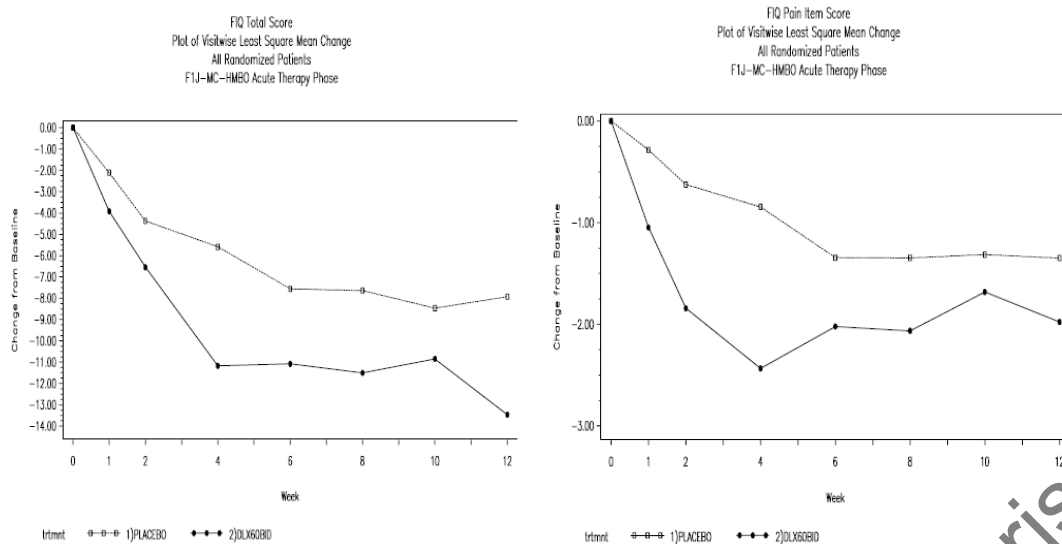   Acute Therapy Phase

Therapy	Visit (Week)	N	LSMean	LSMean Change	SE	T	DF	w/in p-Val	p-Val vs. 1)
1) PLACEBO	4(1)	102	47.14	-2.11	1.23			.088	
2) DLX60BID		96	45.34	-3.92	1.26	-1.05	189	.002	.293
1) PLACEBO	5(2)	93	44.88	-4.37	1.41			.002	
2) DLX60BID		87	42.71	-6.55	1.45	-1.10	176	<.001	.273
1) PLACEBO	6(4)	87	43.67	-5.58	1.41			<.001	
2) DLX60BID		78	38.09	-11.17	1.46	-2.81	168	<.001	.005
1) PLACEBO	7(6)	78	41.70	-7.56	1.60			<.001	
2) DLX60BID		67	38.18	-11.08	1.70	-1.53	152	<.001	.128
1) PLACEBO	8(8)	73	41.61	-7.64	1.82			<.001	
2) DLX60BID		63	37.75	-11.50	1.92	-1.48	145	<.001	.142
1) PLACEBO	9(10)	66	40.79	-8.47	1.63			<.001	
2) DLX60BID		61	38.41	-10.84	1.69	-1.03	146	<.001	.206
1) PLACEBO	10(12)	65	41.32	-7.93	1.73			<.001	
2) DLX60BID		57	35.79	-13.46	1.82	-2.23	144	<.001	.027

95% CI at visit 10: 2vs1(-10.43,-0.63)
Model fiqtotal=trtmnt visit poolinv trtmnt*visit basval basval*visit; Cov. Structure=Unstructured
T and DF refers to contrasts with Placebo; w/in p-values are from t-tests for LSMean change
Program: RMP.F1JSHMBO.SASPGM(RMFIQP1A) QCA700
Data: RMP.SAS.F1JM.MCHMBOSW.FINAL

Table HMBO.11.11.   FIQ Pain Item Score
                      Repeated Measures Analysis
                      All Randomized Patients
                      Acute Therapy Phase

Therapy	Visit (Week)	N	LSMean	LSMean Change	SE	T	DF	w/in p-Val	p-Val vs. 1)
1) PLACEBO	4(1)	103	6.69	-0.28	0.19			.133	
2) DLX60BID		101	5.92	-1.05	0.19	-2.94	193	<.001	.004
1) PLACEBO	5(2)	94	6.34	-0.62	0.22			.005	
2) DLX60BID		90	5.13	-1.84	0.22	-3.97	182	<.001	<.001
1) PLACEBO	6(4)	88	6.12	-0.85	0.24			<.001	
2) DLX60BID		79	4.54	-2.43	0.25	-4.58	167	<.001	<.001
1) PLACEBO	7(6)	81	5.63	-1.34	0.27			<.001	
2) DLX60BID		67	4.95	-2.02	0.29	-1.73	156	<.001	.085
1) PLACEBO	8(8)	73	5.62	-1.35	0.29			<.001	
2) DLX60BID		64	4.91	-2.06	0.31	-1.71	144	<.001	.089
1) PLACEBO	9(10)	67	5.66	-1.31	0.27			<.001	
2) DLX60BID		62	5.29	-1.68	0.28	-0.95	133	<.001	.346
1) PLACEBO	10(12)	66	5.62	-1.35	0.29			<.001	
2) DLX60BID		57	4.99	-1.98	0.30	-1.52	136	<.001	.130

95% CI at visit 10: 2vs1(-1.45,0.19)
Model fiqpain=trtmnt visit poolinv trtmnt*visit basval basval*visit; Cov. Structure=Unstructured
T and DF refers to contrasts with Placebo; w/in p-values are from t-tests for LSMean change
Program: RMP.F1JSHMBO.SASPGM(RMFIQP3A) QCA700
Data: RMP.SAS.F1JM.MCHMBOSW.FINAL

FIQ Total Score
Plot of Visitwise Least Square Mean Change
All Randomized Patients
F1J-MC-HMBO Acute Therapy Phase

FIQ Pain Item Score
Plot of Visitwise Least Square Mean Change
All Randomized Patients
F1J-MC-HMBO Acute Therapy Phase

Subgroup analysis of primary endpoints

Subgroup analyses were performed accounting by demographical, investigator and baseline imbalanced variables.

- Gender: Duloxetine-treated female patients showed statistically significant improvement for both primary efficacy measures (FIQ Total Score and FIQ Pain Item Score) compared with the placebo-treated female patients. In contrast, in male patients, outcomes on these measures were either marginally statistically significant or statistically significant in favour of placebo (FIQ Total Score, p=.076; FIQ Pain Item Score, p=.037).
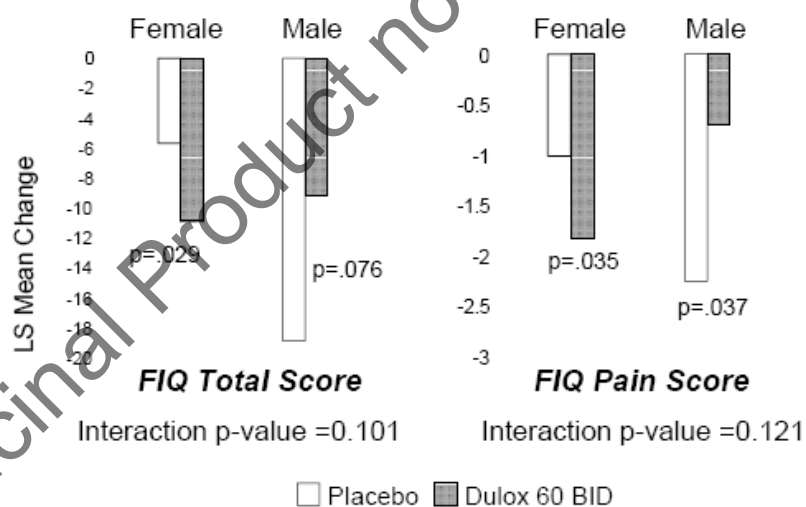
- After accounting for baseline imbalance in previous antidepressant use, statistically significant treatment superiority of duloxetine over placebo was observed for FIQ Total Score (p=.042) and a marginally statistically significant treatment effect was observed for FIQ Pain Item Score (p=.053).

- Baseline imbalance on previous antidepressant use was also observed between treatment groups for female patients (placebo 51.1% versus duloxetine 34.8%, p=.037). By accounting for this imbalance while evaluating the treatment effect, treatment-group differences observed were more significant than when the analysis was performed without accounting for this baseline difference. For FIQ Total and FIQ Pain scores in randomized female patients, statistically significant superiority of duloxetine over placebo was observed at the significance level of p=.017 and p=.024, respectively.

- No statistically significant treatment-by-MDD interaction was observed for either FIQ Total or FIQ Pain Item Score in the whole population studied or the female subgroup. The repeated measures analysis did not demonstrate statistically significant superiority of duloxetine over placebo in FIQ Pain Item Score for patients with or without MDD at the last visit of the acute therapy phase (Visit 10). Duloxetine was statistically significantly superior to placebo at relieving pain severity in non-depressed patients at Visits 4, 5, and 6. The results for the depressed patients followed this trend, but were not statistically significant.

Secondary outcome measures

On all secondary efficacy measures, except for FIQ Fatigue and Rest Item scores and BPI relationships with people score, duloxetine-treated patients demonstrated statistically significantly greater improvement compared with placebo-treated patients (by mean change analysis or repeated measures analysis).

Results for Mood and Anxiety Efficacy Assessments

The mean change analysis did not demonstrate statistically significant superiority of duloxetine over placebo in either efficacy assessment. There was no significant treatment-by-MDD interaction observed for either of the variables.

Analyses of Response on FIQ Pain Item Score

There was no treatment group difference observed on response rates at endpoint. However, the duloxetine treatment group demonstrated statistically significant superiority on time-to-first response compared with the placebo treatment group. No treatment group difference was observed for in the analysis of FIQ Pain Item Score sustained response.

Path Analysis for the Direct Analgesic Effect

The path analysis was performed only on the female population, for which the mean change analysis demonstrated a statistically significant treatment difference on FIQ Pain Item Score. The direct effect of duloxetine on the reduction on the FIQ Pain Item Score accounted for 61.1% of the total treatment effect with p= .313. Indirect treatment effect through the improvement of mood symptoms (reflected in change in Beck Depression Inventory-II (BDI-II)) and anxiety symptoms (reflected in change in Beck Anxiety Inventory (BAI)) accounted for 38.5% and 0.5%, respectively. To confirm these findings, a similar analysis was conducted for BPI Average Pain Score in randomized female patients. The direct effect of duloxetine on the reduction of BPI Average Pain accounted for 83.3% of the total treatment effect, which was statistically significant (p= .015). Indirect treatment effect through the improvement of mood symptoms (reflected in change in BDI-II) and anxiety symptoms (reflected in change in BAI) accounted for 15.3% and 1.5%, respectively.

Health Outcomes Measures

The superiority of duloxetine over placebo on the improvement of health outcome status was demonstrated for all measures obtained from SDS, for the total score of QLDS, and for 6 out of 10 variables obtained from SF-36.

Further Evaluation of Treatment-by-Gender Interaction

Among the 11 secondary variables analyzed, statistically significant treatment-by-gender interaction was observed for two variables (BPI Average Pain and SDS total scores). Marginally significant interaction was observed for three variables (FIQ Total, FIQ Pain Item, and BPI Worst Pain scores). All of these scores were patient-rated scores. It is notable that on the physician-rated scores, such as two variables from the Tender Point assessment and CGI-Severity, both male and female patients responded to study drug in the same direction.

HMCA Study
Study HMCA was a Phase 3, parallel, double-blind, placebo-controlled study in women treated with either duloxetine 60 mg BID or 60 mg QD (once daily).

The primary objective was to assess the efficacy of duloxetine 60 mg BID compared with placebo on the reduction of pain severity as measured by the average pain item of the BPI during a 12-week, double-blind, placebo-controlled, therapy phase in women with ACR-defined primary fibromyalgia, with or without MDD.

Results

This study included only women. No statistically significant differences between treatment groups in age, gender, origin, weight, presence of MDD, or presence of secondary anxiety disorder were observed. No significant differences were observed for baseline measures of severity of illness, nor for alcohol consumption, caffeine consumption, or smoking practices, historical diagnoses, previous pain control treatments, previous treatments for depression, anxiety disorder, panic disorder, fatigue, or other. A significant difference among treatment groups was observed with regard to concomitant use of zolpidem being much more infrequent in the placebo group. A significant treatment-group difference in study drug compliance was observed at Visit 7. Fewer placebo-treated patients were compliant with study drug at Visit 7.

Primary Efficacy Analysis

- BPI Average Pain Score: Both duloxetine 60 mg BID and duloxetine 60 mg QD were statistically superior to placebo in the mean change analysis of the BPI average pain score for all randomly assigned patients in the acute therapy phase (12 weeks).

Table HMCA.11.7.   Brief Pain Inventory Average Pain Score
                    Change From Baseline to Endpoint
                    All Randomly Assigned Patients
                    Acute Therapy Phase

```
                       Baseline                          Endpoint                          Change
              ----------------------------    ----------------------------    ----------------------------
          N   Mean   SD  Median Min  Max      Mean   SD  Median Min  Max      Mean   SD  Median Min  Max

PLACEBO  118  6.47  1.47   6.0  4.0  10.0     5.22  2.36   5.0  0.0   9.0    -1.25  2.27  -1.0  -8.0  3.0
DLX60QD  116  6.38  1.41   6.0  4.0  10.0     3.97  2.45   4.0  0.0  10.0    -2.41  2.61  -2.0  -9.0  2.0
DLX60BID 114  6.36  1.60   6.0  2.0  10.0     3.94  2.69   4.0  0.0  10.0    -2.42  2.57  -2.0  -9.0  4.0

Interaction (Type II SS)    Raw Data      Therapy-by-Investigator  F=0.97   df=28,302   p=0.652

Main Effects (Type II SS)              Raw Data
Therapy                   F=11.34  df=2,330   p=<.001
Investigator              F=1.43   df=14,330  p=0.139

Least Squares Means for Change from Baseline
PLACEBO     -1.16    (SE=0.21)
DLX60QD     -2.39    (SE=0.22)
DLX60BID    -2.40    (SE=0.22)

Pairwise Comparison of LS Means
DLX60QD  - PLACEBO    diff=-1.23    Two-sided 95% CI : (-1.82 , -0.64)    t=-4.11    p=<.001
DLX60BID - PLACEBO    diff=-1.24    Two-sided 95% CI : (-1.83 , -0.65)    t=-4.12    p=<.001
DLX60BID - DLX60QD    diff=-0.01    Two-sided 95% CI : (-0.59 , 0.58)     t=-0.03    p=0.976

Type II Sums of Squares from ANOVA: Model: CHANGE OF BPIPAIN = POOLINV TRTMNT BASELINE for main effect p-value.
Model: CHANGE OF BPIPAIN = POOLINV TRTMNT BASELINE TRTMNT*POOLINV for the interaction p-value.
Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.
Program: RMP.F1JSHMCA.SASPGM(LOBPIL1A)  QCA700
Data: RMD.SAS.F1JM.L.MIRRASK.PIHAL
```

- In the repeated measures analysis for the BPI average pain score for all randomly assigned patients, significant treatment-group differences between placebo and both duloxetine 60 mg BID and duloxetine 60 mg QD were observed beginning 1 week after randomization and continuing through the acute phase. In general, responses to duloxetine doubled that of placebo in all the acute phase. No differences between duloxetine 60 mg BID and duloxetine 60 mg QD were observed.

12

Table HMCA.11.8.   Brief Pain Inventory Average Pain Score
                    Repeated Measures Analysis
                    All Randomly Assigned Patients
                    Acute Therapy Phase

Therapy	Visit(Week)	N	LSMean	LSMean Change	SE	T	DDF	Within p-Value	Pairwise p-Value vs. 1)	vs. 2)
1)PLACEBO	3(1)	118	6.02	-0.41	0.17			.015		
2)DLX60QD		116	4.95	-1.49	0.17	-4.55	332	<.001	<.001	
3)DLX60BID		114	4.77	-1.66	0.17	-5.27	332	<.001	<.001	.463
1)PLACEBO	4(2)	111	5.54	-0.90	0.20			<.001		
2)DLX60QD		100	4.45	-1.99	0.20	-3.87	317	<.001	<.001	
3)DLX60BID		98	4.30	-2.13	0.21	-4.36	317	<.001	<.001	.614
1)PLACEBO	5(4)	100	5.27	-1.16	0.21			<.001		
2)DLX60QD		95	4.25	-2.18	0.21	-3.46	297	<.001	<.001	
3)DLX60BID		91	4.21	-2.23	0.22	-3.58	299	<.001	<.001	.889
1)PLACEBO	6(6)	88	4.97	-1.46	0.23			<.001		
2)DLX60QD		88	4.15	-2.28	0.23	-2.57	282	<.001	.011	
3)DLX60BID		82	3.80	-2.64	0.23	-3.64	285	<.001	<.001	.275
1)PLACEBO	7(8)	81	4.95	-1.49	0.23			<.001		
2)DLX60QD		84	4.11	-2.33	0.23	-2.56	273	<.001	.011	
3)DLX60BID		79	3.77	-2.66	0.24	-3.52	275	<.001	<.001	.316
1)PLACEBO	8(10)	70	5.22	-1.21	0.25			<.001		
2)DLX60QD		83	4.07	-2.37	0.24	-3.32	268	<.001	.001	
3)DLX60BID		76	3.71	-2.73	0.25	-4.30	271	<.001	<.001	.297

Therapy	Visit(Week)	N	LSMean	LSMean Change	SE	T	DDF	Within p-Value	Pairwise p-Value vs. 1)	vs. 2)
1)PLACEBO	9(12)	69	5.00	-1.44	0.25			<.001		
2)DLX60QD		78	3.58	-2.86	0.24	-4.14	250	<.001	<.001	
3)DLX60BID		72	3.68	-2.75	0.25	-3.77	252	<.001	<.001	.763

95% CI at last visit: 2vs1(-2.09,-0.74); 3vs1(-2,-0.63); 3vs2(-0.57,0.78)
MODEL BPIDAIN=TRTMNT DOOLINV VISIT TRTMNT*VISIT BASTAL BASVAL*VISIT; Cov. Structure=Unstructured
T and DDF refers to contrasts with Placebo; w/in p-values are from t-tests for LSMean change
Program: RMP.P1JSBMCA.SASPGM(RMEPIB1A) QCA700
Data: RMP.SAS.P1JM.L.MCBMCASW.FINAL

BPI Average Pain Score
Visitwise Least Square Means from Repeated Measures
All Randomized Patients
F1J-MC-HMCA Acute Therapy Phase
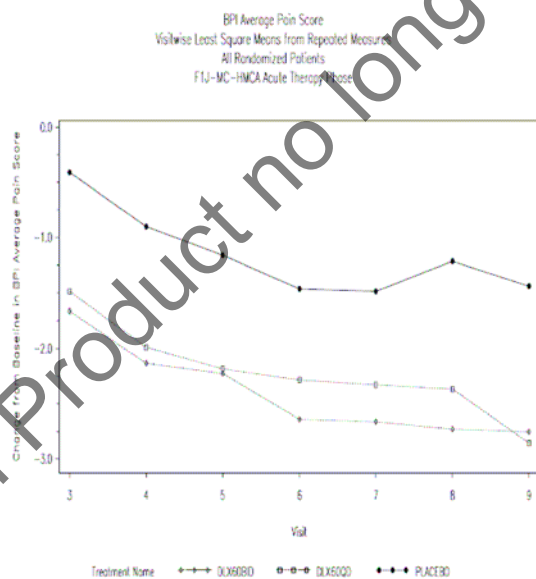
Secondary Efficacy Analyses

- Area under the Curve (AUC) of Pain Relief. Both duloxetine 60 mg BID and duloxetine 60 mg QD were statistically superior to placebo (p<.001) in the mean change analysis of the AUC of pain relief.

- FIQ total score : Both duloxetine 60 mg BID and duloxetine 60 mg QD were statistically superior to placebo (p<.001) in the repeated measures and mean change analysis of the FIQ total score, with average improvement of 16.5% in placebo and around 32% in both groups of duloxetine.

- Other Pain and General Illness/Improvement Efficacy Assessments: In the mean change analyses, duloxetine 60 mg QD was statistically superior to placebo on all secondary measures (including BPI Worst Pain Severity, BPI Least Pain Severity, BPI Severity: Pain Right Now, BPI Interference, CGI-Severity, PGI –Improvement and HAMD17), except for mean of 18 tender point thresholds (kg/cm^2) and number of tender points with a low threshold.

- Duloxetine 60 mg BID was statistically superior to placebo on all secondary measures except for HAMD17 total score. There were no significant differences between duloxetine 60 mg BID and duloxetine 60 mg QD.

- Analyses of BPI Average Pain Response Rates: Sixty-one (54%) patients treated with duloxetine 60 mg BID and 64 (55%) patients treated with duloxetine 60 mg QD achieved a response defined as a 30% reduction from baseline to endpoint compared with 39 (33%) patients treated with placebo.

- Path Analysis for the Direct Analgesic Effect: For duloxetine 60 mg BID, the direct effect of duloxetine on the reduction on the BPI average pain score accounted for 87.5% of the total treatment effect with p=.001. Indirect treatment effect through the improvement of mood symptoms (reflected in change in HAMD17) accounted for 12.5%. For duloxetine 60 mg QD, the direct effect of duloxetine on the reduction of the BPI average pain score accounted for 75.7% of the total treatment effect with p=.006. Indirect treatment effect through the improvement of mood symptoms (reflected in change in HAMD17) accounted for 24.4%.

Subgroup Analyses

Subgroups were defined by age, origin, diagnosis of MDD, diagnosis of secondary anxiety, and prior antidepressant medication use. No statistically significant therapy-by-subgroup interactions were observed.

Drug Dose, Drug Concentration, and Relationships to Response

Overall, both doses of duloxetine were found to be effective in the treatment of women with fibromyalgia symptoms. On numerous measures, the 60 mg BID dose was found to be numerically superior to the 60 mg QD dose, but these differences tended to not be statistically significant.

Drug-Drug and Drug-Disease Interactions

There were no significant differences in concomitant acetaminophen use among the treatment groups. However, duloxetine 60 mg BID-treated patients used a significantly lower mean daily dose of concomitant acetaminophen compared with duloxetine 60 mg QD-treated and placebo-treated patients.

Health Outcomes/Quality of Life Evaluation

Both duloxetine treatment groups were statistically superior to placebo on a majority of the SF-36 Items, QLDS index score and on the SDS total score.

HMCJ Study

Study HMCJ was a Phase 3, multicentre, randomized, double-blind, parallel-group, fixed dose, placebo-controlled study in male and female patients designed to assess the efficacy of duloxetine 120 mg QD compared with placebo on the treatment of pain in patients with ACR-defined primary fibromyalgia, with or without MDD in the 3-month therapy phase of the study.

Results

No statistically significant differences between treatment groups in age, gender, origin, weight, presence of MDD, or presence of secondary anxiety disorder were observed. Significant differences between groups included: a) the average number of beers consumed, with placebo showing the highest mean average number consumed, (b) a significantly higher rate of postmenopause in the duloxetine 20/60 group, (c) some secondary conditions with statistically significant treatment-group differences (although not clinically relevant), (d) a higher incidence of use for methylprednisolone previous therapy for fibromyalgia and/or depression in duloxetine 20/60 mg QD and (e) a higher incidence of use for calcium as concomitant therapy in duloxetine 20/60 mg QD. No significant differences were observed for the BPI average pain, FIQ total score, Mean Tender Point Threshold, Count of Low Threshold, CGI-Severity or PGI-Severity. No significant differences among treatment groups were observed for baseline HAMD17 scores by MDD status. No significant treatment group differences in overall treatment compliance were observed.

Primary Efficacy Analysis

- Co-Primary Efficacy Analyses – 3-month Therapy Phase: Duloxetine 120 mg QD and duloxetine 60 mg QD showed a significantly greater mean decrease (improvement) compared with placebo in the mean change analysis of the BPI average pain score for all randomized patients during the 3-month therapy phase. Mean decrease in BPI average pain score were 21% for placebo, 30% for duloxetine 20 QD, 30% for duloxetine 60 QD and 35% for duloxetine 120 QD.

Table HMCJ.11.9.   Brief Pain Inventory Average Pain Score
Mean Change from Baseline to Endpoint
All Randomized Patients
3-Month Therapy 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) PLACEBO	139	6.57	1.70	7.0	4.0	10.0	5.19	2.52	5.0	0.0	10.0	-1.38	2.37	-1.0		3.0
2) DLX20QD	77	6.74	1.62	7.0	4.0	10.0	4.74	2.37	5.0	0.0	10.0	-2.00	2.39	-2.0		3.0
3) DLX60QD	144	6.46	1.41	6.5	4.0	10.0	4.51	2.28	5.0	0.0	10.0	-1.94	2.25			4.0
4) DLX120QD	142	6.41	1.59	6.0	4.0	10.0	4.18	2.44	4.0	0.0	10.0	-2.23	2.44			4.0

Interaction (Type II SS)   Raw Data   Treatment-by-Pooled Investigator F= 0.66 df= 42,441 p= .951

Main Effects (Type II SS)   Raw Data
Treatment   F= 4.08 df= 3,483 p= .007
Pooled Investigator   F= 0.95 df= 14,483 p= .503

Least Squares Means for Change from Baseline
1) PLACEBO   -1.38   (SE= 0.20)
2) DLX20QD   -1.92   (SE= 0.27)
3) DLX60QD   -2.00   (SE= 0.20)
4) DLX120QD   -2.31   (SE= 0.20)

Pairwise Comparison of LS Means
DLX20QD - PLACEBO   diff= -0.53 Two-sided 95% CI : (-1.16, 0.10) t= -1.66 p= .097
DLX60QD - PLACEBO   diff= -0.62 Two-sided 95% CI : (-1.15, -0.09) t= -2.31 p= .022
DLX120QD - PLACEBO   diff= -0.93 Two-sided 95% CI : (-1.45, -0.40) t= -3.44 p= <.001
DLX60QD - DLX20QD   diff= -0.08 Two-sided 95% CI : (-0.71, 0.54) t= -0.27 p= .791
DLX120QD - DLX20QD   diff= -0.39 Two-sided 95% CI : (-1.02, 0.24) t= -1.23 p= .221
DLX120QD - DLX60QD   diff= -0.31 Two-sided 95% CI : (-0.83, 0.22) t= -1.15 p= .250

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

Report: RMP.F1JO.HMCJSTAT.INTRM1(LOBPIA11)
Program: RMP.F1JSHMCJ.SASPGM(LOBPIA1)
Data: RMP.SAS.F1JS.L.MCHMCJ.ADS.INTRM1

All duloxetine treatment groups showed significantly greater patient-rated improvement at endpoint compared with placebo in the PGI–Improvement mean score at endpoint for all randomized patients during the 3-month therapy phase.

Table HMCJ.11.10.   Patient's Global Impressions of Improvement
Mean Score at Endpoint
All Randomized Patients
3-Month Therapy Phase

PGI-Improvement

		Endpoint				
	N	Mean	SD	Median	Min	Max
1) PLACEBO	138	3.49	1.49	3.0	1.0	7.0
2) DLX20QD	77	2.97	1.48	3.0	1.0	6.0
3) DLX60QD	141	3.12	1.48	3.0	1.0	7.0
4) DLX120QD	141	3.00	1.54	3.0	1.0	7.0

Interaction (Type II SS)   Raw Data   Treatment-by-Pooled Investigator F= 1.04 df= 42,436 p= .409

Main Effects (Type II SS)   Raw Data
Treatment   F= 3.57 df= 3,478 p= .014
Pooled Investigator   F= 3.00 df= 14,478 p= <.001

Least Squares Means for Endpoint
1) PLACEBO   3.39   (SE= 0.13)
2) DLX20QD   2.85   (SE= 0.17)
3) DLX60QD   3.04   (SE= 0.13)
4) DLX120QD   2.89   (SE= 0.13)

Pairwise Comparison of LS Means
DLX20QD - PLACEBO   diff= -0.55 Two-sided 95% CI : (-0.95, -0.14) t= -2.64 p= .009
DLX60QD - PLACEBO   diff= -0.35 Two-sided 95% CI : (-0.70, -0.01) t= -2.02 p= .044
DLX120QD - PLACEBO   diff= -0.50 Two-sided 95% CI : (-0.84, -0.16) t= -2.86 p= .004
DLX60QD - DLX20QD   diff= 0.19 Two-sided 95% CI : (-0.21, 0.60) t= 0.93 p= .351
DLX120QD - DLX20QD   diff= 0.05 Two-sided 95% CI : (-0.36, 0.45) t= 0.23 p= .820
DLX120QD - DLX60QD   diff= -0.15 Two-sided 95% CI : (-0.49, 0.19) t= -0.84 p= .400

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 PGI-S, and Treatment*Pooled Investigator for interaction p-value. N = Number of patients with baseline PGI-S and at least one non-missing post-baseline PGI-I value.

Report: RMP.F1JO.HMCJSTAT.INTRM1(LOPGIA11)
Program: RMP.F1JSHMCJ.SASPGM(LOPGIA1)
Data: RMP.SAS.F1JS.L.MCHMCJ.ADS.INTRM1

- BPI Average Pain Score and PGI-Improvement – 6-Month Therapy Phase: All duloxetine treatment groups showed a significantly greater mean decrease (improvement) compared with placebo in the mean change analysis of the BPI average pain score for all randomized patients

at the 6th month endpoint. Mean decrease in BPI average pain score were 21% for placebo, 32% for duloxetine 20 QD, 34% for duloxetine 60 QD and 30% for duloxetine 120 QD.

Table HMCJ.11.11.　　Brief Pain Inventory Average Pain Score
　　　　　　　　　　 Mean Change from Baseline to Endpoint
　　　　　　　　　　 All Randomized Patients
　　　　　　　　　　 6-Month Therapy 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) PLACEBO	139	6.57	1.70	7.0	4.0	10.0	5.17	2.56	5.0	0.0	10.0	-1.40	2.53	-1.0	-9.0	3.0
2) DLX60QD	144	6.46	1.41	6.5	4.0	10.0	4.56	2.49	5.0	0.0	10.0	-1.90	2.52	-2.0	-8.0	4.0
3) DLX120QD	142	6.41	1.59	6.0	4.0	10.0	4.27	2.48	4.0	0.0	10.0	-2.14	2.30	-2.0	-9.0	4.0
4) DLX20/60QD	77	6.74	1.62	7.0	4.0	10.0	4.47	2.50	4.0	0.0	10.0	-2.27	2.51	-2.0	-9.0	3.0

Interaction (Type II SS)　　Raw Data　　Treatment-by-Pooled Investigator F= 0.82　df= 42,441　p= .783

Main Effects (Type II SS)　　　　Raw Data
Treatment　　　　　　　　　　F= 3.48　df= 3,483　p= .016
Pooled Investigator　　　　　　F= 1.52　df= 14,483　p= .099

Least Squares Means for Change from Baseline
1) PLACEBO　　　　　-1.42　(SE= 0.21)
2) DLX60QD　　　　　-1.90　(SE= 0.21)
3) DLX120QD　　　　　-2.25　(SE= 0.21)
4) DLX20/60QD　　　　-2.22　(SE= 0.28)

Pairwise Comparison of LS Means
DLX60QD　　 - PLACEBO　　diff= -0.57　Two-sided 95% CI : (-1.12, -0.02)　t= -2.05　p= .041
DLX120QD　 - PLACEBO　　diff= -0.83　Two-sided 95% CI : (-1.38, -0.28)　t= -2.97　p= .003
DLX20/60QD - PLACEBO　　diff= -0.79　Two-sided 95% CI : (-1.45, -0.14)　t= -2.38　p= .018
DLX120QD　 - DLX60QD　 diff= -0.26　Two-sided 95% CI : (-0.81, 0.28)　t= -0.94　p= .348
DLX20/60QD - DLX60QD　 diff= -0.22　Two-sided 95% CI : (-0.87, 0.43)　t= -0.67　p= .503
DLX20/60QD - DLX120QD　diff= 0.04　Two-sided 95% CI : (-0.61, 0.69)　t= 0.11　p= .909

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

Report: RMP.F1JO.HMCJSTAT.INTRM1(LOBPIA12)
Program: RMP.F1JSHMCJ.SASPGM(LOBPIA1)
Data: RMP.SAS.F1JS.L.MCHMCJ.ADS.INTRM1

Duloxetine 120 mg QD and 20/60 mg QD (but not duloxetine 60 QD) showed significantly greater patient-rated improvement at 6th month endpoint compared with placebo in the PGI–Improvement mean score.

Table HMCJ.11.12.　　Patient's Global Impressions of Improvement
　　　　　　　　　　 Mean Score at Endpoint
　　　　　　　　　　 All Randomized Patients
　　　　　　　　　　 6-Month Therapy Phase

PGI-Improvement

		Endpoint				
	N	Mean	SD	Median	Min	Max
1) PLACEBO	138	3.44	1.48	3.0	1.0	7.0
2) DLX60QD	141	3.14	1.54	3.0	1.0	7.0
3) DLX120QD	141	3.01	1.53	3.0	1.0	7.0
4) DLX20/60QD	77	2.91	1.48	3.0	1.0	6.0

Interaction (Type II SS)　　Raw Data　　Treatment-by-Pooled Investigator F= 0.82　df= 42,436　p= .783

Main Effects (Type II SS)　　　　Raw Data
Treatment　　　　　　　　　　F= 3.25　df= 3,478　p= .022
Pooled Investigator　　　　　　F= 2.46　df= 14,478　p= .002

Least Squares Means for Endpoint
1) PLACEBO　　　　　3.37　(SE= 0.13)
2) DLX60QD　　　　　3.09　(SE= 0.13)
3) DLX120QD　　　　　2.93　(SE= 0.13)
4) DLX20/60QD　　　　2.80　(SE= 0.17)

Pairwise Comparison of LS Means
DLX60QD　　 - PLACEBO　　diff= -0.29　Two-sided 95% CI : (-0.64, 0.06)　t= -1.61　p= .108
DLX120QD　 - PLACEBO　　diff= -0.45　Two-sided 95% CI : (-0.80, -0.10)　t= -2.52　p= .012
DLX20/60QD - PLACEBO　　diff= -0.58　Two-sided 95% CI : (-0.99, -0.16)　t= -2.74　p= .006
DLX120QD　 - DLX60QD　 diff= -0.16　Two-sided 95% CI : (-0.51, 0.19)　t= -0.91　p= .362
DLX20/60QD - DLX60QD　 diff= -0.29　Two-sided 95% CI : (-0.71, 0.12)　t= -1.38　p= .169
DLX20/60QD - DLX120QD　diff= -0.13　Two-sided 95% CI : (-0.54, 0.28)　t= -0.62　p= .538

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 PGI-S, and Treatment*Pooled Investigator for interaction p-value. N = Number of patients with baseline PGI-S and at least one non-missing post-baseline PGI-I value.
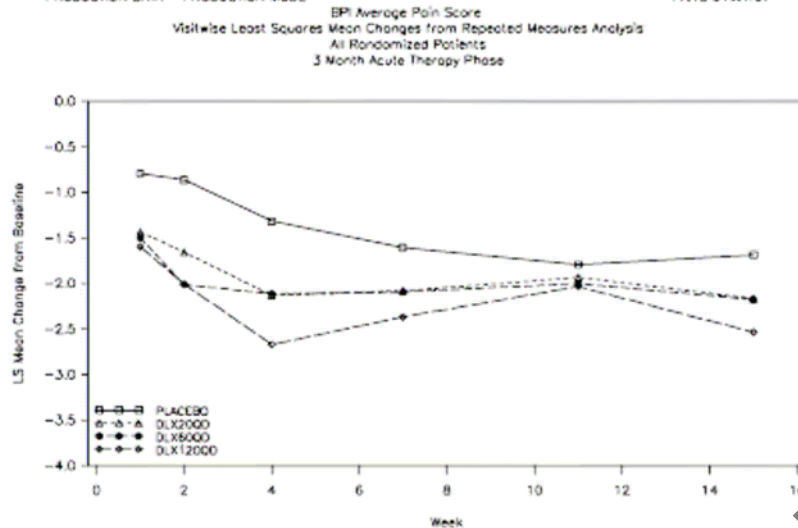
Report: RMP.F1JO.HMCJSTAT.INTRM1(LOPGIA12)
Program: RMP.F1JSHMCJ.SASPGM(LOPGIA1)
Data: RMP.SAS.F1JS.L.MCHMCJ.ADS.INTRM1

- SDS Global Functioning Impairment Total Score – at 3 or 6-Month Therapy Phase. No significant treatment group differences were observed.

Secondary Efficacy Analyses: 3-Month Therapy Phase

- BPI average pain score: Duloxetine was statistically superior to placebo in repeated measures analysis only at discrete time points (1st to 4th week for duloxetine 20 QD, 1st to 7th week for duloxetine 60 QD and 1st to 7th week and 15th week for duloxetine 120 QD. Analysis of the AUC was statistically significant for all three doses.

BPI Average Pain Score
Visitwise Least Squares Mean Changes from Repeated Measures Analysis
All Randomized Patients
3 Month Acute Therapy Phase

[Figure: Line chart plotting LS Mean Change from Baseline (y-axis, 0.0 to -4.0) against Week (x-axis, 0 to 16). Legend: PLACEBO, DLX20QD, DLX60QD, DLX120QD.]

Model Change = Treatment, Pooled Investigator, Visit, Baseline, Baseline*Visit; Covariance Structure = Unstructured

Report: RMP.F1JO.HMCJSTAT.INTRM1(RMBPIA21)
Program: RMP.F1JSHMCJ.SASPGM(RMBPIA2)
Data: RMP.SAS.F1JS.L.MCHMCJ.ADS.INTRM1

Table HMCJ.11.16.   Brief Pain Inventory Average Pain Score
Area Under the Curve
All Randomized Patients
3-Month Therapy Phase

BPI Average Pain Score

```
                          BPI AUC
           ----------------------------------------
            N    Mean     SD   Median    Min    Max
           ---  ------  ------ ------   -----  -----
1) PLACEBO  144 119.06  182.61   49.8  -285.0  794.5
2) DLX20QD   79 165.43  178.23  170.0   -97.5  622.0
3) DLX60QD  150 160.79  196.64  128.5  -189.0  833.5
4) DLX120QD 147 173.69  174.62  157.0  -127.0  717.0
```

Interaction (Type II SS)   Raw Data   Treatment-by-Pooled Investigator   F= 0.93   df= 42,459   p= .607

Main Effects (Type II SS)   Raw Data
Treatment   F= 3.77   df= 3,501   p= .011
Pooled Investigator   F= 1.22   df= 14,501   p= .253

```
Least Squares Means for BPI AUC
1) PLACEBO    124.60   (SE=15.46)
2) DLX20QD    183.94   (SE=20.35)
3) DLX60QD    171.53   (SE=15.23)
4) DLX120QD   187.66   (SE=15.39)

Pairwise Comparison of LS Means
DLX20QD  - PLACEBO   diff=  59.34  Two-sided 95% CI : ( 11.26, 107.42)  t=  2.42  p= .016
DLX60QD  - PLACEBO   diff=  46.92  Two-sided 95% CI : (  6.87,  86.98)  t=  2.30  p= .022
DLX120QD - PLACEBO   diff=  63.05  Two-sided 95% CI : ( 22.78, 103.33)  t=  3.08  p= .002
DLX60QD  - DLX20QD   diff= -12.41  Two-sided 95% CI : (-60.20,  35.37)  t= -0.51  p= .610
DLX120QD - DLX20QD   diff=   3.72  Two-sided 95% CI : (-44.27,  51.71)  t=  0.15  p= .879
DLX120QD - DLX60QD   diff=  16.13  Two-sided 95% CI : (-23.72,  55.98)  t=  0.80  p= .427
```

Type II sums of squares from ANCOVA Model = Treatment, Pooled Investigator, and Baseline of BPI Average Pain Score for main effects p-values. Model = Treatment, Pooled Investigator, Baseline of BPI Average Pain Score, and Treatment*Pooled Investigator for the interaction p-value. N = Number of patients with non-missing baseline for BPI Average Pain Score and Area Under the Curve of Pain Relief score.

Report: RMP.F1JO.HMCJSTAT.INTRM1(ACBPIA11)
Program: RMP.F1JSHMCJ.SASPGM(ACBPIA1)
Data: RMP.SAS.F1JS.L.MCHMCJ.ADS.INTRM1

- Other BPI scores. Only duloxetine 120 mg QD was statistically superior to placebo in other BPI scores (BPI worst pain, BPI least pain, BPI pain right now and BPI average interference scores) by both mean change and repeated measures analysis, although only at discrete time points). Duloxetine 60 mg QD was statistically superior in BPI worst pain and BPI least pain but not BPI pain right now and BPI average interference. Duloxetine 20 mg QD was not superior to placebo in any BPI scores by mean change analysis. By repeated measures analysis superiority was observed only at discrete time points.

- Percentage of responders. Only duloxetine 120 mg QD showed a significantly higher response rate at endpoint compared with placebo. Duloxetine 60 mg QD and 120 mg QD showed a significantly earlier time to first response compared with placebo based on the stratified log-rank test. Duloxetine 120 mg QD showed a significantly higher sustained response rate compared with placebo.

Table HMCJ.11.20.   Brief Pain Inventory Average Pain Score
                     Response Rate at Endpoint
                     All Randomized Patients
                     3-Month Therapy Phase

Responder at end time

		Responders	Overall	Pairwise p-Value*			Dose Response
Treatment	N	n(%)	p-Value*	vs 2)	vs 3)	vs 4)	p-Value**
1) PLACEBO	139	33(23.7%)	.031	.200	.067	.003	.226
2) DLX20QD	77	25(32.5%)			.882	.307	
3) DLX60QD	144	49(34.0%)				.328	
4) DLX120QD	142	57(40.1%)					

N = Number of randomized patients with non missing response values.
Response is defined as a 50% or greater reduction from baseline in BPI Average Pain Score.
*Frequencies are analyzed using Fisher's exact test.
**Dose response is analyzed using the CMH non-zero correlation test among the duloxetine groups controlling for pooled investigator.

Report: RMP.F1JO.HMCJSTAT.INTRM1(RABPIA31)
Program: RMP.F1JSHMCJ.SASPGM(RABPIA3)
Data: RMP.SAS.F1JS.L.MCHMCJ.ADS.INTRM1

Table HMCJ.11.21.   Sustained Response
                     All Randomized Patients
                     3-Month Therapy Phase

Sustained Responder

		Responders	Overall	Pairwise p-Value*			Dose Response
Treatment	N	n(%)	p-Value*	vs 2)	vs 3)	vs 4)	p-Value**
1) PLACEBO	139	25(18.0%)	.180	.290	.150	.035	.449
2) DLX20QD	77	19(24.7%)			1.000	.530	
3) DLX60QD	144	37(25.7%)				.596	
4) DLX120QD	142	41(28.9%)					

N = Number of randomized patients with non missing response values.
Sustained Response: at least 50% reduction from baseline to endpoint, with at least 50% reduction from baseline at an earlier than last visit, and at least 30% reduction from baseline at every visit with data in between, if there are any intervening visits.
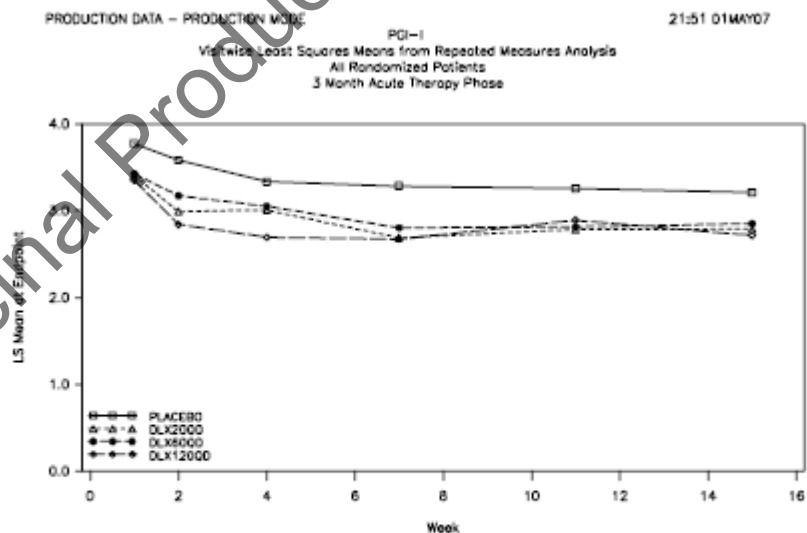*Frequencies are analyzed using Fisher's exact test.
**Dose response is analyzed using the CMH non-zero correlation test among the duloxetine groups controlling for pooled investigator.

Report: RMP.F1JO.HMCJSTAT.INTRM1(RABPIA41)
Program: RMP.F1JSHMCJ.SASPGM(RABPIA4)
Data: RMP.SAS.F1JS.L.MCHMCJ.ADS.INTRM1

- PGI-Improvement: All three doses of duloxetine showed statistically significant superiority over placebo in the mean change analysis and at different visits in the repeated measures analysis.

PRODUCTION DATA – PRODUCTION MODE   21:51 01MAY07

PGI-I
Visitwise Least Squares Means from Repeated Measures Analysis
All Randomized Patients
3 Month Acute Therapy Phase

Model = Treatment, Pooled Investigator, Visit, Treatment*Visit, Baseline of PGI-S, Baseline of PGI-S*Visit;
Covariance Structure = Unstructured.

Report: RMP.F1JO.HMCJSTAT.INTRM1(RMPGIA21)
Program: RMP.F1JSHMCJ.SASPGM(RMPGIA2)
Data: RMP.SAS.F1JS.L.MCHMCJ.ADS.INTRM1

- Other secondary endpoints at 3 months: All three doses of duloxetine showed statistically significant superiority over placebo in the mean change analysis and at different visits in the repeated measures analysis in the FIQ Total score and CGI-Severity score (except for duloxetine 20 QD). None of doses were statistically superior to placebo in the Tender Point Pain Thresholds.

Medicinal Product no longer authorised

- Analysis of Dose-Response: No statistically significant linear dose response was demonstrated among the duloxetine 20 mg QD, 60 mg QD and 120 mg QD doses on the BPI average pain score, PGI-Improvement score at endpoint, SDS Global Functioning total score, response rates, or sustained response rates. Duloxetine 20 mg QD did not show significant improvement compared with placebo on the analysis of mean change from baseline to endpoint on the BPI average pain score. In addition, duloxetine 20 mg QD did not show significant improvement compared with placebo on the majority of the secondary efficacy measures as analyzed by mean change from baseline to endpoint.

Secondary Efficacy Analyses: 6-Month Therapy Phase

- BPI average pain score: Duloxetine was statistically superior to placebo in repeated measures analysis only at discrete time points (1st to 4th week and 28th week for duloxetine 20 QD, 1st to 4th week for duloxetine 60 QD and 1st to 7th week and 15th week for duloxetine 120 QD. Analysis of the AUC was statistically significant for the 20/60 mg QD and 120 mg QD but not for 60 mg QD.

PRODUCTION DATA – PRODUCTION MODE   17:18 01MAY0V

BPI Average Pain Score
Visitwise Least Squares Mean Changes from Repeated Measures Analysis
All Randomized Patients
6 Month Acute Therapy Phase

Model Change = Treatment, Pooled Investigator, Visit, Baseline, Baseline*Visit; Covariance Structure = Unstructured.
Report: RMP.F1JO.HMCJSTAT.INTRM1(RMBPIA22)
Program: RMP.F1JSHMCJ.SASPGM(RMBPA2)
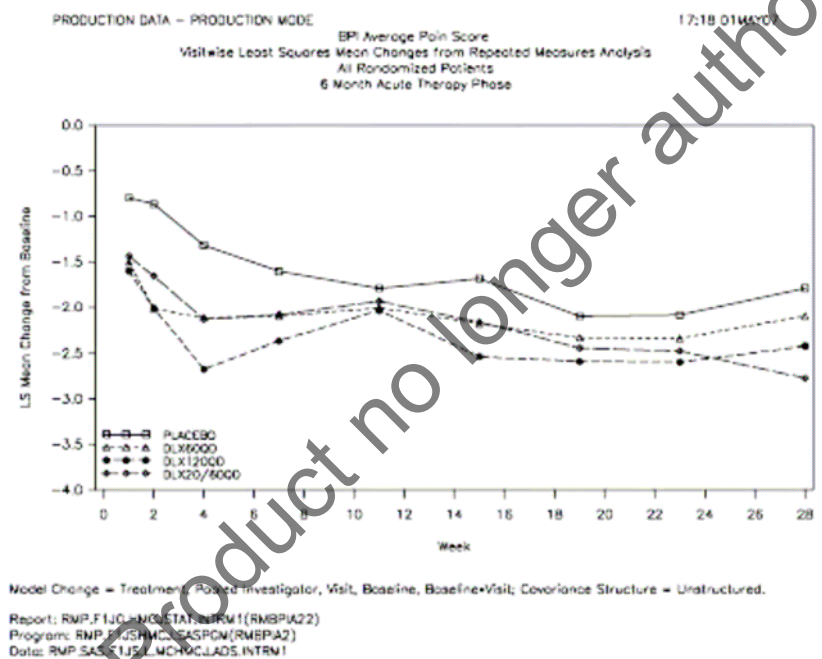Data: RMP.SAS.F1JS.L.MCHMCJ.ADS.INTRM1

Table HMCJ.11.27.   Brief Pain Inventory Average Pain Score
Area Under the Curve
All Randomized Patients
6-Month Therapy Phase

BPI Average Pain Score

BPI AUC

	N	Mean	SD	Median	Min	Max
1) PLACEBO	144	225.90	332.09	98.0	-366.0	1557.5
2) DLX60QD	150	291.43	358.86	209.8	-262.5	1684.5
3) DLX120QD	147	308.62	331.37	241.5	-198.0	1432.0
4) DLX20/60QD	79	341.91	346.07	264.0	-116.5	1486.0

Interaction (Type II SS)   Raw Data   Treatment-by-Pooled Investigator F= 1.10   df= 42,459   p= .307

Main Effects (Type II SS)   Raw Data
Treatment   F= 2.82   df= 3,501 p= .039
Pooled Investigator   F= 1.70   df= 14,501 p= .052

Least Squares Means for BPI AUC
1) PLACEBO   236.56   (SE=28.83)
2) DLX60QD   311.01   (SE=28.40)
3) DLX120QD   334.02   (SE=28.70)
4) DLX20/60QD   340.66   (SE=37.95)

Pairwise Comparison of LS Means
		diff=				t=	p=
DLX60QD - PLACEBO	diff=	74.46	Two-sided 95% CI : (-0.26, 149.18)	t=	1.96	p= .051
DLX120QD - PLACEBO	diff=	97.47	Two-sided 95% CI : (22.34, 172.59)	t=	2.55	p= .011
DLX20/60QD - PLACEBO	diff=	104.10	Two-sided 95% CI : (14.42, 193.78)	t=	2.28	p= .023
DLX120QD - DLX60QD	diff=	23.01	Two-sided 95% CI : (-51.32, 97.34)	t=	0.61	p= .543
DLX20/60QD - DLX60QD	diff=	29.64	Two-sided 95% CI : (-59.48, 118.77)	t=	0.65	p= .514
DLX20/60QD - DLX120QD	diff=	6.63	Two-sided 95% CI : (-82.88, 96.15)	t=	0.15	p= .884

Type II sums of squares from ANCOVA Model = Treatment, Pooled Investigator, and Baseline of BPI Average Pain Score for main effects p-values. Model = Treatment, Pooled Investigator, Baseline of BPI Average Pain Score, and Treatment*Pooled Investigator for the interaction p-value. N = Number of patients with non-missing baseline for BPI Average Pain Score and Area Under the Curve of Pain Relief score.
Report: RMP.F1JO.HMCJSTAT.INTRM1(ACBPIA12)
Program: RMP.F1JSHMCJ.SASPGM(ACBPIA1)
Data: RMP.SAS.F1JS.L.MCHMCJ.ADS.INTRM1

- Other BPI scores: Only duloxetine 120 mg QD was statistically superior to placebo in other BPI scores (BPI worst pain, BPI least pain, BPI pain right now and BPI average interference scores) by both mean change and repeated measures analysis, although only at discrete time points). Duloxetine 60 mg QD was statistically superior in BPI least pain and BPI average interference but not BPI pain right now and BPI worst pain. Duloxetine 20/60 mg QD was not superior to placebo in any BPI scores by mean change analysis except average interference. By repeated measures analysis superiority was observed only at discrete time points.

- Percentage of responders: All three doses showed a significantly higher response rate at endpoint compared with placebo, although differences were small.

- Duloxetine 60 mg QD and 120 mg QD showed a significantly earlier time to first response compared with placebo based on the stratified log-rank test. Duloxetine 120 mg QD showed a significantly higher sustained response rate compared with placebo.

Table HMCJ.11.31. Brief Pain Inventory Average Pain Score
Response Rate at Endpoint
All Randomized Patients
6-Month Therapy Phase

Responder at end time

Treatment	N	Responders n(%)	Overall p-Value*	Pairwise p-Value*		
				vs 2)	vs 3)	vs 4)
1) PLACEBO	139	30(21.6%)	.031	.045	.009	.025
2) DLX60QD	144	47(32.6%)			.610	.555
3) DLX120QD	142	51(35.9%)				1.000
4) DLX20/60QD	77	28(36.4%)				

N = Number of randomized patients with non missing response values.
Response is defined as a 50% or greater reduction from baseline in BPI Average Pain Score.
*Frequencies are analyzed using Fisher's exact test.

Report: RMP.P1JO.HMCJSTAT.INTRM1(RABPIA11)
Program: RMP.P1JSHMCJ.SASPGM(RABPIA1)
Data: RMP.SAS.P1JS.L.MCHMCJ.ADS.INTRM1

Table HMCJ.11.32. Brief Pain Inventory Average Pain Score
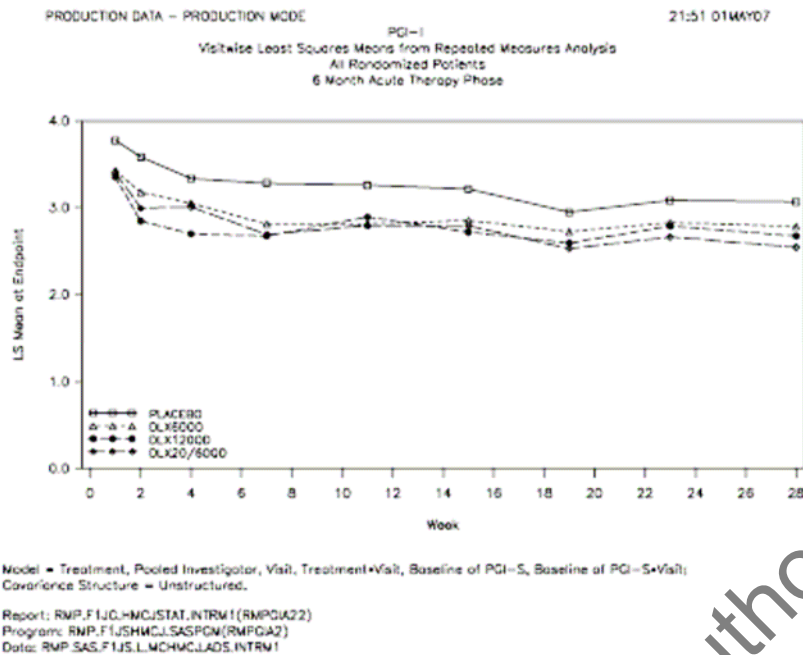Sustained Response
All Randomized Patients
6-Month Therapy Phase

Sustained Responder

Treatment	N	Responders n(%)	Overall p-Value*	Pairwise p-Value*		
				vs 2)	vs 3)	vs 4)
1) PLACEBO	139	25(18.0%)	.169	.116	.115	.060
2) DLX60QD	144	38(26.4%)			1.000	.636
3) DLX120QD	142	37(26.1%)				.634
4) DLX20/60QD	77	23(29.9%)				

N = Number of randomized patients with non missing response values.
Sustained Response: at least 50% reduction from baseline to endpoint, with at least 50% reduction from baseline at an earlier than last visit, and at least 30% reduction from baseline at every visit with data in between, if there are any intervening visits.
*Frequencies are analyzed using Fisher's exact test.

Report: RMP.P1JO.HMCJSTAT.INTRM1(RABPIA21)
Program: RMP.P1JSHMCJ.SASPGM(RABPIA2)
Data: RMP.SAS.P1JS.L.MCHMCJ.ADS.INTRM1

- PGI-Improvement: All three doses of duloxetine showed statistically significant superiority over placebo at different visits in the repeated measures analysis.

20

PGI-1
Visitwise Least Squares Means from Repeated Measures Analysis
All Randomized Patients
6 Month Acute Therapy Phase

Model = Treatment, Pooled Investigator, Visit, Treatment*Visit, Baseline of PGI-S, Baseline of PGI-S*Visit;
Covariance Structure = Unstructured.

Report: RMP.F1JC.HMCJSTAT.INTRM1(RMPGIA22)
Program: RMP.F1JSHMCJ.SASPGM(RMPGIA2)
Data: RMP.SAS.F1JS.L.MCHMCJLADS.INTRM1

- Other secondary endpoints at 3 months: All three doses of duloxetine showed statistically significant superiority over placebo in the mean change analysis and at different visits in the repeated measures analysis in CGI-Severity score. None of doses were statistically superior to placebo in the FIQ Total score and Tender Point Pain Thresholds.

Health Outcomes/Quality-of-Life Evaluation

- 3-Month Therapy Phase. No statistically significant treatment-group differences were observed for all 4 measures of the SDS. Duloxetine 60 mg QD and 120 mg QD showed a greater mean increase (improvement) compared with placebo on the mental component summary, bodily pain, mental health, and role emotional score of the SF-36. The mean change analysis of the EQ-5D for all randomized patients during the 3-month therapy phase showed that Duloxetine 20 mg QD showed a greater mean increase (improvement) compared with placebo.

- 6-Month Therapy Phase: No significant treatment group differences were observed on the mean change analysis of the SDS for all randomized. Duloxetine 60 mg QD showed a greater mean increase (improvement) compared with placebo on the bodily pain and mental health scores. Duloxetine 120 mg QD showed a greater mean increase (improvement) compared with placebo on the mental component summary and mental health score of SF-36. Duloxetine 20/60 mg QD showed a significantly greater mean increase (improvement) compared with placebo in the EQ-5D.

Subgroup Analyses

- 3-Month Therapy Phase: No significant treatment-by-subgroup interactions were observed on the mean change analysis by investigator on the BPI average pain score or by subgroup (age, sex, race, diagnosis of MDD, secondary diagnosis of anxiety, or previous antidepressant use) No significant treatment-by-subgroup interactions were observed on the mean change analysis by investigator of the PGI-Improvement score or by subgroup.

- 6-Month Therapy Phase: No significant treatment-by-subgroup interactions were observed on the mean change analyses of the BPI average pain score by investigator or by subgroup. No significant treatment-by-subgroup interactions were observed on the mean change analysis of PGI-Improvement score by investigator or by subgroup.

HMEF Study

Study HMEF was a Phase 3, parallel, double-blind, placebo-controlled flexible-dose study in male and female patients designed to assess the efficacy of duloxetine 60/120 mg QD compared with placebo on the treatment of pain in patients with ACR-defined primary fibromyalgia, with or without MDD, during the 6-month therapy phase of the study.

Results

There were no differences in terms of incidence of historical diagnoses, secondary conditions (except for a higher incidence of hyperlipidaemia in duloxetine-treated patients), previous therapy for fibromyalgia and/or depression (except for higher incidence of amitriptyline and citalopram and lower incidence of tramadol in duloxetine-treated patients), and tobacco use and average alcohol consumption. A significant treatment group difference was observed for the use of zolpidem as concomitant therapy, with the highest incidence of use in duloxetine patients. No significant differences were observed for the BPI average pain, FIQ total score, Mean Tender Point Threshold, Count of Low Threshold, CGI-Severity or PGI-Severity. No significant differences among treatment groups were observed for baseline HAMD17 scores by MDD status. Significantly more duloxetine-treated patients were not compliant at Visit 3 compared with placebo-treated patients. At Visit 7 significantly more placebo-treated patients were not compliant compared with duloxetine-treated patients.

Primary Efficacy Analysis

- BPI average pain score: Duloxetine-treated patients showed greater numerically improvement than did placebo-treated patients, but the difference was not statistically significant (p=.053). BPI average pain score mean change was -1.11 (17.2%) in placebo and -1.66 (25.1%) in duloxetine groups. There was a statistically significant treatment-by investigator interaction (p=.015).

Table HMEF.11.5.   Brief Pain Inventory - Average Pain Score
Mean Change from Baseline to Endpoint
All Randomized Patients
6-month Therapy 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) PLACEBO	167	6.45	1.47	6.0	4.0	10.0	5.34	2.43	6.0	0.0	10.0	-1.11	2.38	-1.0	-8.0	4.0
2) DLX60/120QD	159	6.58	1.51	7.0	3.0	10.0	4.94	2.38	5.0	0.0	10.0	-1.66	2.44	-1.0	-10.0	5.0

Interaction (Type II SS)   Raw Data   Therapy-by-Investigator   F=1.92   df=18,286   p= .015

Main Effects (Type II SS)   Raw Data
    Therapy   F=3.76   df=1,304   p= .053
    Investigator   F=1.19   df=18,304 p= .265

Least Squares Means for Change from Baseline
    1) PLACEBO   -1.13   (SE= 0.19)
    2) DLX60/120QD   -1.62   (SE= 0.20)

Pairwise Comparison of LS Means
    DLX60/120QD - PLACEBO   diff=-0.49   Two-sided 95% CI : (-0.99 , 0.01)   t=-1.94   p= .053

Type II sums of squares from ANOVA 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.
N=Number of patients with a baseline and at least one non-missing post-baseline value.
Report: /lillyce/prd/fij_mc_hmef/programs_stat/job_log/lobpiaii.rtf
Program: /lillyce/prd/fij_mc_hmef/programs_stat/lobpiai.sas
Data: /lillyce/prd/fij_mc_hmef/data/ads_interim

- PGI-Improvement: Duloxetine-treated patients showed greater numerically improvement than did placebo-treated patients, but the difference was not statistically significant (p=.064). Placebo patients rated their improvement 3.75±1.37 while duloxetine patients rated 3.45±1.56. There was a statistically significant treatment-by-investigator interaction (p=.004).

```
Table HMEF.11.6.      Patient's Global Impressions of Improvement
                      Mean at Endpoint
                      All Randomized Patients
                      6-month Therapy Phase

PGI-Improvement

                                   Endpoint
                      ------------------------------------------
                      N    Mean   SD    Median  Min   Max
                      ---  -----  ----  ------  ----  ----
1) PLACEBO            165  3.75   1.37   4.0    1.0   7.0
2) DLX60/120QD        157  3.45   1.56   3.0    1.0   7.0


Interaction (Type II SS)          Raw Data      Therapy-by-Investigator      F=2.20   df=18,283   p= .004


Main Effects (Type II SS)                       Raw Data
   Therapy                            F=3.46   df=1,301   p= .064
   Investigator                       F=0.92   df=18,301  p= .549


Least Squares Means for Endpoint
   1) PLACEBO            3.73      (SE= 0.12)
   2) DLX60/120QD        3.42      (SE= 0.13)


Pairwise Comparison of LS Means
   DLX60/120QD - PLACEBO   diff=-0.31    Two-sided 95% CI : (-0.63 ,  0.02)   t=-1.86   p= .064


Type II sums of squares from ANOVA Model=Treatment, Pooled Investigator, and Baseline PGI-S for main effects p-values.
Model=Treatment, Pooled Investigator, Baseline PGI-S, and Treatment*Pooled Investigator for the interaction p-value.
N=Number of patients with baseline PGI-S and at least one non-missing post-baseline PGI-I value.
Report: /lillyce/prd/f1j_mc_hmef/programs_stat/job_log/lopgia11.rtf
Program: /lillyce/prd/f1j_mc_hmef/programs_stat/lopgia1.sas
Data: /lillyce/prd/f1j_mc_hmef/data/ads_interim
```

- Secondary Gatekeeper Efficacy Analysis: There was no statistically significant difference between treatment groups in the mean change analysis of the SDS total score.

Secondary Efficacy Analysis

- 3-month Comparison for all randomized patients: There were no statistically significant differences between treatment groups in the mean change analysis of the BPI average pain score, PGI-Improvement or SDS total score.

- 6-month analysis of qualified patients: Duloxetine-treated patients showed greater numerically improvement in BPI average pain score than did placebo-treated patients at the BPI average pain score, but the difference was not statistically significant. The mean PGI-Improvement at endpoint for all qualified patients was significantly greater in duloxetine compared with placebo.

- 6-month analysis of BPI for all randomized patients: 1) Mean change analysis: No significant differences were observed in BPI worst pain score and BPI pain right now score. Only a significant greater decrease in the BPI least pain score and BPI average interference score were observed in duloxetine patients. 2) Repeated measures analysis: Overall, BPI pain scales only showed statistically significant superiority over placebo at a few points. When only patients who remained on duloxetine 60 mg QD after Visit 8 (Week 13), were compared with those whose dose was increased to 120 mg QD (duloxetine 60/120 mg QD), patients on 60 mg QD showed greater improvement on the BPI average pain score. Sub-analysis on patients excluding those with C-reactive protein >12 mg/L or an incorrect case report form (CRF) worksheet render no differences by treatment group.

- 6-month analysis of FIQ for all randomized patients: Duloxetine-treated patients experienced significantly greater improvement only on the FIQ pain score compared with placebo-treated patients.

- Percentage of responders: No differences were observed in the percentage of responders at 6 months.

```
Table HMEF.11.17.    Brief Pain Inventory Average Pain Score
                     Response Rate at Endpoint
                     All Randomized Patients
                     6-month Therapy Phase


                              Responders
    Therapy          N      n      (%)    p-Value*
    ---------------  -----  ------------  --------
    PLACEBO          167    42  (25.1)      .455
    DLX60/120QD      158    46  (29.1)


    Response is defined as a 50% or greater reduction from baseline in BPI Average Pain
    Score.

    *Frequencies are analyzed using Fisher's exact test.

    Report: /lillyce/prd/f1j_mc_hmef/programs_stat/job_log/rabpia11.rtf
    Program: /lillyce/prd/f1j_mc_hmef/programs_stat/rabpia11.sas
    Data: /lillyce/prd/f1j_mc_hmef/data/ads_interim
```

Health Outcomes/Quality-of-Life Evaluation

- 3-Month Therapy Phase: No statistically significant treatment-group differences were observed for all randomized patients or subgroup analysis (minor differences were observed between duloxetine 60 mg QD and duloxetine 60/120 mg QD groups) in SDS. Duloxetine-treated patients experienced a significant improvement for the SF-36 mental component summary and the mental health domain compared with placebo-treated patients on the mean change from baseline to endpoint for all randomized patients in the acute therapy phase. Duloxetine also showed greater improvement compared with placebo on the SF-36 physical component summary, bodily pain, general health, physical functioning, role-emotional, role-physical, social functioning, and vitality, but these differences were not statistically significant. There were no significant differences among treatment groups in EQ-5D.

Subgroup Analyses

There was a statistically significant treatment-by-subgroup interaction for previous antidepressant use, for which duloxetine treated patients had statistically significantly greater improvement compared with placebo-treated patients, but not for patients without previous antidepressant use.

A statistically significant treatment-by-investigator interaction was observed in the mean change analysis of the BPI average pain score. There were 36 investigators that enrolled patients; these were in Germany, Spain, Sweden, the United Kingdom (UK), and the United States (US). Half of these investigators had fewer than 8 patients with baseline and endpoint data for the BPI average pain score and were pooled into 1 investigator, 999, for analysis purposes. The pooled investigator showed a better BPI average pain result for duloxetine than for placebo. There were 10 of the 18 unpooled investigators that had better BPI results for placebo than for duloxetine. These were from Spain, Germany, Sweden, and the US (all UK sites were pooled). For each country with more than 1 investigator, the results were not consistently better for 1 treatment than the other, suggesting that the treatment-by investigator interaction was not attributable to country-specific factors.

HMEH Study

Study HMEH was a 1-year safety study consisting of an 8-week open-label period, followed by a 52-week double-blind, randomized period. The primary objective was to assess the long-term safety and tolerability of duloxetine at doses up to 120 mg QD for up to 60 weeks in patients with ACR-defined primary fibromyalgia, with or without MDD. Additionally, Study HMEH contained an assessment of persistence of efficacy of duloxetine on pain based on those patients who, at the completion of the 60 mg QD open-label phase of the study, were randomized to remain on 60 mg QD.

Results

No significant treatment group differences were observed in the baseline severity of fibromyalgia with a BPI average pain score of, FIQ Total, CGI-severity score and PGI-severity score. A significantly greater rate of non-compliance for the last study visit (Visit 301) was observed within the duloxetine 120 mg QD treatment group when compared with duloxetine 60 mg QD treatment group. For all other visits and overall compliance, no significant differences in treatment compliance were observed between treatment groups.

Efficacy Analyses for the 8-week open-label study phase

Consistent improvement was noted across all efficacy measures, as denoted by the significant changes in mean score observed from baseline to endpoint for all efficacy measures (BPI Worst Pain, Least Pain, Average Pain, Pain Right Now, and Average Interference scores, BDI-II Total, BDI Item 9 Score, FIQ Total Score, FIQ Tiredness, FIQ Restedness FIQ Pain, Mean Tender Point Threshold, Count of Low Threshold, SDS Global Functional Impairment Total Score, CGI-Severity, PGI-Improvement). A total of 34.8% of patients were BPI responders at Visit 4, the end of the open-label study phase.

Table HMEH.11.12. Brief Pain Inventory Average Pain Score
Response Rate at Endpoint
All Enrolled Patients
Open-Label Study Phase

```
                                            Responders
Therapy              N                       n (%)
------------------------------------------------------
DLX60QD              330                     118(34.81)
```

N = Number of patients with a baseline and at least one post-baseline measurement.
Response is defined as a 50% or greater reduction from baseline in BPI Average Pain Score.

Report: RMP.F1J0.HMEHSTAT.FINAL(RABPI211)
Program: RMP.F1JSHMEH.SASPGM(RABPI21)
Data: RMP.SAS.F1JS.L.MCEMEH.ADS.DBF

Efficacy Analyses for the double-blind study phase

- BPI: No significant difference in mean change in average pain scores was observed with comparisons between treatment groups. The mean change in BPI average pain scores by BPI response status at Visit 4 for all randomized patients were also non significant different.

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	191	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	4.77	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.F1J0.HMEHSTAT.FINAL(LOBPI311)
Program: RMP.F1JSHMEH.SASPGM(LOBPI31)
Data: RMP.SAS.F1JS.L.MCEMEH.ADS.DBF

For persistence of efficacy analysis, mean change in BPI average pain 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 Visit 2.

In addition, decreases (improvements) in mean average pain score were observed for no responders within both treatment groups. Response rates at endpoint were 40.2% for duloxetine 60QD and 39.11% for duloxetine 120QD.

Table HMEH.11.19. Brief Pain Inventory Average Pain Score
Response Rate at Endpoint
All Randomized Patients
Double-Blind Study Phase

Therapy	N	Responders n (%)	P-value
1)DLX60QD	102	41(40.20)	.901
2)DLX120QD	202	79(39.11)	

N = Number of patients with a baseline and at least one post-baseline measurement.
Response is defined as a 50% or greater reduction from baseline in BPI Average Pain Score.

*Frequencies are analyzed using Fisher's exact test.

Report: RMP.P1JO.HMEHSTAT.FINAL(RABPI311)
Program: RMP.P1JSHMEH.SASPGM(RABPI31)
Data: RMP.SAS.P1JS.L.MCHMEH.ADS.DBF

Table HMEH.11.20. Brief Pain Inventory Average Pain Score
Response Rate at Endpoint
All Randomized Patients by Brief Pain Inventory Response Status at Visit 4
Double-Blind Study Phase

Response Status	Treatment	N	Responders n(%)	p-Value*
No	1)DLX60QD	66	19(28.79)	1.00
	2)DLX120QD	128	37(28.91)	
Yes	1)DLX60QD	36	22(61.11)	.686
	2)DLX120QD	74	42(56.76)	

Response is defined as a 50% or greater reduction from baseline in BPI Average Pain Score.
*Frequencies are analyzed using Fisher's exact test.

Report: RMP.P1JO.HMEHSTAT.FINAL(RABPI321)
Program: RMP.P1JSHMEH.SASPGM(RABPI32)
Data: RMP.SAS.P1JS.L.MCHMEH.ADS.DBF

- PGI-Improvement Score: A significantly lower (improvement) mean PGI-Improvement score at endpoint was observed with duloxetine 60 mg QD when compared with duloxetine 120 mg QD.

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

PGI-Improvement

	N	Endpoint 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.P1JO.HMEHSTAT.FINAL(LOPGI311)
Program: RMP.P1JSHMEH.SASPGM(LOPGI31)
Data: RMP.SAS.P1JS.L.MCHMEH.ADS.DBF

Subgroups analysis by BPI response status during the double-blind study phase showed a significant difference with initial responders experiencing a lower (improvement) mean score at endpoint when compared with no responders. Within the no responder subgroup, a significantly lower (improvement) mean PGI-Improvement score at endpoint was observed with duloxetine 60 mg QD when compared with duloxetine 120 mg QD.

26

- FIQ: The difference in the FIQ total score between treatment groups was significant where duloxetine 60 mg QD experienced a decrease (improvement) and duloxetine 120 mg QD experienced an increase (negative impact). For all other items, no significant differences were observed with comparisons between treatment groups. Subgroup analysis does not show relevant differences between groups.

- Tender Point Threshold: A significantly greater increase (improvement) in Mean Tender Point Threshold was observed with duloxetine 60 mg QD when compared with duloxetine 120 mg QD. Analysis by BPI response status in the double-blind study phase showed that within the no responder subgroup, a significantly greater increase in Mean Tender Point Threshold was observed with duloxetine 60 mg QD when compared with duloxetine 120 mg QD. Several sub-analyses render no differences or differences favouring those with duloxetine 60 mg QD.

- Clinical Global Impression of Severity: Comparisons between treatment groups were not significant.

- Health Outcomes: Mean change in the SDS Global Functional Impairment total score for all randomized patients in the double-blind study phase showed a significant mean difference in the SDS total score was observed with comparisons between treatment groups where duloxetine 60 mg QD experienced a mean score decrease (improvement) while duloxetine 120 mg QD experienced a slight increase (negative impact).

CHMP Assessment of Efficacy data

Further to the evaluation of the initially submitted data supporting this variation, the CHMP considered that although some degree of effect could be observed across short-term studies, the robustness of the efficacy database was insufficient to conclude a relevant effect of duloxetine in patients with fibromyalgia. The MAH was requested to provide additional analyses in order to explore whether the modest effect could be regarded as consistently demonstrated and clinically relevant for the intended target population. In addition, the MAH was requested to demonstrate the persistence of efficacy at one year, since no significant benefit with increasing the duloxetine dose from 60 mg QD to 120 mg was shown.

The CHMP major objections dealt with the following key aspects:

Short-term efficacy of duloxetine in fibromyalgia

Only one study (HMCA) performed entirely in the USA and including only woman had robust results in both primary and secondary variables. This study was designed after the preliminary study HMBO rendered negative results on primary outcome variables (FIQ total and FIQ pain) on the whole population and only positive results in the subgroup analysis by gender. Study HMCJ also obtained positive results in primary outcome variables, but again it was only developed in the USA, included male patients, and the results on secondary variables were less predictable than in the HMCA study. The first multinational study (HMEF) failed to show differences between active treatment and placebo due to a significant treatment-by-investigator interaction for primary and secondary efficacy variables.

The CHMP pointed out that a robust and clinically relevant short-term effect in the intended target population has not been convincingly demonstrated. Results from pivotal studies show inconsistent results regarding primary endpoints with a modest magnitude of effect. Moreover, the impact of the effect on primary endpoints on relevant secondary effect has not been consistently shown across studies. The responder data presented as an illustration of clinical relevance of the mean effects demonstrated in the primary analyses are not impressive. Furthermore, it is not obvious how discontinuations are treated in the responder analyses.

In reply to CHMP concerns, the MAH has submitted several 3-month post-hoc responder analyses where discontinuing patients, those who did not have a post baseline value or who did not have a final visit value, were considered as non-responders (named withdrawal failure approach). The results of these additional analyses can be summarized as follows:

- Responder definition in terms of reduction of pain after 3 month treatment. A lower magnitude of reduction of pain (for both placebo and active patients) is shown when the withdrawal failure approach is used. When using the more restrictive approach of at least 50% improvement as a

definition of responder, slightly above 25% of patients responded to duloxetine, while slightly above 15% responded to placebo. This meaning that when this more conservative handling of missing data approach is adopted, the results in terms of differences from placebo remain constant (absolute difference between treatment arms of 10.8% in the pooled analysis) as compared to the LOCF approach (absolute difference between treatment arms of 11.4% in the pooled analysis), though the total number of patients responding falls from 35% to 27% among duloxetine treated patients and from 24% to 17% among placebo treated patients. The same trend is observed for sustained response: lower response rate for duloxetine and PBO when the Baseline Observation Carried Forward (BOCF) approach is used, though the net difference between treatment arms in the pooled analysis is kept (around 11%). No significant benefit with increasing doses from 60 mg BID or 120 mg QD is observed as compared to 60 mg QD. Remarkably, this flat response curve also involves the 20 mg dose.

- Responder definition in terms of PGI-Improvement: When response was presented according the patient perception of general functioning, 32% duloxetine patients defined their improvement as very much better or much better at the end of the treatment (3 months therapy) versus 18% of placebo patients.

- When both criteria (pain alleviation and personal improvement) were put together in order to better define the effect of duloxetine in reliable terms 14% patient reduced at least 30% their initial level of pain, feeling better or much better after placebo treatment. A modest response of 25% (in all studies lower than 30%, whatever dose is considered, except with 60 mg QD in study HMCA where the response rate was 30.5%) was observed after 3 months of duloxetine treatment.

The CHMP considered that these additional analyses confirmed its initial opinion: the observed effect is modest and its clinical relevance is questionable. Furthermore, despite the consistent trend, overall only 1 out of 4 studies showed a consistent effect in both primary and secondary endpoints (despite the results of the pooled analyses). The CHMP pointed out that the preliminary study HMBO was negative in its primary endpoint (a disease specific instrument), study HMCJ showed a positive results in its primary analysis, but not consistently supported by the results on relevant secondary endpoints, and finally, study HMEF had non-significant results (negative study). This aspect should be considered when putting in perspective the value of the pooled analyses provided by the MAH. The CHMP concluded that the magnitude of the short-term effect is small and not consistently accompanied by a robust effect on secondary endpoints, including disease specific variables and quality of life. In addition, 2 out of 4 clinical studies failed to reach statistical significance in their primary endpoints.

Representativeness of the studied population

The CHMP considered that looking into the characteristics of patients included in pivotal studies, they are thought to represent a population of moderate severity in clinical setting. No special criteria were requested for the selection of severe, resistant or non-responder to previous treatment patients. Moreover, since duloxetine/placebo were not given as add-on therapy to background therapy, but all background treatments were removed before study therapy was initiated, it could be considered that the enrolled patient population would in principle be reasonably likely to respond to treatment. Therefore the CHMP concluded that his fact adds doubts on the clinical relevance of the modest effect observed in clinical trials, which further question its relevance for real clinical practice.
The claimed effect of duloxetine has not been replicated in all studies. Unfortunately the more negative trial was the only study in which EU citizens were enrolled. In the MAH's opinion the lack of statistical differences between US and EU patients guarantees the extrapolation of results among different regions. The significant treatment-by-investigator interaction for primary and secondary variables detected in the multinational (EU) study does not support these conclusions. This fact may be especially relevant considering that information on non-pharmacological approaches to treat patients with fibromyalgia is limited or non-existing. Whether it might have an impact on the finally observed treatment effect and whether the application of these non-drug measures was homogeneous between US and EU remains unknown.

The CHMP concluded that effect has not been demonstrated in an EU clinical setting. It is uncertain whether regional differences in medical and social culture (non-pharmacological treatment, diagnosis in clinical practice, etc.) preclude extrapolation from non-EU studies.

<u>Independence of the observed effect from the known effect of duloxetine on mood disorders</u>

The CHMP observed that the influence of the potential effect of duloxetine on depression in the global response of fibromyalgia was evaluated taking into account the HAMD scores stratification and MDD diagnosis. When the population was analyzed according the HAMD score, it can be observed a numerical trend toward a lower placebo response inversely related to HAMD scoring categories. The opposite can be observed with duloxetine effect. This finding result in a consistent higher numerical treatment differences in terms of BPI as with higher HAMD scores, which is not completely consistent with a true independent effect. The same trend is observed when patients with MDD diagnosis at baseline are considered as compared to non-MDD patients (independently from the HAMD scoring). The CHMP concluded that these findings support a strong non-specific component of the treatment effect and partially contradict the path analyses for the direct analgesic effect of duloxetine performed in the clinical studies. In clinical studies, the direct effect of duloxetine on the reduction on the pain appears to account for the most of the total treatment effect versus an indirect effect through the improvement of mood symptoms.

<u>Long-term efficacy</u>

The CHMP pointed out that the complete absence of a dose-response relationship and the lack of a placebo arm in the long-term study preclude drawing conclusions on the maintenance of the effect with duloxetine in the long-term. The additional analysis provided by the MAH does not overcome this essential limitation of the study. The MAH proposed to include in the SPC a statement advising to stop treatment in patients not responding after an initial period of treatment. The CHMP believes that this is a reasonable proposal to be considered on an individual basis, but does not prevent the need for demonstrating that a long-term maintenance effect is present in the whole population. In addition, no data are available for the effect longer than 6-month period time. Only uncontrolled data of treatment up 1 year-treatment period are available. In reply to this concern, the MAH proposed to evaluate the response after 2 months of treatment. The CHMP argued that a modest short-term effect on pain is not deemed enough to get a long-term indication on the whole condition. Therefore, long-term placebo-controlled data have been requested from CHMP since the long-term maintenance of the effect remains unproven.

<u>Conclusions</u>

The concerns raised by CHMP remain. The short-term effect has not been robustly demonstrated. Only a small effect has been shown, which on the other hand has not been consistently demonstrated in all trials. Furthermore it is unlikely to be truly independent from the drug effect on mood disorders, a frequent co-morbid condition in patients with fibromyalgia. Importantly, there are still caveats on whether the observed results from pivotal studies are relevant and reasonably applicable to an EU clinical setting. No demonstration on the long-term maintenance of the effect has been provided. The B/R remains negative.

3.5 Clinical safety

Patient Exposure

The primary overall duloxetine analyses set comprises a total of 1236 duloxetine patients (representing 571.69 patient-years exposure to duloxetine), including patients from the primary placebo-controlled analyses set, the long-term Study HMEH, and 10 patients who entered Study HMCN (Table 2.5.5.2). Among these patients, 574 (46.4%) had ≥6 months of exposure to duloxetine, and 219 (17.7%) had ≥12 months of exposure to duloxetine.

Table 2.5.5.2.   Exposures from the Primary Analyses Sets

	Primary Placebo-Controlled		Primary Long-Term (Study HMEH)	Primary Overall
	Placebo	Duloxetine	Duloxetine	Duloxetine
N	535	876	350	1236
Patient-years	153.96	264.17	285.1	571.69

Source: FQEXPF11, SMEXPO12, FQEXPA11

In the all placebo-controlled analyses set (all indications), 9445 patients were randomized to duloxetine treatment (approximately 1638 patient-years of exposure) and 6770 were randomized to placebo treatment (approximately 1237 patient-years of exposure). The overall duloxetine exposures analyses set included 27,229 duloxetine-treated patients as of 12 May 2007.

Adverse events
The incidence of treatment-emergent adverse events (TEAEs) in the primary placebo-controlled analyses set for events where the incidence in the duloxetine treatment group was ≥5.0% and the rate for duloxetine was significantly higher than placebo is summarized in the table below.

Treatment-Emergent Adverse Events by Decreasing Frequency. Adverse Events Reported in ≥ 5% and Significantly more Frequently in Duloxetine Than Placebo in the Primary Placebo-Controlled Analyses Set.

MedDRA Preferred Term. All Randomized Patients Using the Different Safety Analyses Sets	Primary Placebo-Controlled			Primary Long-Term	Primary Overall	All Placebo-Controlled (all indications)			All DLX Exposures (all indications)
	PBO N=535	DLX N=876		DLX N=350	DLX N=1236	PBO N=6770	DLX N=9445		DLX N=27,229
Event [a]	%	%	p-val	%	%	%	%	p-val	%
ANY EVENT	79.4	88.8	<.001	93.1	90.2	58.2	73.6	<.001	77.1
Nausea	11.4	29.3	<.001	40.6	33.2	7.5	24.3	<.001	25.9
Headache	12.0	20.0	<.001	29.4	22.7	9.9	12.6	<.001	14.1
Dry mouth	5.2	18.2	<.001	17.1	18.0	4.1	12.9	<.001	12.9
Insomnia	9.2	14.5	.003	19.7	16.3	3.9	8.7	<.001	10.5
Fatigue	7.1	13.5	<.001	11.1	13.3	3.8	9.2	<.001	10.0
Constipation	3.6	14.5	<.001	17.4	15.6	3.3	10.3	<.001	10.9
Diarrhea	7.9	11.6	.018	12.9	12.2	4.9	7.6	<.001	8.7
Dizziness	6.7	11.0	.011	18.9	13.3	4.0	9.5	<.001	10.6
Somnolence	2.8	9.6	<.001	14.0	10.8	1.6	6.9	<.001	8.4
Hyperhidrosis	1.1	6.8	<.001	11.4	8.4	1.3	5.7	<.001	6.8
Decreased appetite	0.6	6.5	<.001	4.6	6.0	0.7	3.5	<.001	3.5

Overall, patients who experienced and reported the most common adverse events tended to do so early, and they reported the events as being generally of mild to moderate severity. No single event led to the discontinuation of more than 2% of patients in the primary placebo-controlled studies.

With regard to gender, more females than males reported fatigue (about twice as many) and somnolence (about 5 times as many). However, the clinical relevance of the subgroup analyses was limited by the small number of male patients.

With regards to age, the adverse event profile for older patients was similar to that of the younger group. Decreased appetite was reported approximately 2 times more frequently in the < 55-year-old subgroup compared with the ≥55-year-old subgroup.

The incidence of the most common adverse events was similar in the subgroups of <65 years old and ≥65 years old; however, few patients were in the latter subgroup.

For reasons that are unclear, non-Caucasian patients appeared to report most adverse events more frequently. This finding may be related to cultural differences in the way adverse events were perceived and reported. Somnolence, in particular, was reported more frequently in the non-Caucasian subgroup (21.0%) compared with the Caucasian subgroup (8.0%).

Most Common Adverse Events by Demographics Subgroups. MedDRA Preferred Term
All Duloxetine Patients. Primary Placebo-Controlled Analyses Set

Event a	Duloxetine N=876							
	Age				Gender		Origin	
	<55 N=560 %	≥55 N=316 %	<65 N=799 %	≥65 N=77 %	Female N=829 %	Male N=47 %	Cauc N=771 %	Other N=105 %
ANY EVENT	89.1	88.3	88.6	90.9	88.5	93.6	88.3	92.4
Nausea	30.4	27.5	29.5	27.3	29.6	25.5	28.8	33.3
Headache	18.9	21.8	20.0	19.5	19.9	21.3	18.9	27.6
Dry mouth	16.6	20.9	17.9	20.8	18.5	12.8	17.4	23.8
Insomnia	13.8	15.8	14.9	10.4	14.6	12.8	14.8	12.4
Fatigue	15.0	10.8	13.4	14.3	13.9	6.4	14.0	9.5
Constipation	13.0	17.1	14.3	16.9	14.8	8.5	14.3	16.2
Diarrhoea	12.7	9.8	12.0	7.8	11.5	14.9	12.1	8.6
Dizziness	12.0	9.2	10.9	11.7	11.2	6.4	10.0	18.1
Somnolence	8.8	11.1	9.3	13.0	10.0	2.1	8.0	21.0
Hyperhidrosis	7.3	6.0	6.9	6.5	6.8	8.5	6.9	6.7
Decreased appetite	8.0	3.8	6.6	5.2	6.6	4.3	6.5	6.7

Abbreviations: Cauc = Caucasian; N = number of patients.

a Event list comprises those TEAEs in the primary placebo-controlled analyses set for which the rate for duloxetine was ≥5.0% and significantly higher than placebo.

b Cochran-Mantel-Haenszel test for general association, controlling for study.

Source: FQAESF81

Serious adverse events and deaths

Deaths

No deaths were reported in the fibromyalgia studies.

In the overall duloxetine exposures analyses set (all indications) consisting of more than 27,000 patients, 30 deaths occurred, of which 6 occurred after discontinuation from study participation, and 1 occurred prior to study drug administration. In addition, 2 deaths were reported in ongoing studies.

A total of 20 deaths (14 patients treated with duloxetine and 6 patients treated with placebo) were reported in the all placebo-controlled analyses set (all indications).

Serious Adverse Events
A total of 21 (2.4%) duloxetine-treated and 11 (2.1%) placebo-treated patients reported at least 1 SAE in the primary placebo-controlled analyses set. There were no significant or clinically important treatment differences in the incidence of individual SAEs. No single event was predominant.
A total of 19 (5.4%) duloxetine-treated patients experienced at least 1 SAE in the primary long-term analyses set (Study HMEH). More SAEs were reported in the primary long-term analyses set when compared with the primary placebo-controlled analyses set. This result was most likely due to a longer observation of the patients.
A total of 40 (3.2%) duloxetine-treated patients experienced at least 1 SAE in the primary overall duloxetine analyses set.

Serious Adverse Events by System Organ Class
All Randomized Patients. Primary Analyses Sets

	Placebo-Controlled			Long-Term	Overall
	DLX N=876	PBO N=535		DLX N=350	DLX N=1236
Patients with ≥ 1 SAE (n [%])	21 (2.4)	11 (2.1)		19 (5.4)	40 (3.2)
System Organ Class	%	%	p-val [a]	%	%
Blood and lymphatic system disorders	–	–		–	–
Cardiac disorders	0.1	0.2	.480	0.3	0.2
Endocrine disorders	–	–		0.3	0.1
Eye Disorders	–	–		–	–
Gastrointestinal disorders	0.1	0.4	.245	0.6	0.2
General disorders and administration site conditions	0.3	0.4	.940	–	0.2
Infections and infestations	0.5	0	.134	0.3	0.4
Injury, poisoning, and procedural complications	0.3	0.2	.721	1.1	0.6
Investigations	0.1	0	.474	–	0.1
Metabolism and nutrition disorders	0.1	0	.536	–	0.1
Musculoskeletal and connective tissue disorders	0.3	0.2	.408	–	0.2
Neoplasms benign, malignant, and unspecified	0.2	0	.381	0.3	0.2
Nervous system disorders	0.1	0	.309	0.9	0.3
Psychiatric disorders	0.2	0.2	.938	1.4	0.6
Renal and urinary disorders	0.1	0	.536	0.3	0.2
Reproductive system and breast disorders	0.1	0.6	.071	–	0.1
Respiratory, thoracic, and mediastinal disorders	0.1	0.2	.480	–	0.1
Skin and subcutaneous tissue disorders	–	–		0.3	0.1
Social circumstances	–	–		0.3	0.1
Vascular disorders	–	–		0.3	0.1

A total of 136 patients treated with duloxetine (1.4%) and 83 patients treated with placebo (1.2%) reported at least 1 SAE in the all placebo-controlled analyses set (all indications) and a total of 947 patients (3.5%) reported at least 1 SAE in the overall duloxetine exposures analyses set (all indications). In addition, 53 patients reported new SAEs in ongoing studies.

The frequency of SAEs observed in duloxetine treated patients in the fibromyalgia population (2.4%) tended to be slightly higher than in the all placebo-controlled (all indications) analyses set (1.4%). However, this was also true for patients taking placebo (2.1% versus 1.2%), suggesting that this was a population-specific phenomenon, and not a drug-specific phenomenon.

The discontinuation rate for the most common adverse events for duloxetine in the treatment of fibromyalgia is depicted in the table below.

The overall incidence of adverse events leading to discontinuation was similar between the primary placebo-controlled and the primary long-term analyses sets, providing reassurance that long-term exposure to duloxetine did not increase the likelihood of experiencing an adverse event that would lead to discontinuation.

Event [a]	Primary Placebo-Controlled			Primary Long-Term	Primary Overall	All Placebo-Controlled (all indications)			All DLX Exposures (all indications)
	PBO N=535	DLX N=876		DLX N=350	DLX N=1236	PBO N=6770	DLX N=9445		DLX N=27,229
	%	%	p-val[b]	%	%	%	%	p-val[b]	%
ANY EVENT (% [n])	11.8 (63)	19.5 (171)	<.001	21.1 (74)	20.4 (252)	4.6 (310)	14.0 (1325)	<.001	18.3 (4991)
Nausea	0.7	1.9	.074	1.4	1.9	0.5	3.1	<.001	3.5
Headache	0.2	0.9	.146	0.3	0.7	0.2	0.6	.002	0.6
Dry mouth	0	0.1	.309	-	0.2	0	0.1	.006	0.2
Insomnia	0.7	1.1	.411	2.6	1.6	0.2	0.7	<.001	0.9
Fatigue	0.2	1.3	.073	0.6	1.1	0.2	0.8	<.001	1.0
Constipation	0.2	0.3	.721	0.6	0.5	0.1	0.2	.104	0.5
Diarrhoea	0.2	0.8	.077	1.4	1.0	0.1	0.3	.001	0.5
Dizziness	0.6	0.7	.672	1.4	0.9	0.2	0.8	<.001	1.0
Somnolence	0	1.5	.003	0.3	1.1	0.0	0.7	<.001	0.8
Hyperhidrosis	0	0.5	.149	0.3	0.4	0	0.1	.002	0.2
Decreased appetite	-	-	-	-	-	-	-	-	0.0

Safety Topics of Special Interest

Suicidality
A full assessment of suicide-related events in the primary placebo-controlled analyses set and the all placebo-controlled analyses set (all indications) has been conducted.
There were 3 cases of suicide ideation (1 on duloxetine, 2 on placebo), but no suicide behaviours were reported during the *placebo-controlled fibromyalgia studies*. No statistically significant differences of Mantel-Haenszel incidence differences and incidence ratios for suicidal behaviour or ideation were observed from these analyses.
Analyses of depression scale item data from fibromyalgia studies revealed that significantly more placebo-treated patients reported the emergence of any suicidal ideation compared with duloxetine-treated patients. There was also a significantly higher proportion of worsening of suicidal ideation in placebo-treated patients compared with duloxetine-treated patients. There was no statistically significant difference between the treatment groups in the frequency of improvement.
Among patients with depression at baseline, statistically significantly more placebo-treated patients reported the emergence of any suicidal ideation and worsening of suicidal ideation compared with duloxetine-treated patients. There was a statistically significantly higher proportion of improvement of suicidal ideation in duloxetine-treated patients who had depression at baseline. There were no statistically significant differences in the scale outcomes among patients without depression at baseline.
In addition to events found in the placebo-controlled fibromyalgia studies, there were 4 patients from Study HMEH who had suicide-related behaviour (3 suicidal ideation and 1 suicide attempt).
In the updated analysis of suicide-related events for the all *placebo-controlled analyses set (all indications)*, the meta-analysis of the duloxetine placebo-controlled data did not show evidence of a statistically significant increased risk of suicide-related behaviors and/or ideation in patients treated with duloxetine compared with those treated with placebo. A numerically, but not statistically significantly, greater incidence of Suicide Behaviour or Ideation events (Mantel-Haenszel Incidence Difference [MHID] = 1.70, p=.065) was observed in duloxetine-treated patients compared with placebo-treated patients in the 18 to <25 years of age subgroup. This finding was primarily driven by suicidal ideation events in MDD patients.

Within placebo-controlled studies (all indications), there were 2 completed suicides (1 duloxetine-treated and 1 placebo-treated), both from an MDD study. There were 9 non-fatal suicide attempts (7 duloxetine-treated, 2 placebo-treated), all from MDD studies. The majority of events were related to suicidal ideation (37 [0.40%] in duloxetine-treated and 24 [0.36%] in placebo-treated patients), most occurring in psychiatric conditions. Suicide-related thoughts and behaviours within non-psychiatric conditions were very infrequent, and there were no completed suicides or suicide attempts.

Suicidal ideation was the SAE reported most frequently (4 patients; 0.3%). Three of these patients were from the open-label long-term Study HMEH, and 1 patient was from Study HMCJ. In addition, 1 patient from Study HMEH had a suicide attempt.

Overall, the results of the meta-analyses of all duloxetine studies were consistent with results of previous meta-analyses. In the fibromyalgia studies there was no statistical or numerical increased rate of suicide-related events in duloxetine patients compared with the placebo patients; therefore, Lilly does not believe there are any unique risks regarding suicide-related events associated with the use of duloxetine in patients with fibromyalgia.

Hepatic Analyses

In the *primary placebo-controlled analyses set*, duloxetine-treated patients had significantly greater increases from baseline to maximum in mean ALT, aspartate tansaminase (AST), alkaline phosphatase (ALKPH), and gamma glutamyl transferase (GGT) values than placebo-treated patients. There were no differences from baseline to maximum between duloxetine and placebo in mean total bilirubin (TBILI).

There were no significant differences in the incidence of hepatic-related treatment-emergent adverse events and hepatic-related serious adverse events in the primary placebo-controlled analyses set. A small difference was observed in the frequency of transaminemia (ALT >3 times ULN) in the fibromyalgia study population (1.37%) compared with the overall duloxetine population (1.11%). A higher difference was observed between the corresponding placebo treatment groups (fibromyalgia patients: 0.44%; all indications: 0.23%), indicating that there was an indication-specific phenomenon occurrence.

In the primary placebo-controlled analysis set, there was a significantly higher incidence of duloxetine-treated patients (0.57%) who discontinued due to a hepatic-related adverse event compared with placebo-treated patients (none).

Severe Cutaneous Reactions

A small proportion (1.4% duloxetine-treated patients compared with 0.2% of placebo-treated patients) of fibromyalgia patients experienced adverse events potentially indicative of severe cutaneous reactions, although approximately half of the events were isolated reports of conjunctivitis. No patients discontinued due to any of these events and no events were serious. Therefore, the use of duloxetine did not seem to pose a risk of severe cutaneous reactions in fibromyalgia patients.

CHMP assessment of Safety Data

The duloxetine safety data were classified into 5 different analyses sets, three from the five fibromyalgia studies (primary placebo-controlled (876 patients), primary long-term (350 patients), and primary overall duloxetine sets (1236 patients)), and two sets covering all indications (all placebo-controlled analyses (9 445 patients), and overall duloxetine analyses sets (27 229 patients)). The "All placebo-controlled analyses set" included safety data from studies on patients with fibromyalgia, major depressive disorder, general anxiety disorder, diabetic peripheral neuropathic pain, and lower urinary tract disorder.

Overall, the incidence of TEAEs was fairly consistent in all analyses sets. However, the fibromyalgia patients tended to have higher frequency of AEs, following both duloxetine and placebo administration, than the rest of the patients, suggesting a population-specific rather than drug-specific phenomenon. The CHMP considered that since only 5 % of the fibromyalgia patients were males, a gender-specific phenomenon should be considered and discussed by the MAH. In their response, the MAH acknowledged that there is a generally higher rate of AE in the fibromyalgia population compared with other indications for duloxetine. In addition, the MAH pointed out that the number of male patients treated in the fibromyalgia indication is low and the CHMP agreed that no alarming data were found and that there is no obvious increase of AE in male.

Duloxetine showed a higher incidence of adverse events with higher doses except for diarrhoea and fatigue. Although these differences were not significant for any of the adverse events when a formal comparison was made, this trend was consistent for most of events. The MAH requested to provide a more detailed description of the AEs incidence by dose, with aggregated frequency distribution for 60 mg, 120 mg and placebo treated patients in order to further clarify the safety profile of intended dosages. The MAH provided two comparative analyses for the fixed doses studies or the four placebo controlled studies in order to compare the safety profile of the intended doses (initial duloxetine 60 mg QD dose or optional up titration 120 mg QD dose). A similar pattern was reported for both doses. Nausea, headache, dry mouth, insomnia, fatigue, constipation, dizziness, diarrhoea, somnolence, decreased appetite, hyperhidrosis were reported among the common adverse events for duloxetine 60 mg and 120 mg. According to the data provided, patients titrated up to 120 mg are expected to have higher incidence of dry mouth, constipation and sleep disturbances (insomnia/somnolence) than those remained at 60 mg. No new safety concerns had arisen. The CHMP considered this issue to have been resolved.

Increased weight (2.4%) was a significantly increased TEAE in the fibromyalgia patients, but not in the "all indications" patients. Therefore, the MAH was requested to discuss whether this discrepancy could be due to gender differences, and whether a development of weight increase over time can be observed in the long-term safety data base. The MAH pointed out that weight gain was observed in both genders with a slightly higher percentage of females compared with males. Although a female predisposition to gain weight could not be excluded, gender appears to play a minor role in the development of weight gain. In addition the MAH explained that weight gain was observed as increased in the duloxetine treated group and was more obvious in the long-term treated. Furthermore, it was noted by the MAH that weight gain is already included in the SPC. The CHMP considered this issue to have been resolved.

The CHMP mentioned that no deaths were reported in the fibromyalgia studies. More than 40% of patients included in the fibromyalgia studies discontinued due to any reason compared to 28% in other indications studies (all placebo-controlled analyses set). This is true also for placebo treated patients and it was explained as a population-specific phenomenon more than a duloxetine-specific finding. Discontinuation due to AEs was significantly more frequent in the duloxetine group (19.5%) compared with the placebo group (11.8%) particularly for the AE somnolence. In order to reduce the high initial discontinuation rate, the MAH was requested to discuss the possibility of a lower initial dose and a slower and more prolonged dose escalation in the fibromyalgia patient group. In reply to the CHMP concern, the MAH justified the discontinuation rates in fibromyalgia studies as related to an indication-specific and not a treatment-specific issue. The rate of discontinuation does not seem to differ whether the therapeutic doses are achieved in one or more steps. Admittedly, the impact on the efficacy of dosing without escalation appears to be much lower than that observed on the safety. Therefore it is expectable that in terms of tolerability some patients could benefit from slower titration. The CHMP considered that issue to have been solved provided that the SPC is amended appropriately.

According to the findings identified during the continuous safety assessment of duloxetine in its different indications the following key events were closely monitored:
a) Suicidality: A total of seven suicide-related events were reported in fibromyalgia studies, four of them in the open-label long term study. Six cases of suicide ideation (four on duloxetine, two on placebo) and one suicide attempt were reported. These findings indicate that the concerns about suicidal behaviour associated with duloxetine remain and stress the need of keeping and reinforcing ongoing initiatives to further assess this aspect.

b) Hepatic risk: An increased incidence of moderate to severe plasma ALT levels was found in the fibromyalgia group. The MAH related these findings to a specific indication cause. Admittedly, it could also reflect a potential higher risk for this population. The CHMP requested the MAH to discuss the possibility that this is a gender-related AE. In addition, the MAH has been requested to present the occurrence of elevated ALT levels in males and females, respectively, in the overall duloxetine population (all indications). In reply to CHMP concerns, the MAH pointed out that duloxetine treatment induces transaminase increases in females, independently from the indication considered. However, some indications seem to provide an additional risk. Furthermore, the MAH admitted that the nature of this issue deserves to be dealt with in the RMP and it is one of the identified issues continue to be followed-up in it. The CHMP considered that issue to have been solved.

c) Severe cutaneous reactions: Specific risks were not seen in the fibromyalgia study population. With the exception of abnormally high ALT values in the duloxetine-treated patients in the placebo-controlled analyses sets no clinically significant changes were identified in the laboratory evaluations. Hyperglycemia (increase in fasting blood sugar and HbA1c) has been identified in DPNP clinical trials and it has been recently considered in the risk management plan for its monitoring. In principle there appear to be no signal of safety concerns in fibromyalgia population related to duloxetine treatment. However, since only limited data has been obtained in fibromyalgia clinical development this concern cannot be ruled out.

The effect of duloxetine on blood pressure, cardiac frequency and Electrocardiogram (ECG) data (including QT interval) has been repeatedly assessed. The variations observed in cardiovascular parameters were apparently minimal and did not derive in major clinical events. The fibromyalgia patients treated with duloxetine showed incidences of increase blood pressure, heart rate and QTcF increases similar to those observed for other indications. However, the concomitant use of drugs with a potential effect on QT (such as tricyclic antidepressant (TCAs)) could enhance the cardiovascular risk in this population. The MAH was requested to comment on this. The MAH pointed out that there are no specific results coming from pK/pD interaction studies in this population. The MAH mentioned that the current SPC wording appropriately advises caution regarding the combination of duloxetine with other centrally acting medicinal products taking into account that limited, available clinical evidence has not demonstrated an increase in cardiovascular risk associated with co-administration of duloxetine and TCAs. The CHMP considered that issue to have been solved.

As expected in fibromyalgia studies, few males (< 6%) were included in the study population. In addition, the age group 65 years and older was small (<10%) in the fibromyalgia trials. The CHMP asked the MAH to discuss in more detail how safety issues in these small subgroups can be extrapolated from observations in the total duloxetine safety database. In reply to CHMP concerns, the MAH explained that although the numbers of males and older patients (≥65 years of age) were relatively small, results from the subgroup analyses performed as part of the original submission did not suggest a different safety profile compared with females and younger patients. Given the similarity of the overall safety profiles seen in all approved indications and now also in fibromyalgia and given the similar pattern observed across age groups and gender in the DPNP studies, the MAH mentioned that the results from the subgroups of males and elderly patients in the overall database applies equally to all indications and can be reasonably extrapolated to the fibromyalgia indication. The CHMP agreed that in spite of the low numbers, there not appear to be signal of an increased risk in these two subgroups of patients associated with duloxetine treatment.

Regarding pregnancies, a total of 77 pregnancies possibly exposed to duloxetine have been reported during all the indications clinical development of the product. Five out of 77 where reported during fibromyalgia studies. At least 27% of the pregnancies with known outcomes resulted in an unexpected or undesirable result (ectopic pregnancy, abortion, preterm delivery with fetal demise, congenital abnormalities). The CHMP asked the MAH to further discuss it. The MAH agreed with the CHMP that a relationship between duloxetine and miscarriage or abnormalities cannot be ruled out. In addition the MAH mentioned that the current SPC wording on pregnancy appropriately warns the prescribing physician of the need to carefully balance the benefit versus the potential risk before exposing a pregnant woman to duloxetine.

The CHMP concluded that given the low number of reported events and the absence of a specific pattern of the reported miscarriage or abnormalities there seems currently not to be a safety concern. However, fibromyalgia female patients represent a relevant target population at risk of drug exposure during pregnancy.

Conclusions

The overall safety conclusion is that the size of the safety database is considered adequate, and the exposure to duloxetine has been adequately summarised by the MAH. Given the pharmacological properties of duloxetine there is nothing unexpected in the AE profile. Though no specific safety concerns have been detected in fibromyalgia patients, long therapy with duloxetine may be associated with potentially long-term safety concerns, mainly in relation to the high prevalence of co morbid depression in this population. For these reasons only a relevant efficacy assessment could support the potential risks of a non trivial long term treatment.

4. Risk Management Plan

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

5. Conclusions and Benefit / Risk Assessment

The short-term efficacy of duloxetine in fibromyalgia patients was evaluated in 4 placebo controlled studies in which doses of duloxetine ranging from 20 mg to 120 mg per day were tested. After the evaluation of the initially submitted data, the CHMP considered that although some degree of effect could be observed across short-term studies, the robustness of the efficacy database was insufficient to conclude a relevant effect of duloxetine in patients with fibromyalgia.
The MAH was requested to provide additional analyses allowing to further exploring whether the modest effect could be regarded as consistently demonstrated and clinically relevant for the intended target population.

The responses to the CHMP concerns provided by the MAH did not alleviate the CHMP concerns regarding the short-term efficacy of duloxetine in the treatment of fibromyalgia. The estimation of the effect size is not reassuring, and as for published data, it is at best rather smaller than the one observed for other therapies. This applies not only to pain, but also to functional evaluations.

It is accepted that the HAMD might not be an optimal tool to discriminate the differential effect of duloxetine on fibromyalgia, but the fact is that the data show a clear link between drug effect and mood. Whether this is not the case cannot be proven with the submitted data.

Finally, despite the fact that the data does not allow to conclude that there are a differential effect according to patient's origin, the fact is that the only study including EU patients was negative. Whether this might have been influenced by different background therapy strategies need to be confirmed.

All these concerns, reinforces the CHMP view that a clear demonstration of the efficacy of duloxetine in the short-term therapy of fibromyalgia in a patient population that is relevant for the EU setting is still lacking.

Though no specific safety concerns have been detected in fibromyalgia patients, long therapy with duloxetine may be associated with potentially long-term safety concerns, mainly in relation to the high prevalence of co morbid depression in this population. For these reasons only a relevant efficacy assessment could support the potential risks of a non trivial long term treatment.

In conclusion, the B/R on duloxetine for the fibromyalgia indication remains negative.

6. Conclusion

On 23 October 2008 the CHMP considered this Type II variation not to be acceptable .