CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-148

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA 22-148	**Submission Date: August 14, 2007**
Type:	Standard NDA
Generic Name:	Duloxetine hydrochloride (LY248686)
Brand Name:	Cymbalta Delayed Release Capsules
Drug Class:	Selective serotonin and norepinephrine reuptake inhibitor (SSNRI)
Indication:	Fibromyalgia
Dosage Form:	Delayed Release Capsules
Strengths:	20 mg, 30 mg and 60 mg
Route of Administration:	Oral
Dosing regimen:	60 mg QD
Applicant:	Elli Lilly
OCP Division:	DCP2
Clinical Division:	DAARP (OND)
Reviewer:	Emmanuel O. Fadiran, R.Ph., Ph.D.
Team Leader:	Suresh Doddapeneni, Ph. D.
PM Team Leader:	Jogarao V. Gobburu, Ph. D.

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1 EXECUTIVE SUMMARY

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology / Division of Clinical Pharmacology-2 (OCP / DCP-2) has reviewed NDA 22-148's Clinical Pharmacology information submitted on August 14, 2007 and finds it acceptable.

1.2 PHASE IV COMMITMENTS

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Cymbalta® (Duloxetine hydrochloride) is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) approved for the treatment of major depressive disorder (MDD), generalized anxiety disorder (GAD), and diabetic peripheral neuropathic pain (DPNP). The current submission is seeking approval for the ——— of fibromyalgia (FM). FM is a chronic pain syndrome (>3 months) of unknown etiology that occurs in approximately 0.2-3.3% of the general population, with more women (estimated at 1.0-10.5%) than men (0% - 1.6%) diagnosed with FM.

To support the efficacy and safety of Cymbalta® for ——— of FM the Sponsor has submitted the results of 5 clinical studies. Four of the studies were placebo-controlled studies (HMBO, HMCA, HMCJ, and HMEF) and 1 was a long-term uncontrolled safety study (HMEH). Study HMBO is a Phase 2 fixed-dose efficacy study that compared duloxetine 60 mg twice daily (BID) with placebo. Study HMCA, Study HMCJ, and Study HMEF were all Phase 3 placebo-controlled studies. The primary objective of these studies was to assess the efficacy of duloxetine on the reduction of pain severity as measured by the average pain item of the Brief Pain Inventory (BPI) in patients with FM with or without MDD (doses ranging from 60 mg once daily (QD) to 120 mg QD), after 3 months of therapy in Study HMCA and Study HMCJ, and after 6 months of therapy in Study HMEF. Both Study HMCJ and Study HMEF employed a co-primary measure, the Patient's Global Impressions of Improvement (PGI-Improvement) scale, to assess patient-reported improvement. Study HMEH was a 1-year safety and tolerability study consisting of an 8-week open-label period, followed by a 52-week double-blind, randomized period. Statistically significant efficacy was demonstrated only in Study HMCA and Study HMCJ.

Sparse plasma samples were obtained in Study HMEF and pooled with data from previous studies to enable identification of covariates because demographic distribution of the patients in HMEF consisted of mainly nonsmoking Caucasian females. Duloxetine PK 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 1). The results from this population PK analysis are consistent with prior results with ethnic origin being the only additional

significant covariate. Duloxetine pharmacokinetics are similar in healthy subjects and in patients with MDD, SUI, DPNP, or FM. The results of the analysis are summarized below.

- The PK of duloxetine were adequately described by a one compartment model with large interpatient variability (60% to 100%).
- The PK of duloxetine in MDD, SUI, DPNP, and FM patients are similar.
- Body weight, disease condition and dosing regimen did not have any statistically significant effect on duloxetine PK.
- Sex, smoking status, age, ethnic origin, and dose had a statistically significant effect on duloxetine PK. Women and nonsmokers have lower duloxetine oral clearance (CL/F) relative to men and smokers, respectively. Typically, women had 64% higher average duloxetine concentrations at steady state ($C_{av,ss}$) than males receiving the same dose of duloxetine. Similarly, nonsmokers had nearly 43% higher $C_{av,ss}$ than smokers 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. 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. Specific dose recommendations for duloxetine based upon sex, smoking status, age, dose, or ethnic origin are not warranted because the effect of these covariates are small relative to the magnitude of interpatient variability,

Table 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

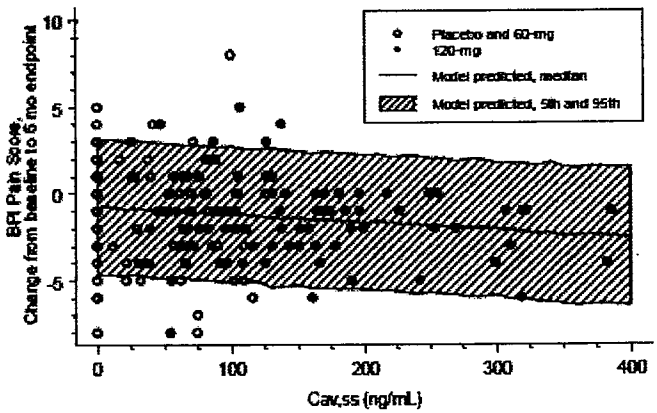
[c] CL/F = 45.1 × Exp[-0.00446 × Dose]

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

[e] V/F (Hispanics) = 814 × [1 + 1.02]

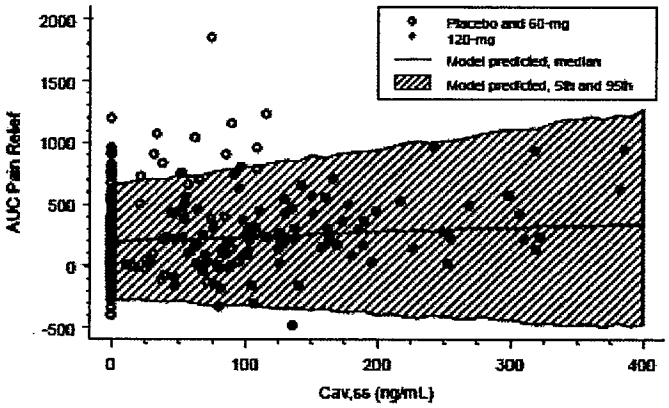
A PK-PD relationship was explored between the baseline-to-endpoint change scores for the BPI average pain score and endpoint of PGI-Improvement during the 6-month acute therapy phase in Study HMEF. Linear, Emax and logistic models were examined to investigate the relationship between Cav,ss and the efficacy endpoints. The effect of duloxetine Cav,ss on change in BPI pain score from baseline to endpoint and on AUC pain relief was characterized by a linear PK-PD model (Figures 1 and 2). The value of the slope suggests that the effect of duloxetine Cav,ss on change in BPI pain score is very small. There did not appear to be an effect of duloxetine Cav,ss on 30% or 50% reduction in BPI pain score (Figure 3). The probability of a patient reporting an improvement on PGI-Improvement score increased with increasing duloxetine Cav,ss, thus suggesting that increasing the dose for an individual patient may increase the probability of achieving improvement on PGI-I score (Figure 4).

Figure 1. The relationship between duloxetine Cav,ss and the BPI pain score change from baseline to endpoint (6 month).



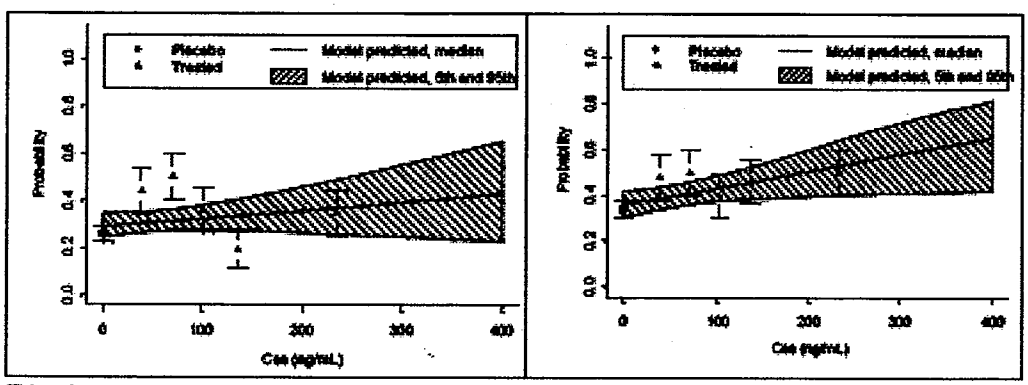
Number of patients treated with placebo, 60 mg and 120 mg were 168, 39 and 92, respectively. For patients treated with duloxetine, only those with available pharmacokinetic data were included.

Figure 2. The relationship between duloxetine Cav,ss and AUC pain relief at 6 month.



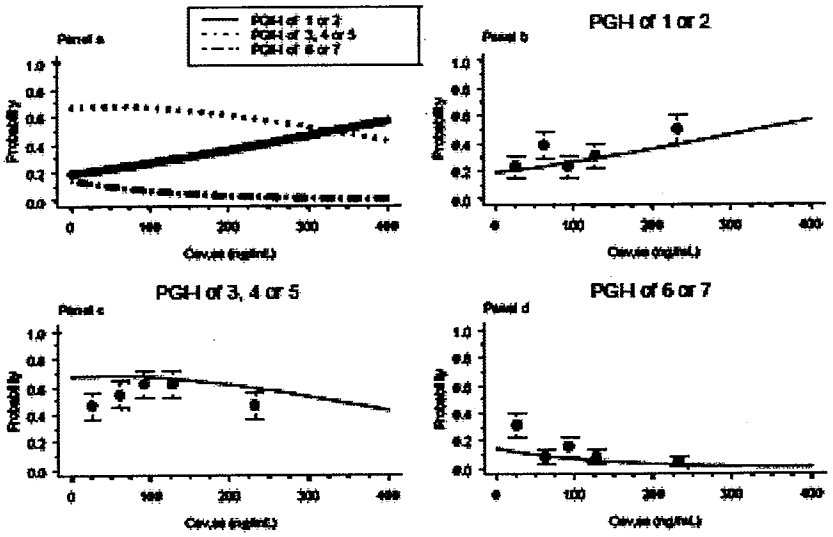
Number of patients treated with placebo, 60 mg and 120 mg were 168, 39 and 92, respectively. For patients treated with duloxetine, only those with available pharmacokinetic data were included.

Figure 3. Comparison of the observed and model predicted probability of achieving 30% (left panel) or 50% (right panel) reduction in pain score from baseline to endpoint (6 month) as a function of increasing duloxetine Cav,ss.



Triangles represent the mean Cav,ss grouped by quantiles (breakpoints at quantiles 0, 20, 40, 60, 80, 100 corresponded to 11.7, 56.5, 86.8, 111, 167, and 386 ng/mL, respectively). Number of patients treated with placebo, 60 mg or 120 mg were 168, 39 and 92, respectively

Figure 4. Model predicted probability of a patient reporting a specific PGI- improvement score as a function of patient's steady state concentration of duloxetine (Cav,ss).



Abbreviations: PGI-I = Patient's Global Impressions of Improvement.
Panel a shows the model predicted probability of a patient reporting a specific PGI-I score. Panels b, c, and d compare the model predictions with the observed data. Lines represent model predictions and solid circles represent observed data. Solid circles represents the mean Cav,ss grouped by quantiles (breakpoints at quantiles 0, 20, 40, 60, 80, 100).

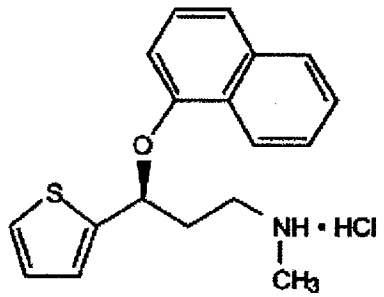
2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the general attributes of duloxetine hydrochloride?

Cymbalta® (duloxetine hydrochloride) is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Its chemical name is (+)-(*S*)-*N*-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride. The empirical formula is $C_{18}H_{19}NOSHCl$, which corresponds to a molecular weight of 333.88. The structural formula is shown in Figure 5.

Figure 5: Duloxetine hydrochloride Structural Formula



Duloxetine hydrochloride is a white to slightly brownish white solid, which is slightly soluble in water.

FORMULATION:

Each capsule contains enteric-coated pellets of 22.4, 33.7, or 67.3 mg of duloxetine hydrochloride equivalent to 20, 30, or 60 mg of duloxetine, respectively. These enteric-coated pellets are designed to prevent degradation of the drug in the acidic environment of the stomach. Inactive ingredients include FD&C Blue No. 2, gelatin, hypromellose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate. The 20 and 60 mg capsules also contain iron oxide yellow.

INDICATION (as per proposed label)

Cymbalta® is indicated for the management of FM ———————

DOSAGE AND ADMINISTRATION (as per proposed label)

60 mg once daily.

2.2 General Clinical Pharmacology

The absorption, distribution, metabolism, and excretion of duloxetine as a molecular entity are described in the current label for Cymbalta® Delayed Release Capsules (updated in November 2007).

To support the efficacy and safety of Cymbalta® for of FM the Sponsor has submitted the results of 5 clinical studies described in Table 2. The summary of the Sponsor's analysis of the results of these studies are shown in Table 3.

Table 2: Description of Fibromyalgia Studies

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.

Table 3: BPI Average Pain and PGI Improvement Score All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: HMBO, HMCA, HMCJ, and HMEF

		BPI Average Pain Score			PGI-I Score	
Study	Treatment Group	Baseline	LSMean Change	p-value[a]	LSMean at Endpoint	p-value[a]
HMBO	Placebo	6.11	-0.67		3.66	
	Duloxetine 60 mg BID	6.13	-1.43	.012	3.18	.034
HMCA	Placebo	6.47	-1.16		3.79	
	Duloxetine 60 mg QD	6.38	-2.39	<.001	3.17	.005
	Duloxetine 60 mg BID	6.36	-2.40	<.001	3.13	.003
HMCJ	Placebo	6.57	-1.38		3.39	
	Duloxetine 20 mg QD	6.74	-1.92	.097	2.85	.009
	Duloxetine 60 mg QD	6.46	-2.00	.022	3.04	.044
	Duloxetine 120 mg QD	6.41	-2.31	<.001	2.89	.004
HMEF	Placebo	6.45	-1.17		3.60	
	Duloxetine 60 mg QD	6.59	-1.50	.209	3.38	.181

Abbreviations: BID = twice daily; BPI = Brief Pain Inventory; HMBO = Study F1J-MC-HMBO; HMCA = Study F1J-MC-HMCA; HMCJ = Study F1J-MC-HMCJ; HMEF = Study F1J-MC-HMEF; LSMean = least-squares mean; PGI-I = Patient's Global Impressions of Improvement; QD = once daily.

[a] p-values are from comparisons with placebo.

Source: LOBPIWO3, LOBPIWA3, LOBPIA11, LOBPIA51, LOPGIWO3, LOPGIWA3, LOPGIA11, LOPGIA41

2.2.1 What are the characteristics of the exposure-response relationship for efficacy?

Population PK Analysis

A total of 235 duloxetine plasma concentrations from 131 patients at 60 mg QD dosing were obtained from Study HMEF. The majority of the patients in Study HMEF were female (73.9%), nonsmokers (78.9%), and Caucasian (77.9%). Population PK analysis was conducted using PK data from study HMEF only; however, during covariate identification step no significant covariates were identified. Therefore, the PK data from Study HMEF was pooled with existing PK dataset for duloxetine to characterize the PK data from Study HMEF.

Duloxetine PK 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 4).

Table 4: PK 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
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Residual Error				
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[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]

This analysis showed that gender, smoking status, age, duloxetine dose (all identified in previous analyses) and ethnic origin (not identified in previous analyses) had a statistically significant effect on duloxetine's PK.

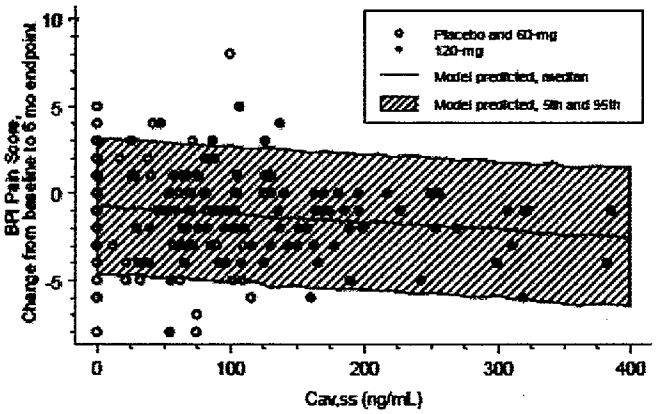
Duloxetine is primarily metabolized by CYP1A2 enzyme and to a lesser extent by CYP2D6 enzyme. The expression and activity of CYP1A2 are affected by gender and smoking. Higher CYP1A2 activity in males may lead to a greater extent of metabolism of duloxetine resulting in lower duloxetine bioavailability noted in males compared to females. The lower duloxetine bioavailability noted in smokers compared to nonsmokers may be explained by increase in the expression of CYP1A2 by smoking. The decrease in CL/F of duloxetine with increasing dose may be due to the moderate inhibition of CYP2D6 and therefore its own metabolism with increasing dose. Despite the statistical significance, the combined effects of all the 5 covariates minimally decreased the interpatient variability in CL/F and V/F from 66.5% and 123% in the base model (without covariates) to 58.9% and 96.6% in the final model (with covariates). Additionally the magnitude of the covariate effects is relatively small compared to the large interpatient variability. Therefore, dose adjustments based on these observed covariate effects are not warranted.

PK-PD Relationship

Exposure-response relationship analysis was conducted between average steady state duloxetine concentration (Cav,ss) and the BPI average pain score and PGI-Improvement during the 6-month acute therapy phase in Study HMEF. Linear, Emax and logistic

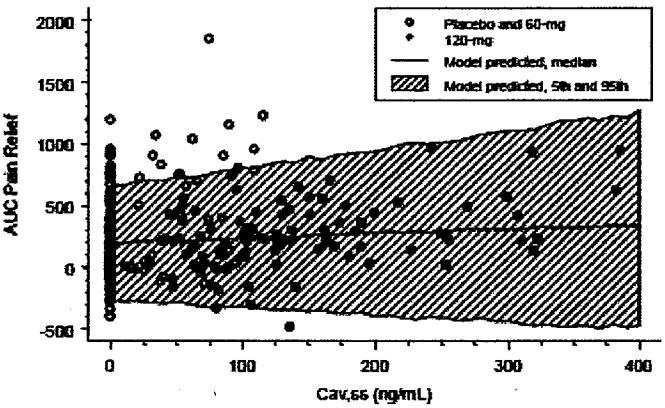
models were examined to investigate the relationship between duloxetine Cav,ss and the efficacy endpoints. The magnitude of the effect of duloxetine Cav,ss on change in BPI average pain score and AUC pain relief is small (Figures 6 and 7). This may be due to the high interpatient variability in duloxetine Cav,ss as well as high interpatient variability in response for a given duloxetine Cav,ss. The relationship between duloxetine Cav,ss and probability of achieving 30% or 50% reduction in pain suggests that the probability of achieving 30% or 50% reduction in pain score is similar to that observed in the placebo or independent of duloxetine Cav,ss (Figure 8). Results of the PGI-Improvement score analyses showed that increase in duloxetine concentration increases the probability that a patient would report an improvement on PGI-Improvement score after duloxetine treatment (Figure 9).

Figure 6. The relationship between duloxetine Cav,ss and the BPI pain score change from baseline to endpoint (6 month).



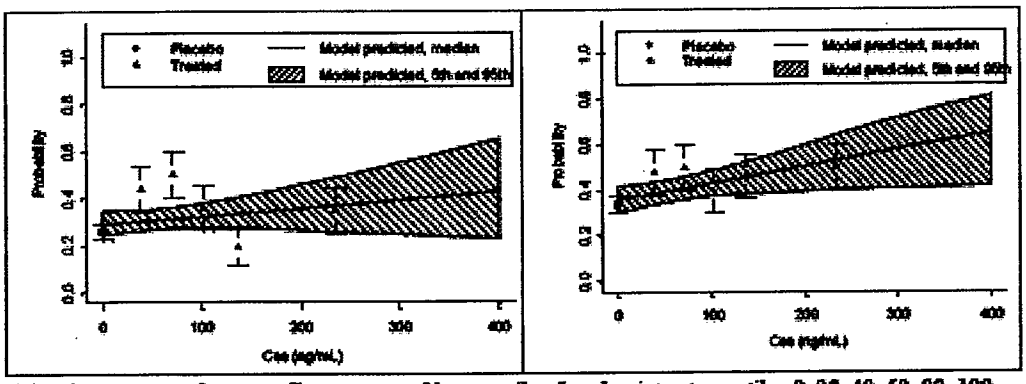
Number of patients treated with placebo, 60 mg and 120 mg were 168, 39 and 92, respectively. For patients treated with duloxetine, only those with available pharmacokinetic data were included.

Figure 7. The relationship between duloxetine Cav,ss and AUC pain relief at 6 month.



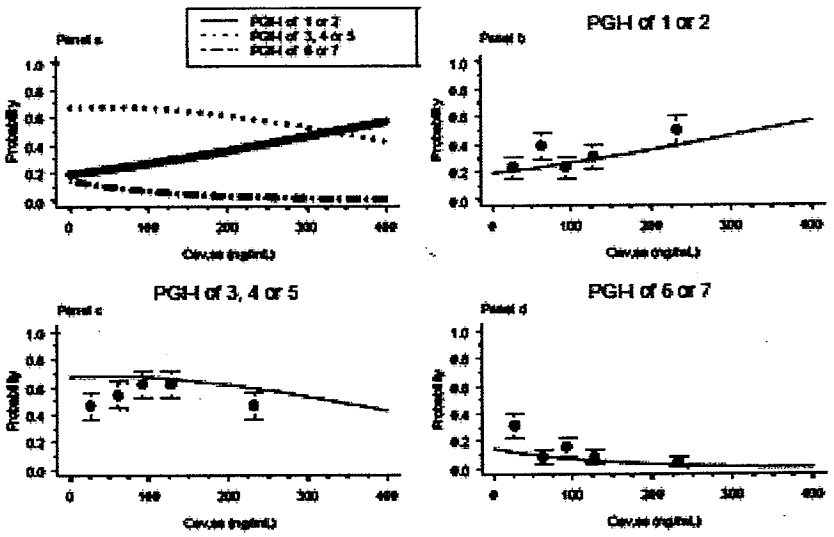
Number of patients treated with placebo, 60 mg and 120 mg were 168, 39 and 92, respectively. For patients treated with duloxetine, only those with available pharmacokinetic data were included.

Figure 8. Comparison of the observed and model predicted probability of achieving 30% (left panel) or 50% (right panel) reduction in pain score from baseline to endpoint (6 month) as a function of increasing duloxetine Cav,ss.



Triangles represent the mean Cav,ss grouped by quantiles (breakpoints at quantiles 0, 20, 40, 60, 80, 100 corresponded to 11.7, 56.5, 86.8, 111, 167, and 386 ng/mL, respectively). Number of patients treated with placebo, 60 mg or 120 mg were 168, 39 and 92, respectively

Figure 9. Model predicted probability of a patient reporting a specific PGI- improvement score as a function of patient's steady state concentration of duloxetine (Cav,ss).



Abbreviations: PGI-I = Patient's Global Impressions of Improvement.
Panel a shows the model predicted probability of a patient reporting a specific PGI-I score. Panels b, c, and d compare the model predictions with the observed data. Lines represent model predictions and solid circles represent observed data. Solid circles represents the mean Cav,ss grouped by quantiles (breakpoints at quantiles 0, 20, 40, 60, 80, 100).

2.3 Analytical Section

Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Yes. Plasma samples obtained during this study were analyzed for duloxetine using a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) method at [redacted] The lower limit of quantification was 0.5 ng/mL, and the upper limit of quantification was 100 ng/mL. Samples above the upper limit of quantification were diluted and reanalyzed to yield results within the calibrated range. During validation, the interassay accuracy (absolute % relative error) was ≤3.58% and the interassay precision (% relative SD) was ≤4.32%.

3. DETAILED LABELING RECOMMENDATIONS

There are no Clin Pharm related labeling changes proposed either by the sponsor or this reviewer.

4. APPENDICES

4.1 POPULATION PK AND PK-PD ANALYSIS

Introduction

The population PK of duloxetine have been well characterized in patients with depression (MDD), stress urinary incontinence (SUI), diabetic neuropathic pain (DPNP), and although gender, smoking status, duloxetine dose, and age were found to be significant covariates, the large intersubject variability (approximately 50% for CL/F) in duloxetine PK does not justify dose adjustments for these patient factors. A total of 235 duloxetine plasma concentrations from 131 patients at 60 mg QD dosing were obtained from Study HMEF for the purpose of population PK analysis of duloxetine in fibromyalgia (FM) patients. The majority of the patients in Study HMEF were female (73.9%), nonsmokers (78.9%), and Caucasian (77.9%).

PK Objectives

- To evaluate steady state duloxetine concentrations in patients with FM using descriptive and graphical PK analysis
- To characterize the PK of oral duloxetine in patients with FM using population PK modeling
- To estimate the inter- and intra-subject variability of the duloxetine PK in patients with FM
- To identify potential patient factors that may influence duloxetine PK
- To obtain individual post-hoc estimates for AUC_{ss} and $C_{avg,ss}$ for exploratory PK-PD analysis.

PK-PD Objectives

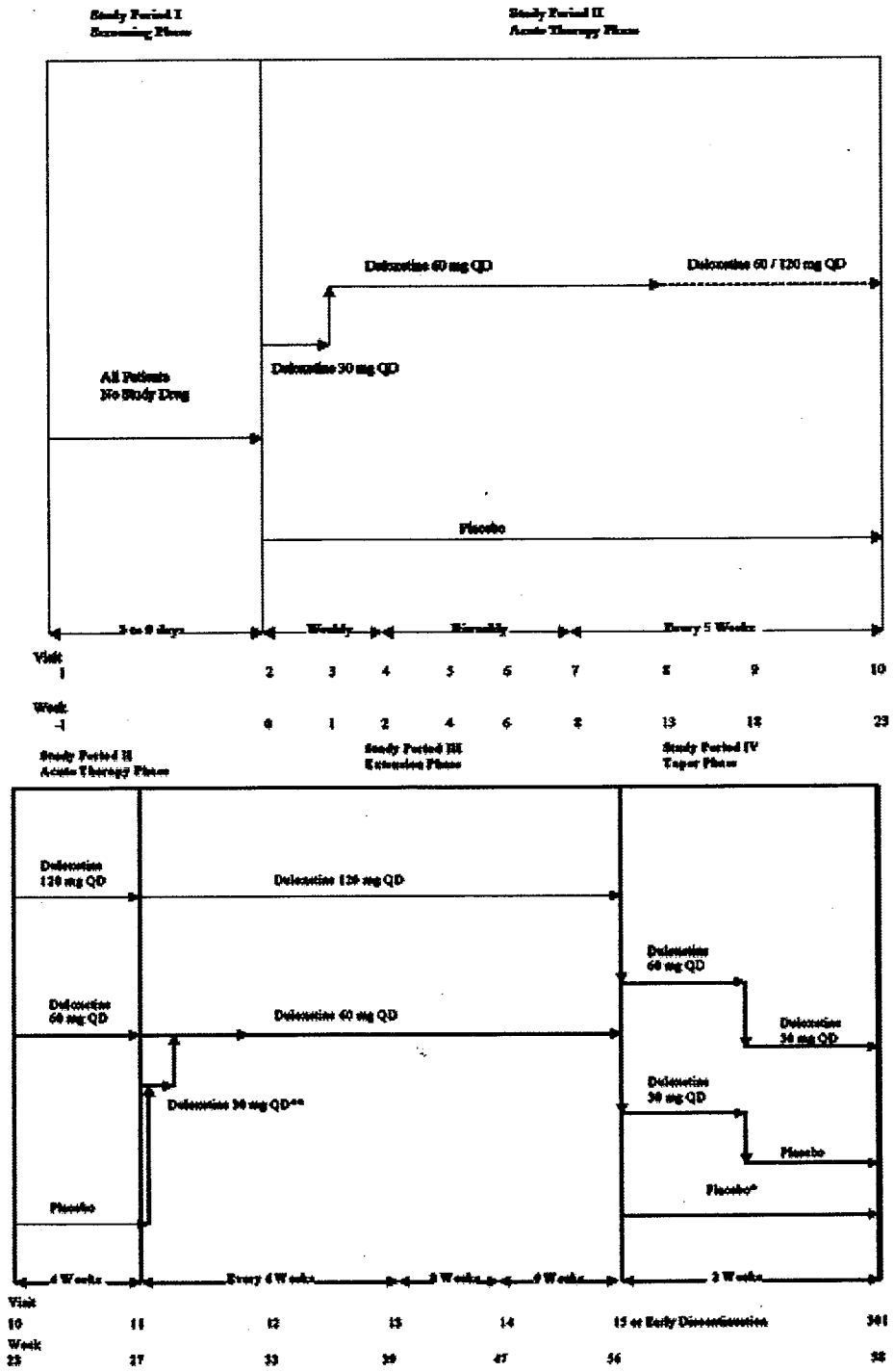
- To investigate the relationship between duloxetine exposure (AUC_{ss} and/or $C_{avg,ss}$) and the following primary efficacy endpoints:

1. Brief Pain Inventory (BPI) average pain score
2. Patient's Global impressions of Improvement (PGI) score.

Study and Sampling Information

Study HMEF was a phase 3, parallel, double-blind, placebo-controlled study of approximately 320 patients. Figure 1 illustrates the study design. Patients who meet entry criteria in the screening phase were randomly assigned to duloxetine 60 mg once daily (QD) or placebo. Following the screening phase, patients were treated for 6-months during the acute therapy phase. Patients randomized to the duloxetine therapy group received duloxetine 30 mg QD for 1 week followed by 60 mg QD for 12 weeks. At Visit 8, patients who had not had a 50% reduction in BPI average pain were increased to a dose of 120 mg QD. Two blood samples, 1 each at Visit 5 and Visit 7, were collected from each patient for the determination of duloxetine concentrations in plasma.

Figure 1. Illustration of study design for Protocol HMEF.



Abbreviations: QD = once daily.

*Placebo-treated patients will continue on placebo during early discontinuation.

**The duration on 30mg will last one week.

Population PK Dataset Preparation

A PK dataset containing duloxetine plasma concentration, sampling time, dose, dosing time, and demographic information from Study HMEF was combined with a previous pharmacokinetic dataset (F1J-LC-HMAQ [HMAQ] Population Pharmacokinetics Report) containing similar information to produce a meta dataset for population PK modeling. The previous dataset was created from Study HMAQ (patients with MDD), HMAU (patients with MDD), HMAV(a) (HMAV(a)) (patients with DPNP), and SAAW (patients with stress urinary SUI). Table 1 shows the demographics for patients included in the population PK analysis.

Dataset Assembly and Editing

Duloxetine concentration time data were combined with dosing information, covariate data, and the corresponding time-of-event data using SAS to produce the NONMEM dataset for population PK analysis. Missing data were handled according to the recommendations in the Population PK Guidance. Data records that were excluded from the analysis were marked by placement of a "C" as the first character in the record. The following distinctions were made for concentration records omitted from the analysis:
1) records omitted due to missing dosing information or sampling date/time information,
2) non-quantifiable concentrations, and
3) concentration outliers.
Data-visualization techniques (VIVID, S-Plus or Sigmaplot) were used to search for patterns in missing values that could significantly bias the analyses.
Dependent variable values missing a corresponding time from last dose were excluded from the analysis. Samples were collected at steady-state; therefore no concentrations below the quantitation limit (BQL) of the assay were expected. Any concentrations that were BQL in the dataset was confirmed with the bioanalytical lab and treated as missing values for the analysis.
Missing values of independent variables (patient characteristic data) were treated as follows:
1. Data were imputed, within a patient, using the last-observation-carried forward (LOCF) method.
2. Missing baseline values of independent variables were imputed backward.
3. When all values for a patient were missing, then the mean, median or mode value (as appropriate for that data element) for the treatment group were used as the imputed value.

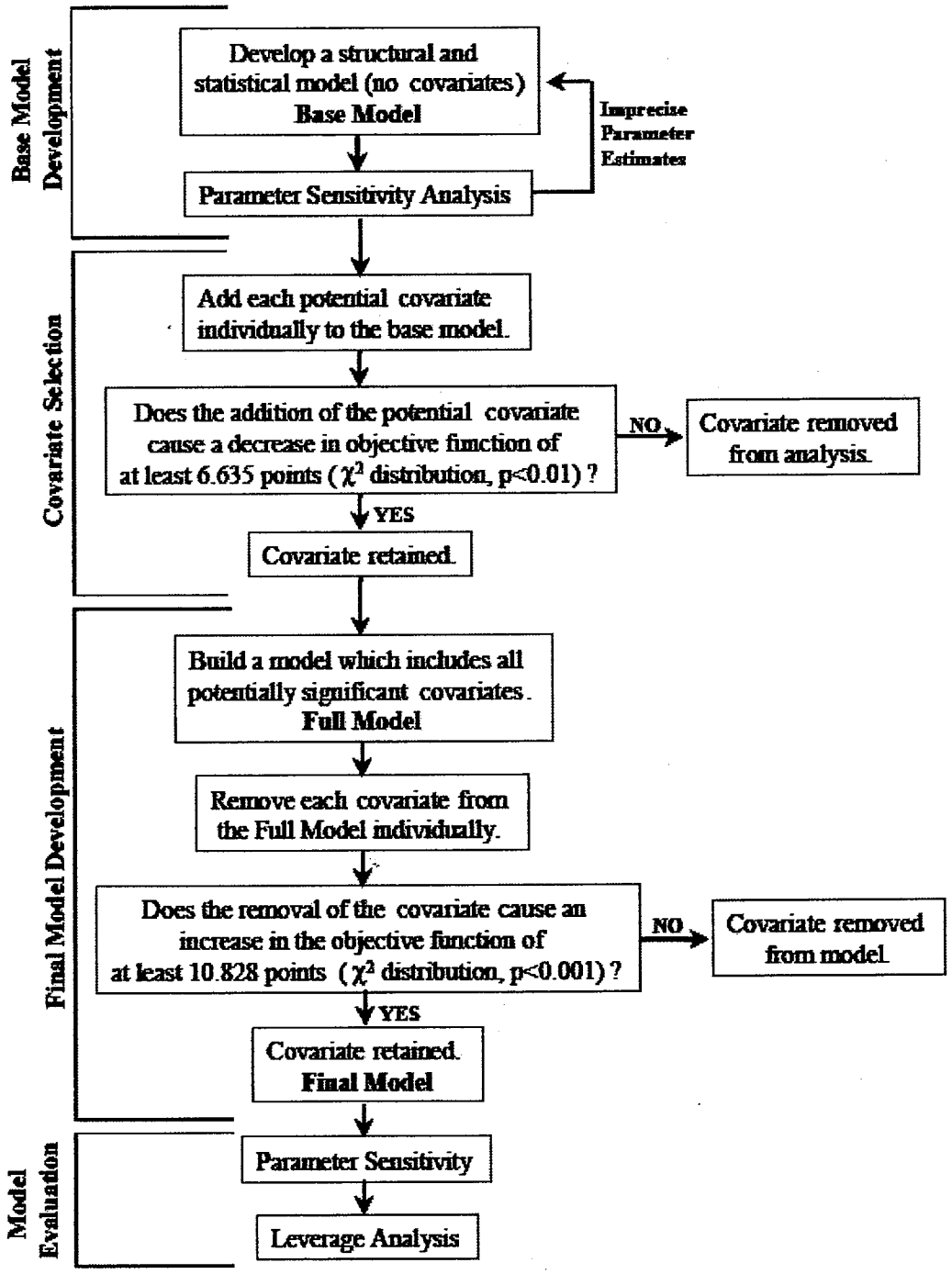
The dependent variable values deemed to be outliers were excluded from the analysis ("commented out") during model building. Excluded values were added back into the data set after the final model was established. Parameter estimates based on inclusion of the outliers were compared to those obtained without the outliers during model building. All outliers excluded from the analysis, either during model building or in the final model analysis, were identified in the study report along with a rationale for their exclusion.

Population Modeling Strategy

A population PK model to characterize the time course of duloxetine plasma concentrations following oral administration of duloxetine was developed using NONMEM, Version V. The first order conditional estimation (FOCE) method with

interaction estimation was used. The modeling methodology included a stepwise approach of developing a base model, determining potential patient factors and evaluation of the final model (Figure 2).

Figure 2. General process for PK modeling.



Base Model Development
Pharmacokinetics of oral duloxetine has previously been characterized by a one-compartmental model (HMAQ Population Pharmacokinetic Report). Therefore, a one-compartment pharmacokinetic model with parameters such as absorption rate constant (Ka), oral clearance (CL/F) and oral volume of distribution (V/F) was initially tested.

Three inter-patient variability models (Equation 1) were tested: η on CL/F, η on V/F and η on CL/F and V/F with covariance (omega block).

$P = \Theta 1 \cdot \exp(\eta)$ ----------Equation 1

where P is the individual parameter estimate (CL/F or V/F), Θ_1 represents the typical or population value of the parameter and η is a random variable with a mean of 0 and variance of ω^2.

The difference between model predicted duloxetine plasma concentration and the observed concentration was modeled using the residual error model. The 2 residual error models evaluated were proportional (Equation 2) and combined additive and proportional (Equation 3).

$Cij = IPRED \cdot (1 + ERR)$ ----------Equation 2
$Cij = IPRED + (IPRED^2 + \Theta^2)^{0.5} \cdot ERR$ ----------Equation 3

where Cij is the predicted jth duloxetine concentration in the i^{th} patient, IPRED is the model predicted duloxetine concentration in the individual, ERR is a random variable with a mean of zero and variance of σ^2 and Θ is the ratio of the additive and proportional variances. The estimated σ^2 accounts for error in the bioanalytical assay, sample collection errors and model misspecification.

Parameter sensitivity analyses were performed on various base models and a final base model was selected for identification of potential significant covariates.

Covariate Model Development
The effects of continuous covariates (body weight, age, dose) on CL/F, V/F or Ka were tested using equations 4 to 6 (proportional, exponential and power models) while those of categorical covariates (gender, ethnic origin, smoking status, disease condition, dosing regimen) were tested using equation 7 (categorical model) below.

$P = \Theta_1 \cdot [1 + \Theta_2 \cdot (COV\text{-}MED)]$ ----------Equation 4
$P = \Theta_1 \cdot EXP[\Theta_2 \cdot (COV\text{-}MED)]$ ----------Equation 5
$P = \Theta_1 \cdot (COV/MED)^{**}\Theta_2$ ----------Equation 6
$P = \Theta_1 \cdot (1 + \Theta_2 \cdot IND)$ ----------Equation 7

where P is the individual parameter estimate, Θ_1 represents a typical value of a parameter, Θ_2 represents the effect of a covariate, COV is the value of the covariate,

MED is the median value of a covariate, IND is an indicator variable with a value of either 0 or 1 assigned for values of a categorical covariate (for example, nonsmoker = 0 and smoker = 1).
A covariate was considered to be potentially significant if the objective function of the base model with the covariate was reduced by 6.635 ($p<0.01$). If a covariate was found to be significant on both CL/F and V/F, then it was tested for significance on duloxetine bioavailability F. For example, gender, smoking status, and dose were also evaluated for their influence on F.

Final Model Development
All potentially significant covariates identified were added in combination to the base model to establish a full model. Each covariate was removed (1 covariate at a time) from the full model. When the removal of a covariate from the full model resulted in a significant increase of the minimal objective function (≥10.828, $p<0.001$), that covariate was retained in the final model.

Final Model Evaluation
Parameter sensitivity analysis and leverage analysis were applied to evaluate the robustness of the final model.

PK-PD Modeling
The Cav,ss in individual patients who remained at 60 mg duloxetine dose was obtained from the posthoc estimates of the final PK model. The individual Cav,ss were utilized to examine the relationship with the Brief Pain Inventory (BPI)-average pain score and Patient's Global Impressions of Improvement (PGI-Improvement) which were the primary efficacy endpoints for the study.

PK-PD models were investigated using S-Plus program (Version 6.2, Insightful Corp) and NONMEM (Version V, Globomax).

BPI-Average Pain Score
The relationship between Cav,ss and response (change from baseline to endpoint in average pain score or area under the curve [AUC] of pain relief) in individual patients was examined using graphical and model-based approach. Linear and Emax models were investigated to determine the exposure-response relationship for duloxetine.

Linear model

$$\textbf{Response} = R_{placebo} - a \cdot Cav,ss \quad \text{————————Equation 8}$$

where Response = change from baseline to endpoint (6 month) in average pain score or $AUC_{pain\ relief}$; $R_{placebo}$ = response in patients treated with placebo; a = the slope of the response versus Cav,ss line; Cav,ss = predicted average steady state duloxetine concentration in individual patient receiving either 60 mg or 120 mg.

Emax model

$$\text{Response} = R_{placebo} - \frac{R_{max} \bullet Cav,ss}{Cav,ss + EC_{50}}$$ .....Equation 9

where Response = change from baseline to endpoint average pain score or $AUC_{pain\ relief}$; $R_{placebo}$ = response in patients treated with placebo; R_{max} = maximum response; Cav,ss = predicted average steady state duloxetine concentration in individual patient receiving either 60 mg QD or 120 mg QD; EC50 = average steady state duloxetine concentration that produces 50% of R_{max}.

Logistic model : The relationship between the proportion of patients achieving a 30% reduction (or 50% reduction) in average pain score from baseline to endpoint (6 month) and Cav,ss were investigated using logistic regression models (Equation 10).

$$P = \frac{e^{a+b\times Cav,ss}}{1+e^{a+b\times Cav,ss}}$$ ----------Equation 10

where P is the probability of observing a 30% (or 50%) reduction in average pain score from baseline to endpoint; e = 2.718; a and b are the parameters of the model, a gives the probability when Cav,ss = 0. The odds ratio [= exp(b)] is a measure of fold increase in observing a 30% (or 50%) reduction in average pain score from baseline to endpoint per 1 ng/mL increase in Cav,ss.

PGI-Improvement

The relationship between proportion of patients reporting a particular PGI-Improvement score (1 to 7) at the end of 6 month acute phase and Cav,ss was examined using the proportional odds model (Equation 11) for ordered categorical response. The PGI-Improvement scores of 1, 2, 3, 4, 5, 6, 7 were categorized into 3 groups: group 1 containing patients with scores of 1 and 2 (very much better and much better); group 2 containing patients with scores of 3, 4 and 5 (a little better, no change and a little worse); and group 3 containing patients with scores of 6 and 7 (much worse and very much worse).

$$P_n = \frac{e^{(A_n)}}{1+e^{(A_n)}}$$

$$A_n = \alpha_n + E \times C_{av,ss}$$ ----------Equation 11

where P_n is the probability of patients in 1 of the 3 groups; n is the group of combined PGI-Improvement scores; α_n is the parameter describing baseline probability for each group of PGI-Improvement scores, E is the effect due to Cav,ss.

Table 1. Baseline Demographics for Patients Included in the PK Modeling (Study HMAQ, Study HMAU, Study HMAV, Study SAAW and Study HMEF)

Demographic	*HMAQ*	*HMAU*	*HMAV*	*SAAW*	*HMEF*	*Total*
n	*473*	*465*	*274*	*555*	*235*	*2002*
N	*142*	*81*	*112*	*128*	*131*	*594*
Age (years)						
Mean±SD	*41.1±10.1*	*43.9±12.9*	*59.5±10.8*	*49.3±8.10*	*50.5±10.0*	*48.8±12.0*
(Min, Max)	*(18.7,62.7)*	*(18.7,70.7)*	*(31.7,84.3)*	*(28.0,64.0)*	*(26.8,82.1)*	*(18.7,84.3)*
Body weight (kg)						
Mean±SD	*82.9±19.2*	*65.3±13.4*	*103±23.5* [a]	*78.0±16.5*	*77.7±16.3*	*82.0±21.4* [b]
(Min, Max)	*(44.5,138.9)*	*(41.0,110.0)*	*(58.1,192.5*	*(50.8,150.3)*	*(49.0-133.0)*	*(41.0,192.5)*
Gender (N)						
Male	*48*	*25*	*69*	*0*	*13*	*155*
Female	*94*	*56*	*43*	*128*	*118*	*439*
Smoking status (N)						
Smoker	*36*	*26* [c]	*17*	*19* [d]	*27*	*125* [e]
Non-smoker	*106*	*54*	*95*	*108*	*104*	*467*
Origin (N)						
Caucasian	*125*	*0*	*97*	*118*	*123*	*463*
Hispanics	*5*	*81*	*7*	*2*	*7*	*102*
African American	*9*	*0*	*3*	*4*	*1*	*17*
Asian	*3*	*0*	*2*	*4*	*0*	*9*
Other	*0*	*0*	*3*	*0*	*0*	*3*
Demographic	***HMAQ***	***HMAU***	***HMAV***	***SAAW***	***HMEF***	***Total***
Indication (N)						
Manic Depressive Disorder	*142*	*81*	*0*	*0*	*0*	*223*
Diabetic Pain Neuropathy	*0*	*0*	*112*	*0*	*0*	*112*
Stress Urinary Incontinence	*0*	*0*	*0*	*128*	*0*	*128*
Fibromyalgia Syndrome	*0*	*0*	*0*	*0*	*131*	*131*
Dosing Regimen						
Dose (mg)	*20, 30, 40, 60*	*20, 40, 60*	*60*	*20, 40*	*60*	-
Regimen	*BID*	*BID*	*QD, BID*	*QD, BID*	*QD*	-

Abbreviations: BID = twice daily; HMAQ = Study F1J-MC-HMAQ; HMAU = Study F1J-MC-HMAU; HMAV = Study F1J-MC-HMAV; HMEF = Study F1J-MC-HMEF; Max = maximum; Min = minimum; n = number of observations; N = number of patients; QD = once daily; SAAW = Study F1J-MC-SAAW; SD = standard deviation.

[a] N = 111.

[b] N = 593.

[c] N = 80.

[d] N = 127.

[e] N = 592.

RESULTS:

Population PK

A total of 235 duloxetine plasma concentrations from 131 patients at 60 mg QD dosing were available from Study HMEF.(Table 1). Figures 3 and 4 respectively show the time course of observed duloxetine concentrations from individual patients in Study HMEF and the distribution of all the duloxetine concentrations available relative to the time from the last dose for PK analysis. Figure 5 shows that the final model adequately describes the population PK data.

The population PK parameters estimated were Ka (0.168 h^{-1}), CL/F (34.5 L/h), V/F (814 L) and half-life of 16.3 h at 60 mg QD (Table 3,). The interpatient variability ranged from 60% to 100% and intrapatient variability was 30%. Body weight, dosing regimen and disease did not influence duloxetine PK. Smoking status and gender had an effect on the bioavailabilty of duloxetine. Dose and age had an effect on CL/F, while ethnic origin had an effect on V/F. The differences in bioavailablity resulted in typical CL/F for a female patient (nonsmoker = 34.5 L/h, smoker = 49.2 L/h) being 40% lower than a male patient (nonsmoker = 56.5 L/h, smoker = 80.5 L/h), and the typical CL/F for a nonsmoking patient being 30% lower than a smoking patient. Thus, on average, females have 64% higher Cav,ss than males receiving the same dose of duloxetine. Similarly, nonsmokers have nearly 43% higher Cav,ss than smokers receiving the same dose of duloxetine. Typically, nonsmoking female patients have Cav,ss nearly 2.3 times the Cav,ss in 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. Given the magnitude of the difference between females and males, smokers and nonsmokers and the large interpatient variability, the effect of gender and smoking status on duloxetine pharmacokinetics are not clinically relevant (Figure 6).

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 Cav,ss, respectively. The decrease in CL/F (Figure 7) of duloxetine with increasing dose may be due to the moderate inhibition of CYP2D6 and therefore its own metabolism with increasing dose.

CL/F decreased with increasing age in the age range of 19 to 84 years. Relative to the median age of 49 years, the Cav,ss are 13% lower in a patient aged 29 years and 17% higher in patient aged 69 years (Figure 8) . The effect of age on CL/F is very small and not clinically relevant.

The V/F (1644 L) in hispanic patients was 2 times the value estimated for non-Hispanics (V/F = 814 L). The lower V/F in Hispanic patients affected the time course of duloxetine concentration at steady state such that the Cmax in Hispanics is 10% lower than in non-Hispanic patients and the Tmax is delayed by 1.5 hours in Hispanics relative to non-Hispanics (Figure 9). Since the Cav,ss is the same for all patients irrespective of their ethnic origin, the effect of ethnic origin is not clinically relevant.
The results of the parameter sensitivity and leverage analyses confirmed the robustness of the final model (Figures 10 & 11, Table 4).

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Figure 5. Goodness of fit plots for the final model. Data from Study HMAQ, Study HMAU, Study HMAV, Study SAAW, and Study HMEF.

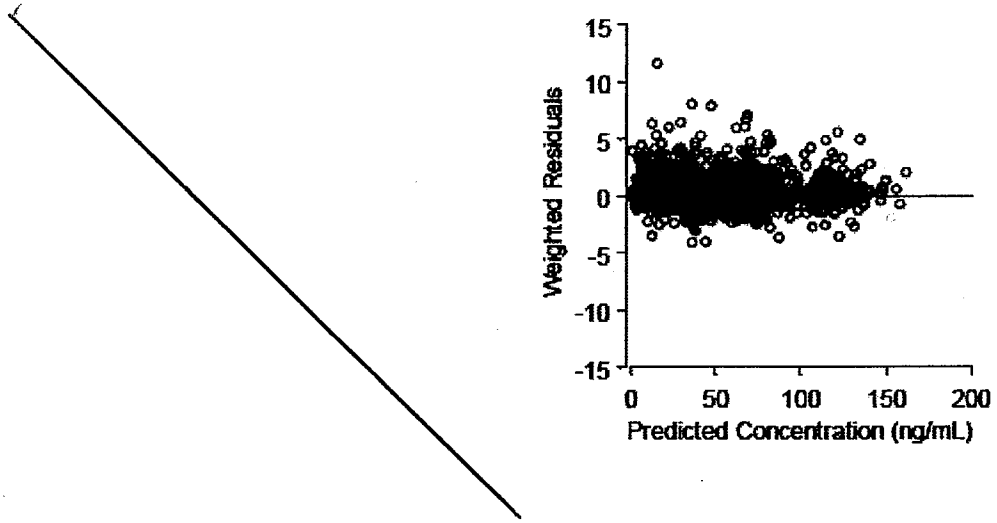


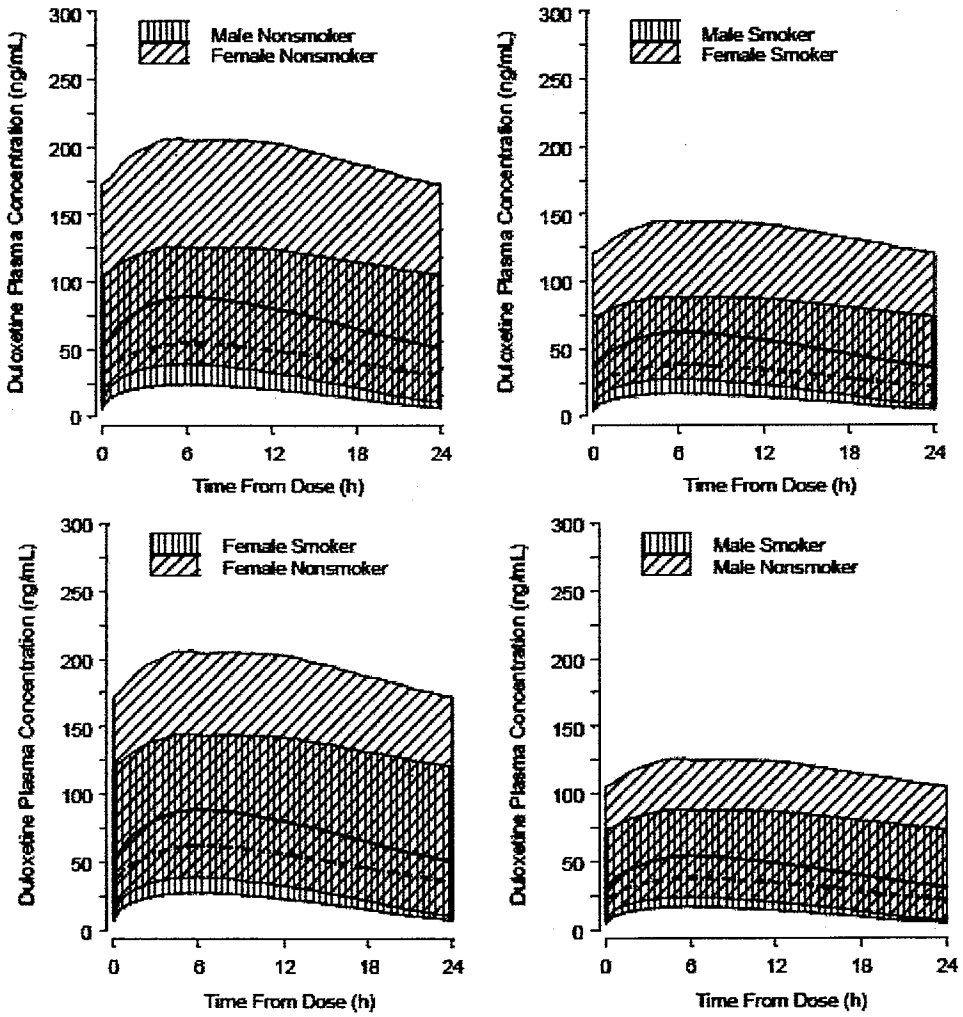
Table 3. PK Parameters for the Final Population Model

	Units	*Estimate*	*%SEE*	*95 % CI*
Pharmacokinetic model				
Effect of smoking on F (Θ5)	-	*-0.298*	*13.9*	*-0.373 – -0.213*
Effect of gender on F (Θ6)	-	*-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 (Θ8)	-	*-0.00725*	*31.7*	*-0.0113 – -0.003026*
Effect of dose on CL/F (Θ9)	-	*-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 (Θ7)	-	*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; SEE = standard error of the estimate; V/F = oral volume of distribution.

Figure 6. GENDER and SMOKING: Predicted effect of gender (top panels) and smoking (bottom panels) on steady state plasma duloxetine concentrations at a 60 mg dose.

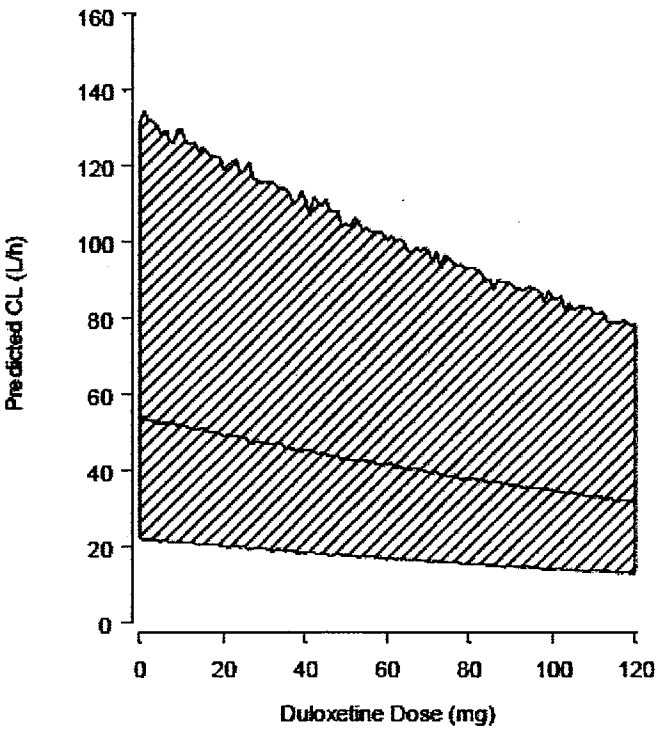
Each panel represents the concentration time profile with the median, 5th and 95th percentiles. Top left panel shows the duloxetine concentration distribution in female (solid line) versus male (dotted line) nonsmokers. Top right panel shows the duloxetine concentration distribution in female (solid line) versus male (dotted line) smokers. Bottom left panel shows the duloxetine concentration distribution in female nonsmokers (solid line) versus smokers (dotted line). Bottom right panel shows the duloxetine concentration distribution in male nonsmokers (solid line) versus smokers (dotted line).



Abbreviations: h = hours.

Note: Predicitions are for 1000 simulated patients at the median age of 49 years.

Figure 7. DOSE: Predicted effect of dose on CL/F. The distribution represents the median, 5th and 95th percentiles.



Note: Predicitions are for 10,000 simulated nonsmoking females at the median age of 49 years.

Figure 8. AGE: Effect of age on a typical plasma duloxetine concentration time profile. Lines represent the minimum, 5th, median, 95th and maximum age from the analysis dataset.

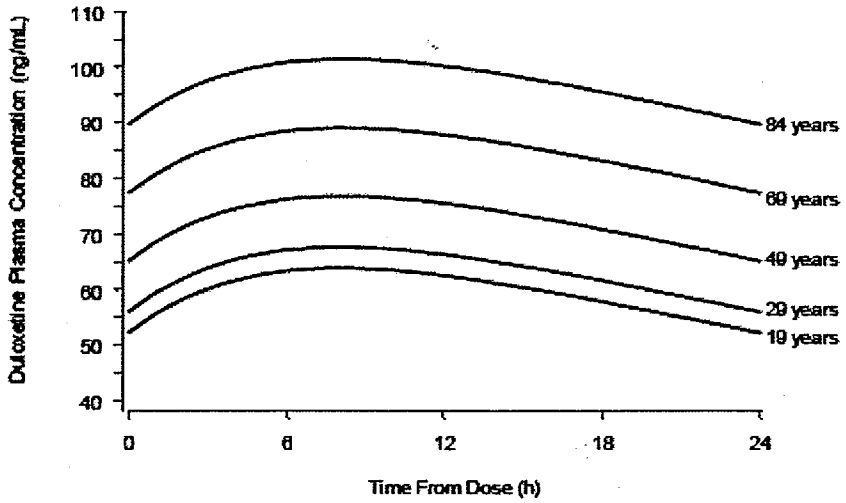
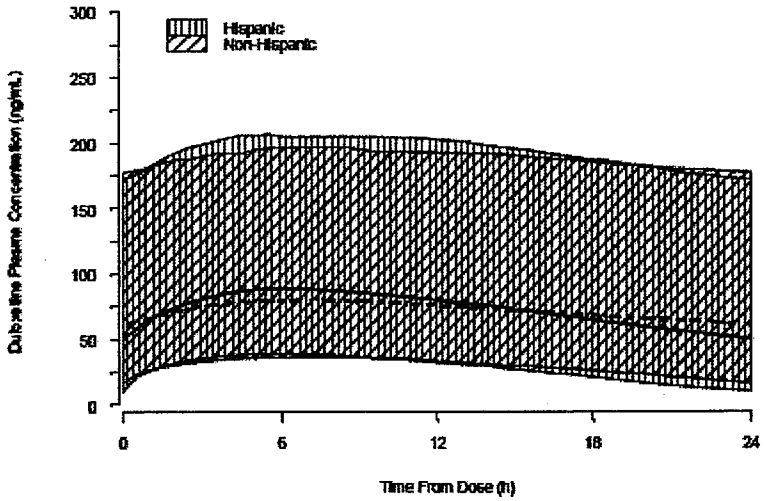


Figure 9. ETHNIC ORIGIN: Predicted effect of Hispanics (dotted line) versus non-Hispanics (solid line) on plasma duloxetine concentration time profiles with the median, 5th and 95th percentiles.



Note: Predicitions are for 1000 simulated nonsmoking females at the median age of 49 years.

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Figure 10. Sensitivity Plots for the Final Model: Θ1, Θ2, Θ3, Θ

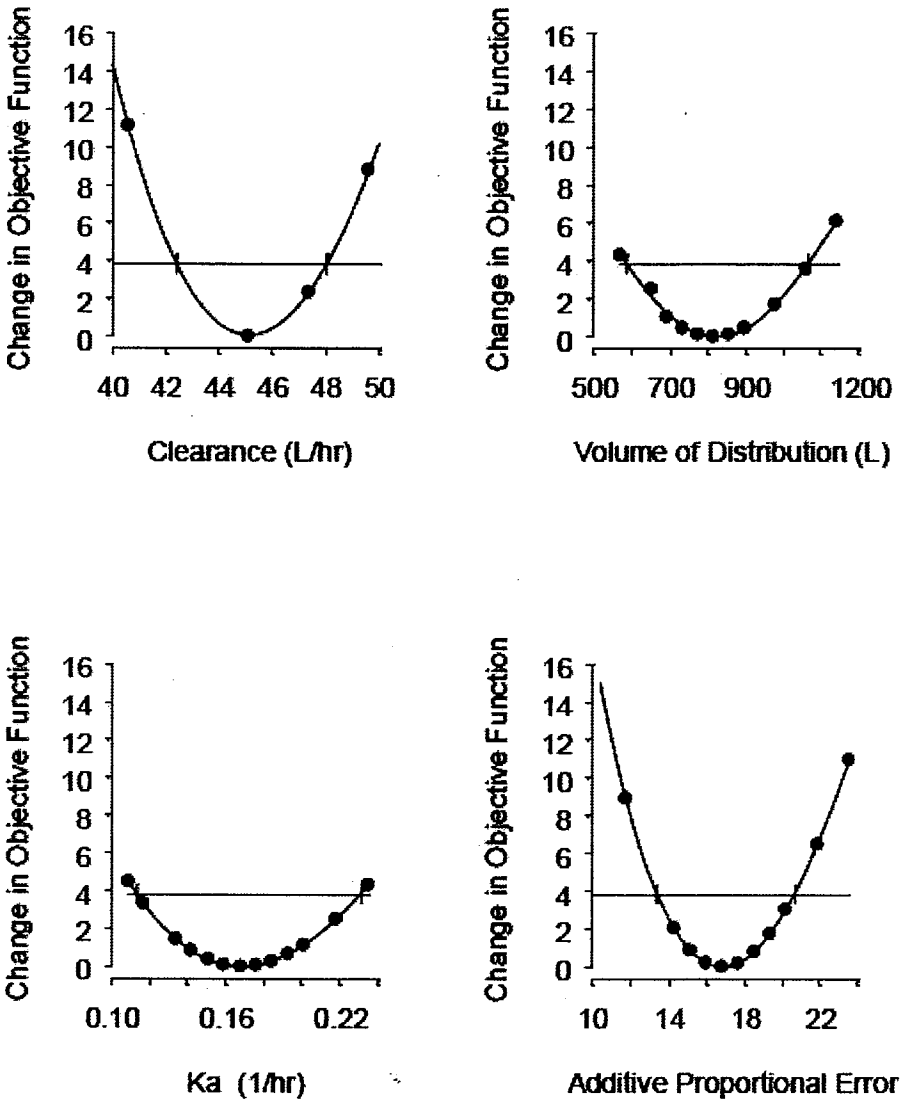

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Figure 11. Sensitivity Plots for the Final Model: Θ5, Θ6, Θ7, Θ8, Θ9

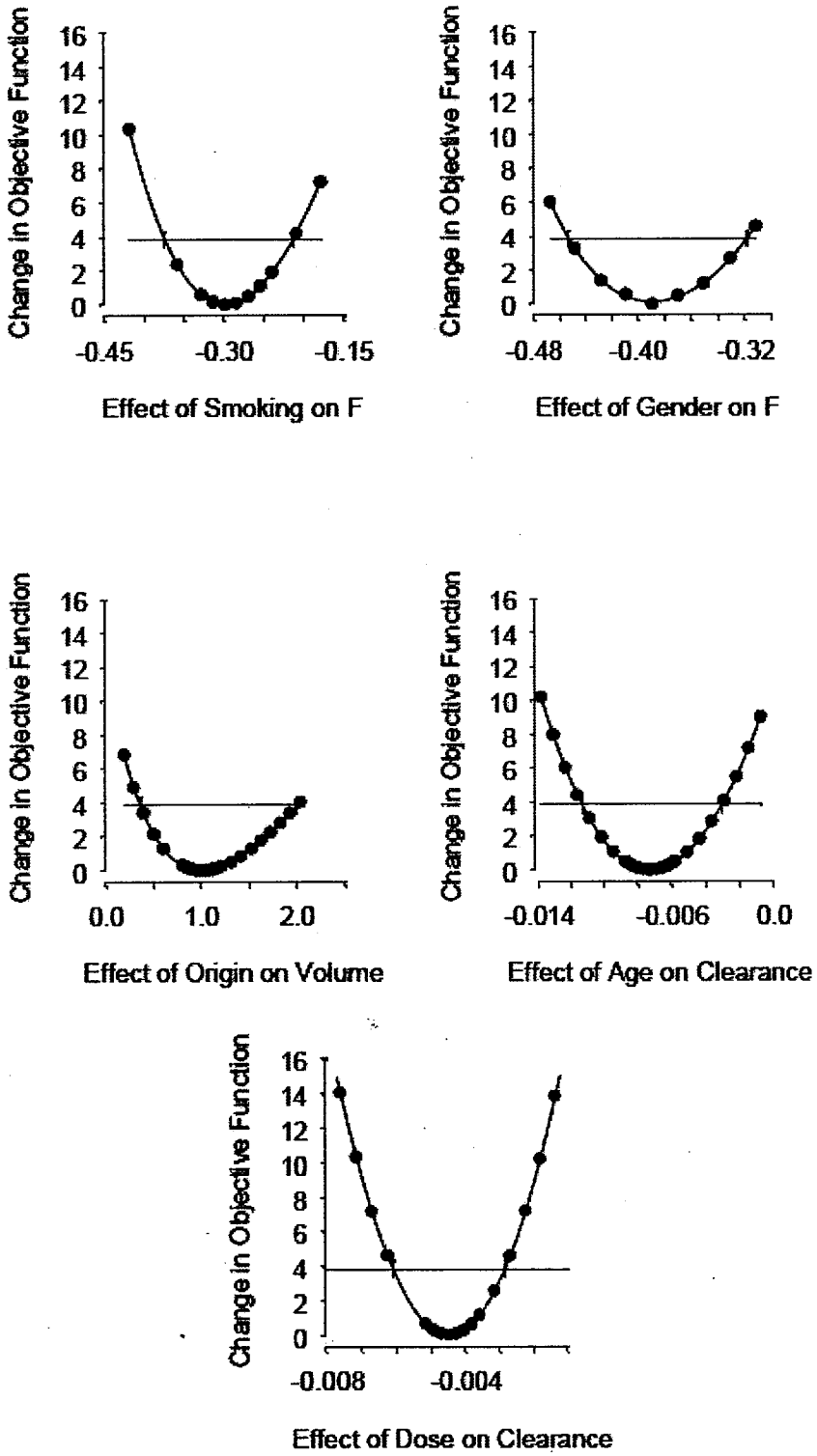


Table 4. Summary of Leverage Analyses

		Parameter Sensitivity	Leverage Analysis	
		95% CI	Range of Values	
Parameter	Estimate	Range	Analysis I	Analysis II
Oral clearance, CL/F	45.1	42.4 – 48.0	44.0 – 46.1	44.8 – 45.7
Oral volume of distribution, V/F	814	587 – 1064	752 – 900	776 – 853
Absorption Rate Constant, Ka	0.168	0.113 – 0.231	0.155 – 0.191	0.157 – 0.179
Additive				
Proportional Error	16.8	13.4 – 20.6	16.0 – 18.0	15.2 – 18.3
Effect of smoking on F	-0.298	-0.373 - -0.213	-0.312 - -0.274	-0.314 - -0.276
Effect of gender on F	-0.389	-0.453 - -0.319	-0.418 - -0.366	-0.407 - -0.372
Effect of origin on V/F	-1.02	0.369 – 2.01	0.789 – 1.22	0.832 – 1.22
Effect of age on CL/F	-0.00725	-0.0113 - -0.00303	-0.00880 - -0.00562	-0.00840 - -0.00584
Effect of dose on CL/F	-0.00446	-0.00610 - -0.00367	-0.00489 - -0.00367	-0.00492 - -0.00406

Abbreviations: CI = confidence interval; CL/F = oral clearance; V/F = oral volume of distribution.

PK-PD

Average pain score

A linear model was able to characterize the effect of duloxetine on reduction in BPI-pain score (Figure 12). The $R_{placebo}$ (response for the placebo treated patients) and the slope of the linear regression were estimated to be -0.757 (% CV = 20%) and 0.00454 (% CV = 32%), respectively. When duloxetine dose is doubled from 60 mg (typical Cav,ss = 72 ng/mL) to 120 mg (Cav,ss =189 ng/mL at 120 mg), there is a 49% increase in BPI pain score reduction (i.e. from -1.08 to -1.62).

A linear model was able to characterize the effect of duloxetine on $AUC_{painrelief}$ (Figure 13). The $R_{placebo}$ and the slope of the linear regression were estimated to be 194 (% CV = 9.8%) and -0.412 (% CV = 42%), respectively. When duloxetine dose is doubled from 60 mg (typical Cav,ss = 72 ng/mL) to 120 mg (Cav,ss = 189 ng/mL), there is a 22% increase in $AUC_{pain\ relief}$ (i.e. from 224 to 272).

The logistic regression model estimated the probability of a placebo treated patient achieving 30% reduction in pain score from baseline to be 0.34 and for achieving 50% reduction to be 0.29 (Figure 14). The odds ratio was estimated to be approximately 1 for both 30% and 50% reduction.

PGI-Improvement

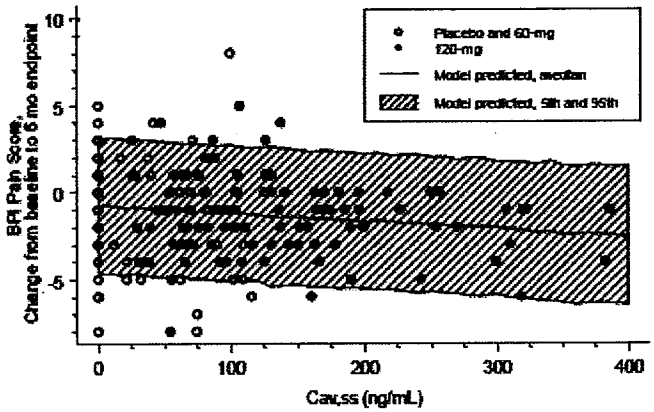
The model estimated the probability of PGI-improvement as follows (Figure 15):

- score of either 3, 4 or 5 (for example, little better, no change or little worse, respectively) is approximately 70.0% in placebo treated patients which decreased to a maximum of 39.6 % in duloxetine treated patients with duloxetine Cav,ss of 400 ng/mL (maximum Cav,ss noted in Study HMEF, Figure 21).
- score of either 1 or 2 (i.e. very much better or much better, respectively) is approximately 18.8 % in placebo treated patients which increased in a

concentration-dependent manner to a maximum of 57.6 % in duloxetine treated patients that had a Cav,ss of 400 ng/mL).

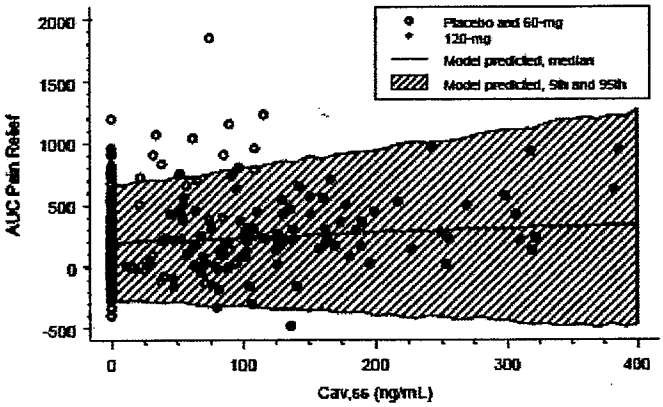
- score of either 6 or 7 (i.e. much worse or very much worse, respectively) is approximately 14.2 % in placebo treated patients which decreased in a concentration-dependent manner to a maximum of 2.74 % in duloxetine treated patients that had a Cav,ss of 400 ng/mL.

Figure 12. The relationship between duloxetine Cav,ss and the BPI pain score change from baseline to endpoint (6 month).



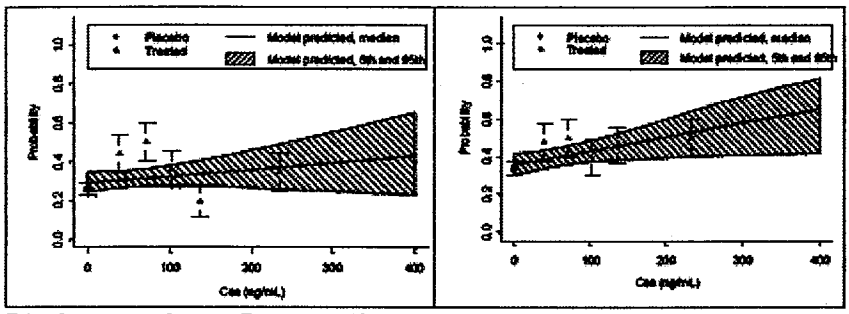
Number of patients treated with placebo, 60 mg and 120 mg were 168, 39 and 92, respectively. For patients treated with duloxetine, only those with available pharmacokinetic data were included.

Figure 13. The relationship between duloxetine Cav,ss and AUC pain relief at 6 month.



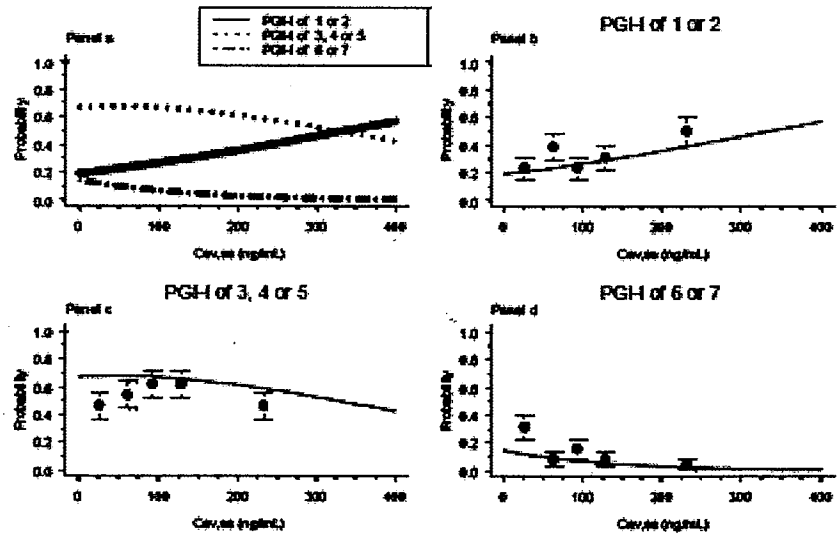
Number of patients treated with placebo, 60 mg and 120 mg were 168, 39 and 92, respectively. For patients treated with duloxetine, only those with available pharmacokinetic data were included.

Figure 14. Comparison of the observed and model predicted probability of achieving 30% (left panel) or 50% (right panel) reduction in pain score from baseline to endpoint (6 month) as a function of increasing duloxetine Cav,ss.



Triangles represent the mean Cav,ss grouped by quantiles (breakpoints at quantiles 0, 20, 40, 60, 80, 100 corresponded to 11.7, 56.5, 86.8, 111, 167, and 386 ng/mL, respectively). Number of patients treated with placebo, 60 mg or 120 mg were 168, 39 and 92, respectively

Figure 15. Model predicted probability of a patient reporting a specific PGI- improvement score as a function of patient's steady state concentration of duloxetine (Cav,ss).



Abbreviations: PGI-I = Patient's Global Impressions of Improvement.
Panel a shows the model predicted probability of a patient reporting a specific PGI-I score. Panels b, c, and d compare the model predictions with the observed data. Lines represent model predictions and solid circles represent observed data. Solid circles represents the mean Cav,ss grouped by quantiles (breakpoints at quantiles 0, 20, 40, 60, 80, 100).

CONCLUSIONS:

Population PK:

The results from this population PK analysis are consistent with prior results and are summarized below.

- The PK of duloxetine was adequately described by a one compartment model with large interpatient variability (60% to 100%).
- The PK of duloxetine in MDD, SUI, DPNP, and FM patients are similar.
- Body weight, disease condition and dosing regimen did not have any statistically significant effect on duloxetine PK.
- Sex, smoking status, age, ethnic origin, and dose had a statistically significant effect on duloxetine PK but the magnitude of the effect of these covariates was small relative to the magnitude of variability. Therefore, specific dose recommendations for duloxetine based upon sex, smoking status, age, dose, or ethnic origin are not warranted.

PK-PD:

The results of the PK-PD analysis showed that:

- The effect of duloxetine Cav,ss on change in BPI pain score from baseline to endpoint and on AUC pain relief was characterized by a linear PK-PD model. The value of the slope suggests that the effect of duloxetine Cav,ss on change in BPI pain score is very small.
- There did not appear to be an effect of duloxetine Cav,ss on 30% or 50% reduction in BPI pain score.
- The probability of a patient reporting an improvement on PGI-Improvement score increased with increasing duloxetine Cav,ss, thus suggesting that increasing the dose for an individual patient may increase the probability of achieving improvement on PGI-I score.

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