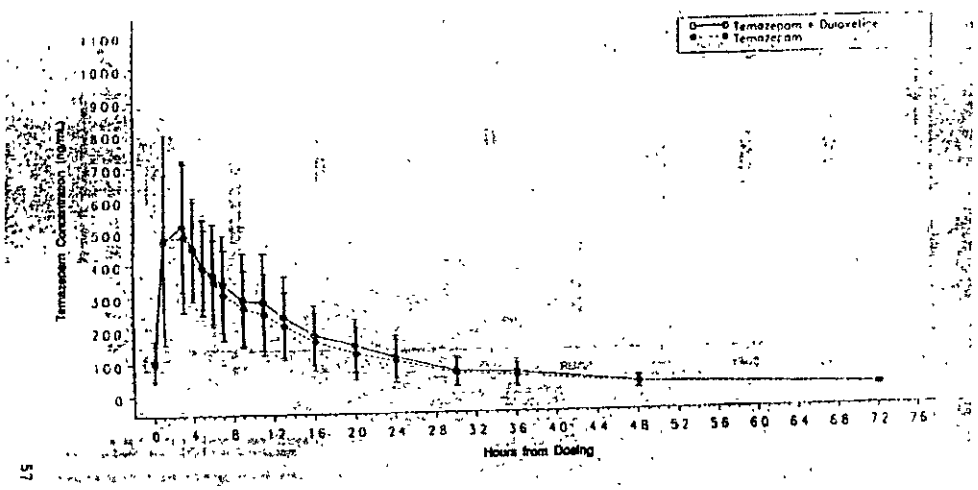
8.10.3.1.3.2.1 Effect of Duloxetine on Temazepam

Table 78 Effect of Duloxetine on Temazepam Pharmacokinetic Metrics (Study HMAJ)

Pharmacokinetic Metric	Test Temazepam + Duloxetine	Reference Temazepam alone	Geometric Mean Ratios [90% CI]
Cmax ng/ml	564.8 ± 183 (32.4)	588.4 ± 242 (41.1)	**100.9 [90.5, 112.5]**
Tmax hours	3 ± 1 (39)	3 ± 1 (33)	—
AUCτ ng/ml x hr^{-1}	6333 ± 2775 (44)	5830 ± 2679 (46)	**111.3 [102.4, 120.9]**
Cav ng/ml	263.9 ± 115.6 (43.8)	242.9 ± 111.6 (46)	111.3 [102.4, 120.8]
Cmin ng/ml	106.1 ± 59.4 (56)	90.7 ± 58 (63.9)	133.6 [117.4, 152]
Fluctuation Index	1.88 ± 0.517 (27.5)	2.189 ± 0.659 (30.1)	—
Ae_{0-48}^{urine}	0.036 ± 0.02 (56.4)	0.033 ± 0.008 (23.8)	—
fu (%)	0.12% ± 0.07% 0.06% - 3.13%	0.11% ± 0.03% 0.07% - 0.16%	—

Figure 42 Naïve Pooled Temazepam Plasma Concentration - Time Profiles in the Presence and Absence of Duloxetine (Study HMAJ)



8.10.3.1.4 Glucuronidation

8.10.3.1.4.1 Lorazepam and Duloxetine

Lorazepam is a benzodiazepine sedative / anxiolytic. After oral administration Tmax occurs with a mean of 2 hours. Lorazepam has a half-life of 12 hours and is eliminated by glucuronidation to an inactive metabolite. Pharmacokinetics are linear and time invariant. The maximum-labeled dose of lorazepam is 10 mg daily in 3 divided doses. Based upon the labeling this translates into a regimen of 3 mg, 3 mg and 4 mg hs for insomnia. As lorazepam is almost completely absorbed, and elimination is via glucuronidation the chance of a pharmacokinetic interaction is low, thus the sponsor chose lorazepam to investigate the potential for a pharmacodynamic interaction. As part of this study (HMBD) the lack of a pharmacokinetic interaction was also documented.

Duloxetine was dosed with the proposed labeled dose of 60 mg bid (8 AM and 8 PM) for 6 days, and lorazepam was dosed at 2 mg bid (8 AM and 8 PM) x 3 days. Thus maximal exposures of duloxetine were obtained. For lorazepam the timing of the doses were acceptable, but the dose is 40% of the maximal daily dose and 50% of the maximal bedtime dose. Consequently, maximal pharmacodynamic and pharmacokinetic effects may not have been seen.

Lorazepam had no effect on duloxetine pharmacokinetics (see Table 79), however, there was a slightly faster absorption and slightly higher Cmax of lorazepam in the presence of duloxetine (see Table 80).

8.10.3.1.4.1.1 Effect of Lorazepam on Duloxetine

Table 79 Pharmacokinetic Metrics and Bioequivalence Assessment of Duloxetine 60 mg q12hr in the Presence and Absence of Lorazepam 2 mg q 12hr (Study HMBD)

Metric	Mean ± SD (CV%) Range [Median]		Least Squares Mean		Geometric Mean Ratio[a,b] [90% CI]
	Test	Reference	Test	Reference	
	Duloxetine + Lorazepam (n = 16)	Duloxetine + PBO (n = 16)	Duloxetine + Lorazepam (n = 16)	Duloxetine + PBO (n = 16)	
$Cmin_{ss}$ (ng/ml)	58.5 ± 24.3 (41.6) [57.1]	52.6 ± 20.9 (39.8) [48.7]	54.0	48.7	110.9 (101.8, 120.9)
$Tmax_{ss}$ (hr)	5.4 ± 1.9 (34.2) [6]	5.3 ± 1.7 (32.8) [6]	—	—	0.1 ± 1.6 (1338.1) -3.0 - 3.0 [0.0]
$Cmax_{ss}$ (ng/ml)	114.8 ± 50.7 (44.2) [110.3]	115 ± 58.0 (50.4) [99.2]	106.4	103.7	102.6 (89.7, 117.3)
Cav_{ss} (ng/ml)	86.8 ± 36.8 (42.4) [79.9]	83.0 ± 33.1 (39.9) [78.4]	80.4	76.7	104.8 (96.3, 114.1)
$AUC\tau_{(0-12)ss}$ (ng/ml x h^{-1})	1042.1 ± 441.4 (42.4) [958.3]	995.4 ± 396.7 (39.86) [940.5]	965.2	920.7	104.8 (96.3, 114.1)
CLp/F (L/hr)	66.8 ± 25.9 (38.7) [62.6]	70.6 ± 29.2 (41.4) [63.9]	—	—	—
$Clp/F^{Weight\ Normalized}$ (L/hr x kg^{-1})	0.98 ± 0.34 (34.6) [0.98]	1.04 ± 0.39 (38.0) [1.01]	—	—	—

a Mean ± SD (CV%) Min – Max [Median]
b For Tmax values are for difference

8.10.3.1.4.1.2 Effect of Duloxetine on Lorazepam

Table 80 Pharmacokinetic Metrics and Bioequivalence Assessment of Lorazepam 2 mg q12hours in the Presence and Absence of Duloxetine 60 mg q12hr (Study HMBD)

Metric	Mean ± SD (CV%) Range [Median]		Least Squares Mean[b]		Geometric Mean Ratio[a,c] [90% CI]
	Test	Reference	Test	Reference	
	Duloxetine + Lorazepam	Duloxetine + PBO	Duloxetine + Lorazepam	Duloxetine + PBO	
	(n=16)	(n=16)	(n=16)	(n=16)	
$Cmin_{ss}$ (ng/ml)	25.5 ± 10.8 (42.6) [24.0]	23.3 ± 10.2 (43.7) [18.0]	23.2 (47.8) [24.0]	21.1 (50.4) [18.0]	110.1 (101.9, 119)
$Tmax_{ss}$ (hr)	1.5 ± 1.0 (64.8) (1)	2.0 ± 1.0 (51.2) (2)	—	—	-0.44 ± 1.32 (-298) -3 - 2 (-0.03)
$Cmax_{ss}$ (ng/ml)	49.8 ± 13.2 (26.4) [48.6]	42.9 ± 10.5 (24.4) [41.3]	48.1 (29.0) [48.6]	41.7 (24.4) [41.3]	115.1 (104.1, 127.3)
Cav_{ss} (ng/ml)	34.1 ± 11.6 (34) [33.2]	31.5 ± 10.8 (34.3) [26.8]	32.1 (37.0) [33.2]	29.8 (36.1) [26.8]	108 (100.3, 116.4)
$AUC\tau_{(0-12)ss}$ (ng/ml x h^{-1})	408.7 ± 1390 (34) [398.8]	377.7 ± 129.4 (34.26) [321.1]	385.6 (37.0) [398.8]	357 (36.1) [321.1]	108 (100.3, 116.4)
CLp/F (L/hr)	17.4 ± 5.7 (32.5) [16.6]	15.8 ± 5.1 (32.3) [16.3]	—	—	—
$Clp/F^{Weight\ Normalized}$ (L/hr x kg^{-1})	0.26 ± 0.10 (37.3) [0.26]	0.24 ± 0.08 (34.6) [0.24]	—	—	—
t1/2 (hrs)	17.4 ± 5.7 (32.5) [16.6]	15.8 ± 5.1 (32.28) [16.4]			110.2 (100.6, 120.7)

a Mean ± SD (CV%) Min – Max [Median]
b Least Squares Geometric Mean CV(%) Min – Max [Median]
c For Tmax values are for difference

8.10.3.1.5 Drugs that May Effect GI Absorption

A single interaction study of drugs that might effect duloxetine absorption from the GI tract was conducted, (study HMBB). This Study was a 4-way study that examined two different potential mechanisms for absorption interactions. These mechanisms and a third are addressed below.

8.10.3.1.5.1 Alteration of Gastric pH

Since duloxetine has an enteric coating, the effects of drugs that effect gastrointestinal pH might effect duloxetine exposure. *A priori* we expect that drugs that increase gastric pH may potentially increase the rate of dissolution of the enteric coating and secondarily the rate of absorption. Drugs that increase gastric pH include antacids, H2 antagonists and proton-pump inhibitors.

8.10.3.1.5.2 Absorbents

As duloxetine is an antidepressant it has a high potential to be used in suicide attempts. Consequently, activated charcoal may be used to prevent absorption and enterohepatic recycling. In addition, there are clinically used drugs that might also absorb duloxetine, e.g. cholestyramine.

8.10.3.1.5.3 Transport Inhibitors / Activators

The effect of transporter inhibitors or activators on duloxetine pharmacokinetics was not examined.

Study Design

Study HMBB was a single dose, 4-way crossover, open-label study in young healthy male Asian adults 21 to 38 yo. Treatments included the following.

- **Treatment A:** Duloxetine 40 mg (2 ×20 mg) alone.
- **Treatment B:** Famotidine 40 mg given 1 hour prior to dosing of duloxetine 40 mg (2 ×20mg).
- **Treatment C:** Mylanta® 20 ml given 15 minutes prior to, then 2 hours and 4 hours after dosing of duloxetine 40 mg (2 ×20mg)
- **Treatment D:** Activated charcoal as an aqueous suspension (50 g of charcoal in 250 mL) given 2 hours after dosing of duloxetine 40 mg (2 ×20 mg)

Duloxetine, famotidine, and Mylanta® were taken with approximately 100 ml of room temperature tap water in the morning after overnight fasting.

In GERD, the maximal labeled single dose of famotidine is 40 mg with peak effect expected between 1 and 3 hours after dosing. Whereas Mylanta® has an acid neutralizing capacity of 12.7 mEq / 5 ml. The maximum labeled dose of most antacids is around 60 - 90 mEq and doses of up to 200 mEq have been recommended in peptic ulcer disease Consequently, the doses of famotidine were acceptable. Although the dose of Mylanta® may has been low. In addition, the activated charcoal dosing was similar to what would be expected in a typical overdose situation.

There was no effect of either famotidine or Mylanta on the pharmacokinetics of duloxetine. Based upon the mean data it does appear that there is a trend for lower exposures with famotidine. However, the lower mean exposure in the presence of famotidine is due to the drop out, due to adverse effects, of the subject with the highest duloxetine exposures, (see Table 81 and Table 82 and Figure 43). This subject may have been a CYP2D6 poor metabolizer. In addition when comparative concentration time profiles in individual subjects are examined the profiles are very similar in each subject in the presence and absence of famotidine or Mylanta® (data not shown). However it should be noted that a more potent acid inhibitor such as a proton-pump inhibitor might effect dissolution rate.

In contrast, activated charcoal did on average decrease the absorption and exposure to duloxetine, (see Table 81 and Table 82 and Figure 43). However, the effect of activated charcoal was highly variable, with

several subjects having very similar duloxetine concentration time profiles in the presence and absence of activated charcoal. Whereas other subjects had greatly diminished, or almost no absorption of duloxetine in the presence of activated charcoal,

Table 81 Comparison of Duloxetine Pharmacokinetic Metrics Alone and in the Presence of Famotidine, Mylanta, or Activated Charcoal (Study HMBB)

Metric	Duloxetine 40 mg Alone	Duloxetine 40 mg + Famotidine 40 mg at – 1 hours	Duloxetine 40 mg + Mylanta 20 ml at – 0.25, 2 & 4 hours	Duloxetine 40 mg + Activated Charcoal 50 gm / 250 ml at 2 hours
n	14	12	14	14
Tlag[a] (hrs)	2.4 ± 1.1 (44.9) [2.0]	1.8 ± 0.5 (25.8) [2.0]	3.0 ± 1.0 (34.6) [3.0]	2.9 ± 2.0 (69.8) [2.0]
Cmax (ng/ml)	22.0 ± 12.6 (57.6) [19.9]	15.9 ± 6.64 (41.8) [16.3]	22.9 ± 10.3 (44.7) [23.1]	15 ± 12.9 (85.8) [13.4]
Tmax (hrs)	7.29 ± 1.684 (23.1) [8]	7.33 ± 1.557 (21.2) [8]	8.29 ± 1.36 (16) [8]	5.71 ± 1.729 (30.3) [6]
AUC_{0-t} ($ng/ml \times hr^{-1}$)	421 ± 366 (87) [352]	290 ± 124 (42.6) [316]	438 ± 342 (78.2) [378]	275 ± 323 (117.5) [221]
$AUC_{0-t}^{weight\ normalized}$ ($ng/ml \times hr^{-1}/kg$)	0.742 ± 0.734 (98.9) [0.617]	0.488 ± 0.197 (40.4) [0.535]	0.755 ± 0.695 (89.7) [0.613]	0.495 ± 6.39 (129) [0.366]
$AUC_{0-\infty}$ ($ng/ml \times hr^{-1}$)	447 ± 408 (91.2) [369]	306 ± 127 (41.6) [332]	459 ± 367 (80) [392]	290 ± 336 (116.1) [232]
$AUC_{0-\infty}^{weight\ normalized}$ ($ng/ml \times hr^{-1}/kg$)	0.791 ± 0.82 (103.7) [0.641]	0.516 ± 0.204 (39.5) [0.554]	0.814 ± 0.747 (92) [0.639]	0.521 ± 0.667 (128) [0.389]
Cl/F (L/hr)	137 ± 88.6 (64.6) [108]	160.5 ± 83.76 (52.2) [120.9]	117 ± 56 (57.8) [103]	386.3 ± 554 (143.5) [172.5]
$Cl/F^{weight\ normalized}$ ($L/hr \times kg^{-1}$)	2.01 ± 1.322 (65.8) [1.56]	2.35 ± 1.228 (52.3) [1.8]	1.73 ± 0.862 (50) [1.6]	5.78 ± 8.58 (148.4) [2.57]
Vz (L)	1847 ± 1073 (58.1) [1547]	2115 ± 959 (45.3) [[1728]	1559 ± 541 (34.7) [1382]	5150 ± 7812 (151.7) [2298]
$Vz^{weight\ normalized}$ (L/kg)	18.4 ± 4.89 (26.6) [17.3]	31 ± 14.1 (45.5) [23.8]	22.89 ± 8.33 (36.4) [21.66]	77.06 ± 121 (156.6) [34.01]
$t_{1/2}$ (hrs)	10.3 ± 3.15 (30.6) [9.54]	9.49 ± 1.66 (17.5) [9.89]	10.1 ± 2.61 (25.9) [9.07]	9.41 ± 2.11 (22.4) [9.16]

a No comparison to duloxetine alone is statistically significant by Wilcoxon Signed Rank Test

Table 82 Statistical Analysis of the Effect of Activated Charcoal, Famotidine, and Mylanta on Duloxetine Pharmacokinetic Metrics

Parameter	Least Squares Mean (95% Confidence Interval)				P-value for Pairwise Comparison			
	Duloxetine 40 mg Alone	Duloxetine 40 mg + Activated Charcoal 50 gm / 250 ml at 2 hours	Duloxetine 40 mg + Famotidine 40 mg at -1 hours	Duloxetine 40 mg + Mylanta 20 ml at -0.25, 2 and 4 hours	Overall Comparison	Duloxetine vs Duloxetine + Activated Charcoal	Duloxetine vs Duloxetine + Famotidine	Duloxetine vs Duloxetine + Mylanta
$AUC_{0-\infty}$ ($ng/ml \times hr^{-1}$)	419.6 (226.5, 612.6)	269.4 (76.4, 462. 5)	383.2 (189.0, 577.4)	454.0 (261.0, 647.1)	0.001	**0.001**	0.282	0.278
AUC_{0-tn} ($ng/ml \times hr^{-1}$)	394.5 (230.0, 559.0)	255.6 (91.1, 420. 0)	350.0 (184.6, 515. 4)	408.5 (244.0, 572.9)	0.001	**0.001**	0.115	0.593
Cmax (ng/ml)	21.4 (15.5, 27.4)	14.7 (8.8, 20.6)	17.8 (11.8, 23.9)	22.5 (16.5, 28 4)	0.001	**0.001**	***0.056***	0.555
CL/F (L/ h)	142.4 (2.5, 282.3)	384.2 (244.4, 524.1)	168.0 (15.8, 320 3)	126.5 (-13 3, 266.3)	0.041	0.018	0.803	0.871
Vz/F (L)	2116.1 (167.2, 4065.0)	5103.8 (3155.8, 7051.8)	2182.6 (61.4, 4303.8)	1660.1 (-287.8, 3608.1)	0.061	0.034	0 963	0.738
$t_{1/2}$ (h)	10.6 (9.1, 12.0)	9.3 (7.8, 10.7)	10.0 (8.5, 11. 5)	10.3 (8.8, 11.8)	0.107	0.020	0.295	0.602
Tmax[a] (h)	8.0	6.0	8.0	8.0	0.001	0.027	0.999	0.180
Tlag[a] (h)	2.0	2.0	3.0	2.0	NS	NS	NS	NS

a Values represent median with minimum and maximum in parentheses, comparisons are based on non-parametric tests.

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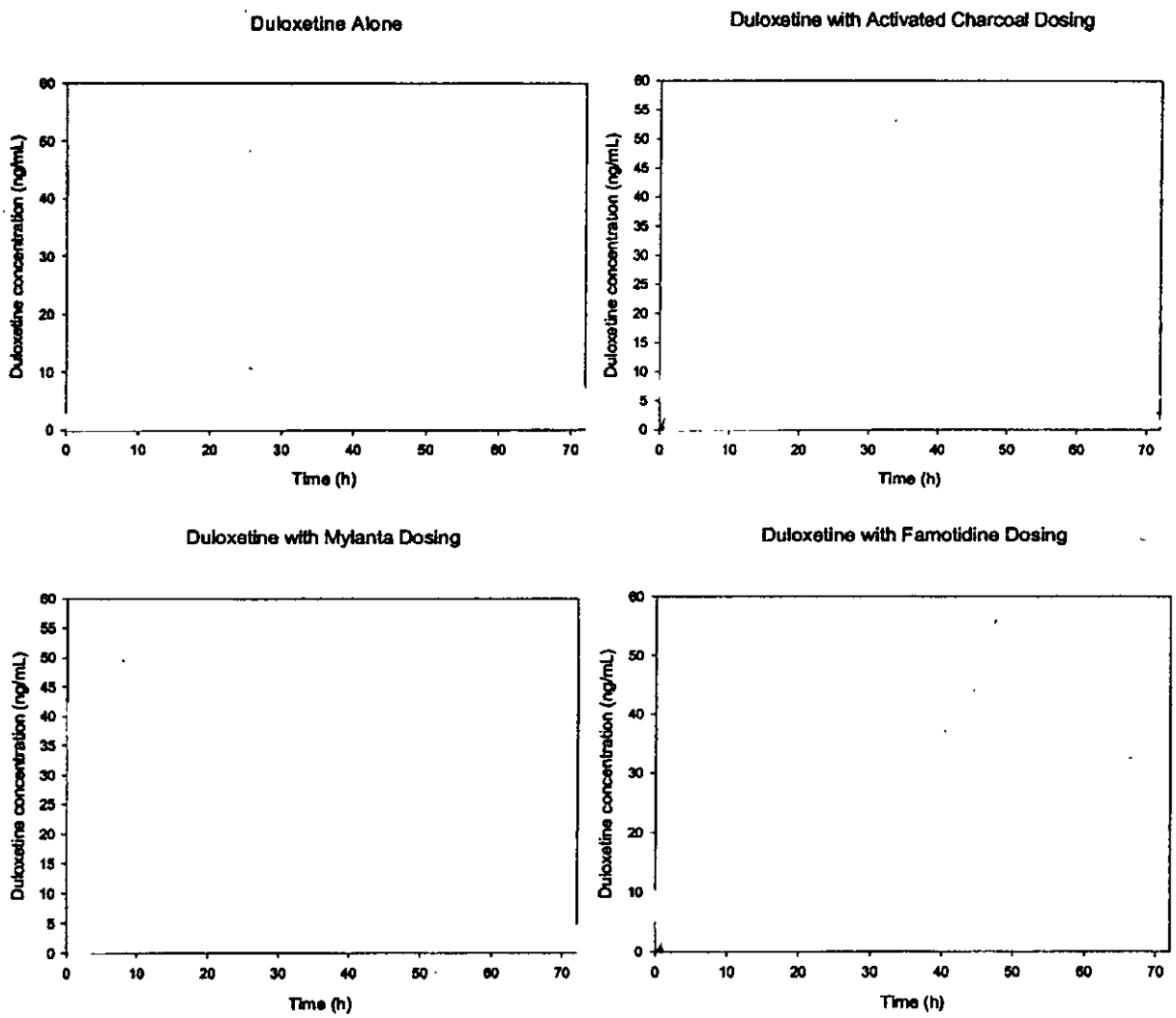
Figure 43 Concentration vs. Time Profiles for Duloxetine 40 mg po alone, or with Famotidine 40 mg at –1 hours, Mylanta 20 ml at –0.25, 1, and 2 hours, or 50 gm of Activated Charcoal 2 hours after Duloxetine.



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8.10.3.1.6 Ethanol and Duloxetine

Study F1J-LC-HMBA was a 3- way single blinded single dose crossover study to determine if duloxetine exacerbated the cognitive and psychomotor effects of ethanol. Subjects included 16 male and female subjects 21 – 58 years of age, all of whom were extensive metabolizers. Of these subjects, only 10 were able to consume and retain their ethanol on each occasion without vomiting.

A test dose of ethanol was administered and blood ethanol concentrations were determined at 0.33, 0.67, 1, 1.5, 2, and 2.5 hrs after beginning ethanol consumption. Mean Cmax was 120 mg% and median observed Tmax was 0.69 hours. An assumption of linear kinetics was then used to predict an ethanol dose that would produce a peak concentration of 100 mg%. Duloxetine or placebo was administered as a single 60 mg dose followed by ethanol or placebo 4 hours later. This would produce peak ethanol concentrations around the median time that peak duloxetine concentrations are achieved at 6 hours post duloxetine dosing.

8.10.3.1.6.1 Effect of Ethanol on Duloxetine:

The data from study F1J-LC-HMBA appears to suggest a lack of effect of ethanol on the pharmacokinetics of duloxetine, (see Table 84). However, the co-administration of ethanol and duloxetine at the same time was not examined. This is a significant concern, if the enteric coating dissolves in the presence of ethanol while the beads are still in the stomach, then the potential exists for acid hydrolysis and exposure to the toxic degradation product naphthol. Consequently, an *in vitro* experiment should be undertaken to determine if this is a potential risk. If this experiment shows a potential risk, then an *in vivo* study should be undertaken.

Table 83 Duloxetine Concentrations Achieved in the Presence and Absence of Ethanol

Subjects		Duloxetine Concentrations (ng/ml)				Direction of Change
		Duloxetine + PBO		Duloxetine + EtOH		
		$C_{0.75}$	$C_{1.75}$	$C_{0.75}$	$C_{1.75}$	
Subjects with PD Data	0001					↑
	0003					↑
	0008					↑
	0009					↑
	0010					↑
	0011					↑
	0012					↑
	0013					—
	0014[b]					↓
	0015					—
	0016					—
Subjects without PD data	0002					↓
	0004					↑
	0007					↓
Mean ± SD (CV%) Range [Median]	Subjects with PD Data	22.9 ± 20.8 91.1 [17.9]	26.1 ± 19.0 73.1 [22.7]	22.2 ± 24.8 111.5 [11.8]	26.0 ± 21.0 81.0 [16.7]	More ↑
	All Subjects	19.3 ± 18.6 (96.4) [11.1]	22.4 ± 17.0 (76.0) [15.2]	19.7 ± 22.1 (112.1) [10.6]	23.0 ± 18.9 (82.2) [15.1]	

8.10.3.1.6.2 Effect of Duloxetine on Ethanol

In the presence and absence of duloxetine ethanol concentrations achieved were close to the 100 mg% goal, suggesting a lack of an effect of duloxetine on ethanol pharmacokinetics (see Table 84).

However, the pharmacokinetic sampling was insufficient to draw any firm conclusions. In addition, the use of a single dose study and inclusion of only extensive metabolizers minimally stresses the system and thus does not provide conclusive evidence of a lack of a pharmacokinetic interaction.

Table 84 Ethanol Doses and Concentrations Achieved

Subject	EtOH Dose[a]	Ethanol Concentrations (mg %)					
		Ethanol & PBO			Ethanol & Duloxetine		
		$C_{0.75}$	$C_{1.75}$	Cmax	$C_{0.75}$	$C_{1.75}$	Cmax
0001	81						
0003	81						
0008	136						
0009	105						
0010	106						
0011	153						
0012	104						
0013	115						
0014[b]	155						
0015	138						
0016	156						
Mean ± SD (CV%) Range		95.0 ± 11.3 (11.9)	85.0 ± 14.0 (16.4)	96.8 ± 10.5 (10.9)	77.5 ± 16.6 (21.4)	82.0 ± 16.4 (20.0)	87.1 ± 14.7 (16.8)

a Ethanol dose: ml of 100 proof Vodka
b Ethanol concentrations in presence of duloxetine excluded from calculation of summary statistics

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8.10.3.2 Pharmacodynamic Drug-Drug Interactions

8.10.3.2.1 Temazepam and Duloxetine

As CNS depressants both temazepam and duloxetine would be expected to decrease CNS latency scores. This was examined in study HMAJ. However, due to the high variability in the measurement of CNS latency, no clear effect of either drug could be established (see Table 85). It should be noted however, that duloxetine was only administered as a 20 mg dose each night at 11 PM. Consequently, this subtherapeutic dose may not have resulted in a maximal effect. In conclusion, no firm conclusions on a pharmacodynamic interaction between temazepam and duloxetine can be drawn from this study.

Table 85 Effect of Duloxetine and Temazepam on CNS Latency (Study (HMAJ)

Treatment Sequence	CNS Latency Mean ± SD			
	Baseline Score	Change from Baseline		
		Temazepam Alone	Duloxetine Alone	Temazepam + Duloxetine
D → T → D+T	202 ± 46	-16 ± 23	-15 ± 18	-10 ± 19
T → T+D → D	200 ± 37	-4 ± 15	-6 ± 12	-16 ± 13
T+D → D → T	181 ± 14	51 ± 76	26 ± 56	16 ± 28

D – Duloxetine Alone
T – Temazepam Alone
T+D – Temazepam & Duloxetine

8.10.3.2.2 Lorazepam and Duloxetine

The potential for a pharmacodynamic interaction of duloxetine with benzodiapines was more rigorously examined in study HMBD. Therapeutic doses of duloxetine were used although the doses of lorazepam used were less than maximal (see § 8.10.3.1.4 for a more complete description of the design and the results of the pharmacokinetic interaction part of the study).

The sponsor concluded that there's no increase in lorazepam's amnestic effects due to duloxetine; however, duloxetine causes sedation and this is increased when lorazepam is initially added.

The sponsor's wording follow, with the experimental results shown in §.10.10 Appendix 10 Results of Pharmacodynamic interaction study of duloxetine and lorazepam.

"Duloxetine at steady-state was not shown to alter the amnestic effects of lorazepam. Compared to lorazepam alone, the combination of lorazepam with duloxetine was associated with an increased sedation on both subjective (increased Alertness score/Bond & Lader) and objective tests (increased TRT and MRT, decreased DSST score) with a peak effect at 3 h and 6 h post-dose on Day 5. Overall, the difference between the 2 combinations seemed to decrease from Day 5 (first dose of lorazepam) to Day 8.

Pharmacodynamic assessments conducted on Day 4 failed to show that duloxetine, when compared to placebo, influenced memory tests (IWR, DWR) or performance on the following psychomotor tests: CFFT, RRT and MRT. However, objective (decreased DSST score) and subjective (increased Alertness score / Bond & Lader) modifications reflecting sedation were detected when compared to placebo.

Addition of lorazepam to steady-state duloxetine 60 mg BID resulted in an increased number of reports of somnolence in male subjects and postural tachycardia in female subjects compared to the combination of lorazepam with placebo. Overall, the number of subjects experiencing these adverse events was similar in the two treatment conditions."

8.10.3.2.3 Ethanol and Duloxetine

As mentioned in § 8.10.3.1.6, in study F1J-LC-HMBA duloxetine or placebo was administered as a single 60 mg dose followed by ethanol or placebo 4 hours later. This would produce peak ethanol concentrations around the median time that peak duloxetine concentrations are achieved at 6 hours post dosing.

Sampling for ethanol and duloxetine concentrations was conducted around the peak time. Comparative pharmacodynamic testing was performed including: the Alcohol Effects Scale (AES) (Martin et al. 1993) and the Automated Performance Test System (APTS) (C
]. Several baseline tests were also performed for comparison. Globally the pharmacodynamic tests assess stimulation and sedation. The time course of events on the study day is shown in Table 86, and the various factors for the Automated Performance Test System (APTS) are shown in Table 88.

Table 86 Time course of events in Duloxetine – Ethanol Interaction Study (F1J-LC-HMBA)

Time (Hours)										
Relative to Duloxetine	-2.5	-2	-1	0	2	4	4.75	5	5.75	6
Relative to EtOH		-6		-4	-2	0	0.5	0.75	1.5	1.75
Clock Time	7:30	8:00	9:00	10:00	Noon	2:00 – 2:20 PM	2:45	3:00	3:45	4:00
Event	Standard breakfast completed			Duloxetine (3 x 20 mg EC capsules) or Placebo	Lunch of clear liquids	EtOH or Placebo as 100 proof vodka or water (placebo) diluted 1:4 in a sugar free non-caffeinated soft drink				
PK Samples								$C_{0.75}$		$C_{1.75}$
PD Assessments										
AES		X		X			X		X	
APTS		X		X			X		X	
ECG & Vital Signs			X							X

Results seem to suggest that there is less of an effect on sedation and simulation when duloxetine is combined with ethanol as compared to ethanol alone, however, the ethanol concentrations were slightly higher when ethanol was given alone compare to the ethanol and duloxetine arm. In addition, there was no comparison of duloxetine alone to placebo (see Table 88 and Table 87).

Most of the pharmacodynamic tests showed no differences between ethanol alone and ethanol and duloxetine combined. The only statistically significant difference was more sedative effects as measured by the Alcohol Effects Scale with ethanol alone, as compared with ethanol in the presence of duloxetine (see Table 88 and Table 87)).

The data from this study suggests a lack of a pharmacodynamic interaction between ethanol and duloxetine. However, the use of a single dose study and inclusion of only extensive metabolizers minimally stresses the system; thus maximal pharmacodynamic effects of duloxetine under steady-state conditions may not be seen. Thus this study does not provide conclusive evidence of a lack of a pharmacodynamic interaction.

Table 87 Automated performance Test System Ethanol vs. Ethanol + Duloxetine Maximum Response Comparison

Test	Psychometric Domain Evaluated	Primary Variable	Difference in Effects	Standard Error	P Value
Grammatical reasoning	Linguistic information integration and manipulation, Abstract verbal reasoning	Number of correct responses	-1.07	1.89	0.57
Code substitution	Associative memory	Number of correct responses	2.52	2.73	0.36
Mathematical processing	Symbolic information integration and manipulation, Mathematical performance	Number of correct responses	-0.38	1.37	0.78
Manikin	Spatial information integration and manipulation	Number of correct responses	-1.05	2.59	0.69
Non-dominant Hand tapping	Output response and execution, Psychomotor speed	Number of alternate pairs	0.42	4.99	0.93
Pattern Comparison (simultaneous)	Perceptual input	Number of correct responses	-1.56	3.42	0.65
Reaction Time	Output response and execution, Psychomotor speed	Number of correct responses	-0.47	1.29	0.72
Sternberg	Associative memory, Short term memory	Number of alternate pairs	0.27	2.05	0.90
Two-hand tapping	Output response and execution, Psychomotor speed	Number of alternate pairs	-1.83	4.62	0.69

Table 88 Mean Scores and Mean Differences in Alcohol Effects Scale for EtOH & Placebo vs. EtOH & Duloxetine

Subscale	Treatment	Placebo	Mean Scores		Difference between EtOH alone and EtOH & Duloxetine 0.5 hours post EtOH		Difference between EtOH alone and EtOH & Duloxetine 1.5 hours post EtOH	
			0.5 hours post EtOH	1.5 hours post EtOH	Mean Difference	p Value	Mean Difference	p Value
Sedative	Test EtOH	1.40	2.96 [a]	3.44 [a]	0.73	0.03	0.84	0.04
	EtOH	1.80	2.47 [a]	3.04 [a]				
	EtOH & Duloxetine	0.97	1.50 [a]	2.49 [a]				
	Duloxetine	0.86	1.40	1.65				
Stimulant	Test EtOH	3.37	4.65 [a]	3.78	0.23	0.79	-0.30	0.42
	EtOH	2.86	3.47	2.93				
	EtOH & Duloxetine	3.36	3.26	2.65				
	Duloxetine	2.99	3.16	2.83				

a $p < 0.05$

8.11 CONFIRMATORY DATA

8.11.1 POPULATION PHARMACOKINETIC STUDIES

8.11.1.1 Overview of Pop PK Analyses Performed

The population pharmacokinetic kinetic studies primarily confirm the conclusions of the tradition pharmacokinetic analyses.

In each of the population pharmacokinetic analyses a one-compartment model with first order absorption was fit to the data, using a fixed absorption rate constant. These model fits do not take into account the absorption lagtime due to the enteric coating nor do they take into account CYP2D6 genotype or phenotype or any other factors that may induce or inhibit the primary elimination pathways.

Population pharmacokinetics was reported in 3 population pharmacokinetic analyses. (AQUApop) combine data from two clinical efficacy studies in major depressive disorder, (MDD); whereas two of these analyses were of data from separate clinical studies in stress urinary incontinence, (SUI). A fourth analysis of combined data from 6 studies in these two indications, SummPop, was also planned, however due to limited information on potential covariates across studies, the analysis was not conducted. Instead only descriptive summary statistics of duloxetine plasma concentrations were reported.

A summary of the 4 planned population pharmacokinetic analyses is shown in Table 89.

Table 89 Summary of Planned Population Pharmacokinetic Analyses

Population PK Analysis	Clinical Studies Included in Analysis	Study Populations
SAAB	SAAB	Females with Stress Urinary Incontinence
SAAW	SAAW	
AQUApop	HMAQ HMAU	Major Depressive Disorder
SummPop	HMAG HMAH HMAI SAAH SAAI SAAL	Major Depressive Disorder & Females with Stress Urinary Incontinence

A summary of the 6 studies included in the planned population pharmacokinetic analysis SummPop is shown in Table 90.

Table 90 Summaries of Studies Utilized for the Combined Population Pharmacokinetic Analysis SummPop

Study	Indication[a]	Patient Population	Dosage Regimens	Formulation(s) Used	Comments
HMAG	MDD	46	20 mg Dose may be reduced to 10 mg per day due to AEs Dose increased to 30 mg per day in case of insufficient response.	10 mg Tablets	
HMAH	MDD	80	20 mg Patients who initially were assigned to duloxetine 20 mg/day and who did not respond adequately to therapy were randomly assigned to either continue the duloxetine 20-mg/day dose or be assigned to an increased dose of duloxetine 30 mg/day.	10 mg Tablets 20 mg Tablets	
HMAI	MDD	217	5 mg/day (Fixed Dose) 10 mg/day (Fixed Dose) 20 mg/day (Fixed Dose)	5 mg Tablets 10 mg Tablets 20 mg Tablets	
[redacted]	SUI	27	10 mg/day (Fixed Dose) 20 mg/day (Fixed Dose) 30 mg/day (Fixed Dose) 40 mg/day (Fixed Dose) (30 mg/day Days 1 - 3 40 mg/day Days 4 – 7)	10 mg Caps 20 mg Caps	
[redacted]	SUI	63 Females	30 mg/day or placebo x 4 weeks Responders continued x 4 weeks. Non-responders - increased to 40 mg/day x 4 weeks Non-responders to placebo were treated with duloxetine 30 mg/day for second 4 week period.	10 mg Caps 20 mg Caps	
[redacted]	SUI	Females	1 week prescreen 1 week placebo lead-in 30 mg/day x 1 week Increased to 40 mg/day x 3 weeks 1 week FU	10 mg Caps 20 mg Caps	Duloxetine plasma concentrations data available from study [redacted] were collected on days when duloxetine treatment was not administered. These concentrations were therefore not utilized for pharmacokinetic evaluation

a - MDD – Major Depressive Disorder, SUI, Stress Urinary Incontinence

Patient specific factors assessed by analysis are shown in Table 91.

Table 91 Patient Factors Assessed in the Population Pharmacokinetic Analyses

Patient Factors	Population Pharmacokinetic Analyses				
	AQUApop		SAAW	SAAB	SummPop
	HMAQ	HMAU			
Dosage	X	X	X	X	X
Age	X	X	X	X	
Gender	X	X		X	X
Ethnic Origin	X	X	X	X	
Smoking status (yes/no)	X	X	X	X	X
Duration of Smoking				X	
Alcohol Use (yes/no)	X	X	X	X	
Weight	X	X	X	X	
Body Mass Index	X	X			
BSA				X	
Serum Creatinine				X	
Creatinine Clearance (CLcr)[a]	X	X	X	X	
Creatine Phosphokinase				X	
Total Bilirubin	X	X	X	X	
Aspartate Transaminase (AST/SGOT)	X	X	X	X	
Alanine Transaminase (ALT)			X	X	
Gamma Glutamyl Transferase (GGT)			X	X	
Alkaline Phosphatase (ALKP)				X	
Total Protein	X	X			
Investigator				X	

a Estimated by Cockcroft-Gault Equation

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8.11.1.2 Patient Demographics and Patient Specific Factors

Summary statistics for patient demographics and patient specific factors for the 3 population pharmacokinetic analyses are shown in Table 92 through Table 95.

Table 92 Patient Demographics in the Pharmacokinetic Evaluation Studies F1J-MC-HMAQ and F1J-MC-HMAU

Covariates	Category	Number of Patients		
		HMAQ	HMAU	Overall
Gender	Female	94	56	150
	Male	48	25	73
Smoker[a]	No	106	54	160
	Yes	36	26	62
Alcohol Use[a]	No	60	63	123
	Yes	82	17	99
Ethnic Origin	Caucasian	125	0	125
	Hispanic	5	81	86
	African Descent	9	0	9
	Asian	3	0	3

a Patient 5174 in HMAU did not have records of smoking status and alcohol use.

Table 93 Table 9.2. Patient Age, Weight and Estimated Creatinine Clearance for Patients Included in the Pharmacokinetic Evaluation Studies F1J-MC-HMAQ and F1J-MC-HMAU

	Study	Age (year)	Weight (kg)[a]	Clcr (mL/min)[a]
Mean (CV) Range n[b]	HMAQ	41.1 (24.6%) 18.7– 62.7	82.4 (23.3%) 42.7– 138	94.5 (27.5%)
		142	142	142
	HMAU	43.9 (29.4%) 18.7–70.7	65.2 (20.6%) 45.0–110	72.9 (23.4%)
		81	81	81
	Overall	42.1 (26.8%) 18.7–70.7	76.1 (25.2%) 42.7–138	86.7 (29.3%)
		223	223	223

Clcr = Creatinine Clearance estimated by Method of Cockroft and Gault.
a For Weight and Clcr statistics are based on the first record per patient.
b n = Number of patients included in the pharmacokinetic analysis.

Table 94 Table SAAW.9.1. Demographics for Patients Included in the Population Pharmacokinetic Analysis for Study SAAW

	Duloxetine Treatment Group	Age (yr)	Body Weight (kg)
Mean (%CV) Range na	20 mg QD	50 (14.7%) 35 – 64	79.0 (23.9%) 53.1 – 150.3
		47	47
	20 mg BID	49 (15.4%) 36 - 64	75.1 (21.0%) 50.8 – 113.5
		40	40
	40 mg BID b	48 (19.2%) 28 – 64	79.8 (18.1%) 54.5– 115.3
		41	41

a n = Total number of patients included in the duloxetine pharmacokinetic analysis.
b Patients were dose-escalated from 20 mg (Week 1) to 30 mg (Week 2) to 40 mg (Week 3-12)

Table 95 Table SAAB.8.1. Summary of Patient-Specific Factors in Study SAAB

Patient Specific Factor	Duloxetine Dose[a] (mg)		
	20 mg	30 mg	30 / 40 mg
n b	22	25	23
AGE	50.9 (26.2) 23.5 - 76.1	55.8 (23.0) 31.7 - 76.8	59.6 (17.8) 42.8 - 73.2
BSA (m^2)	1.82 (10.8) 1.57 - 2.37	1.83 (12.3) 1.48 - 2.20	1.81 (11.3) 1.51 - 2.20
Clcr (ml/min)	83.8 (39.7)	81.3 (38.4)	72.8 (34.2)

a Values are Mean, (CV%), Range
b n = total number of patients.
Clcr = Creatinine Clearance estimated by Method of Cockroft and Gault

8.11.1.3 Results

Simply based upon what we knew *a priori* about duloxetine from *in vitro* experiments, traditional descriptive pharmacokinetic studies, and the design and analysis of the population pharmacokinetic data we can make a number of predictions about what the results of the population pharmacokinetic analyses would be.

These include the following:

- Gender effect with higher exposures in women. This is based upon the contribution of CYP1A2 to overall clearance and the known lower expression of CYP1A2 in women.

- Effect of smoking with lower exposures in smokers. This is based upon the contribution of CYP1A2 to overall clearance and the known induction of CYP1A2 in smokers.

- Lack of effect of duration of smoking rather, however, the # of packs per day might be expected to correlate.

- Dose effect and nonlinear accumulation due to the nonlinear pharmacokinetics of duloxetine clearance via CYP2D6 metabolism.

- Due to the high volume of distribution, we might expect a correlation between volume and total body weight. In addition, due to the high first pass effect and the fact that the clearance and volume terms are apparent metrics that are determined after oral administration, we would also an effect of bioavailability on both apparent clearance and apparent volume.

- Age might be expected to be a potential covariate if sufficient numbers of extreme elderly subjects were included.

- Lack of effect of ethnic origin due to the small numbers of individuals from ethnic backgrounds with high proportions of CYP2D6 poor metabolizers that were included.

- Lack of effect of serum creatinine or Clcr as individuals with severe or endstage renal disease were not included.

- Lack of effect of other laboratory values as most of these lab values are indicative of acute insults that tend to poorly correlate with long term decreases in hepatic metabolism, with the exception of albumin and direct bilirubin.

- An extremely high residual inter-patient variability is expected as CYP2D6 phenotype is expected to be the one of the major determinants of inter-patient variability and this was not examined as a covariate in any pop pk analysis.

Consequently, most other covariates are expected to explain much less of the inter-subject variability.

The sponsor's results tend to confirm these *a priori* expectations.

The sponsor *a priori* defined any change in exposure of <100%, explainable by covariates as clinically insignificant. In this reviewer's opinion this is scientifically inappropriate for several reasons.

- First differences in clinical effects should be correlated with different degrees of exposure and this should define clinically significant differences, not an arbitrary value.

- Second, PK/PD relationships may be more complex than simply difference in overall exposure, i.e. they may be related to rate of change in concentrations, Cmax, metabolite exposures or differences in genetic susceptibility.

- Third, assuming that the sponsor's claim that CYP2D6 and CYP1A2 are each responsible for equivalent amounts of duloxetine's elimination is true, which it is not. We expect that the covariates likely to be statistically significant would be unlikely to explain more than 50% of the inter-subject variability, and likely less than that since they are covariates associated with CYP1A2 variability and as most of the inter-subject variability would reside in CYP2D6's polymorphism and nonlinearity. Since 2D6 phenotype was not evaluated as a covariate and nonlinearity was only grossly addressed by dose. By simple inspection of the data from the descriptive pharmacokinetic studies we would expect *a priori* that it would unlikely to find a combination of covariates that explains a 100% intersubject difference using the covariates that were examined.

- This is not to say that a difference of 100% or even more may be required

Due to the inherent misspecification of the model used, the quantitative results are presumed to be inherently biased. Thus, the sponsor's results are simply reported in the following sections without any attempt at reanalysis.

8.11.1.3.1 AQUApop

In major depressive disorder, gender and smoking status were found to be significant covariates for clearance, and smoking was found to be significant covariate for bioavailability, (see Table 96 through Table 98).

Table 96 Table 9.4. Pharmacokinetic Parameters in Base and Final Population Model Studies F1J-MC-HMAQ and F1J-MC-HMAU

Parameter Description	Base Population Model		Final Population Model	
	Population Estimate (%SEE)	Interpatient Variability (%SEE)	Population Estimate (%SEE)	Interpatient Variability (%SEE)
Rate of Absorption				
Parameter for Ka (hr^{-1})	0.343	---	0.343 a	---
Clearance				
Parameter for Cl/F (L/hr)	55.5 (4.58)	62.0% (11.0)		
Base parameter for CL/F; male(L/hr)			80.5 (7.47)b	50.5% (11.8)
Base parameter for CL/F; female(L/hr)			48.3 (5.78)b	
Effect of dose on CL/F			-0.00547 (18.3)	
Volume of Distribution				
Parameter for V/F(L)	2650 (16.8)	80.9% (19.0)	1690 (9.64)b	81.9% (22.1)
Bioavailability				
Effect of smoking status on F c			0.658 (7.22)	
Residual Error				
Exponential (%)	31.9% (8.87)		31.8% (8.69)	

Abbreviations: SEE = standard error of the estimate; Ka = absorption rate constant; CL/F = apparent clearance; V/F = apparent volume of distribution; F = bioavailability.
a CL/F (male) = 80.5 ×Exp[-0.00547 ×(Dose - 20)]
CL/F (female) = 48.3 ×Exp[-0.00547 ×(Dose - 20)]
b The population estimate for nonsmokers. Smokers had an approximately 1 5-fold higher value according to the relationship between F and smoking status.
c F (smokers) / F (nonsmokers) = 0.658.

Table 97 Table 9.6. Effects of Gender and Dose on Apparent Clearance in Studies F1J-MC-HMAQ and F1J-MC-HMAU

CL/F (L/hr)	Dosage			
	20 mg BID	30 mg BID	40 mg BID	60 mg BID
All Patients				
Geometric Mean	60.3	58.8	49.7	44.0
Range				
N a	146	129	202	171
Female				
Geometric Mean	51.7	50.2	42.6	38.5
Range				
N a	97	84	138	119
Male				
Geometric Mean	82.0	79.2	69.2	59.7
Range				
N a	49	45	64	52

a Number of patients participating in a dosing regimen.

Table 98 Predicted Average Steady-State Concentrations of Duloxetine Studies F1J-MC-HMAQ and F1J-MC-HMAU

Patient Subgroup	Cav^{pred} (ng/ml) Dosage			
	20 mg BID	30 mg BID	40 mg BID	60 mg BID
All Patients	28.9	44.5	69.0	117
n b	145	129	201	171
Female Nonsmokers	37.3	57.6	87.3	143
n b	70	60	98	86
Female Smokers	21.0	33.6	56.3	96.7
n b	26	24	39	33
Male Nonsmokers	21.4	33.9	52.8	90.3
n b	38	35	45	39
Male Smokers	19.4	29.4	38.9	74.2
n b	11	10	19	13

a Values are mean (range)
b Number of patients participating in a dosing regimen.

8.11.1.3.2 SAAB

In study SAAB age was found to be a significant covariate with clearance, (see Table 99 through Table 99).

Table 99 Table SAAB.8.2. Pharmacokinetic Parameters of Duloxetine Estimated by Using the Base Model

Parameter Description	Population Estimate	%SEE
Pharmacokinetic and Covariate Parameters		
Θ_1, Typical value for Cl/F (L/hr)	61.0	8%
Θ_2, Typical value for V/F (L)	1230	9%
Θ_3, Typical value for ka (hr^{-1})	0.351	20%
Variability		
Between-patient variability in CL (ω_{Cl})	63%	25%
Interaction between ω_{CL} and . ω_V	53%	25%
Between-patient variability in V (ωV)	56%	26%
Proportional residual error (σ)	38%	13%

Table 100 Table SAAB.8.3. Identification of Significant Patient-Specific Factors During the Model Building Process

	MOF[a]	ΔMOF[a]	p-value
Covariate on CL/F			
$TVCL = \Theta_1 - \Theta_4 \cdot AGE$	1488.958	15.848	<0.001
$TVCL_b = \Theta_1 \cdot (1 + I1\ \Theta_4)$	1498.767	6.039	<0.05
$TVCL_c = \Theta_1 \cdot (1 + I1\ \Theta_4)$	1500.302	4.504	<0.05
Covariate on V/F			
No significant covariates identified			

a Base Model MOF = 1504.806
b indicator variable for Alcohol (ALC), I1 = 0; If ALC = 2 (Drinker), then I1 = 1
c indicator variable for Dose (DDI), I1 = 0; If DDI = 40000 (40mg), then I1 = 1

Table 101 Table SAAB.8.5. Effect of Age on Oral Clearance of Duloxetine

Age (yr)	Estimate of CL/F (L/hr)
23.5	95.6
55.5	62.3
76.8	40.1

8.11.1.3.3 SAAW

In study SAAW, age was found to be significant covariate for clearance, (see Table 102 and Table 103). In addition, descriptive statistics of concentration vs. dose and sample since beginning treatment indicates the presence of nonlinear kinetics, (see Table 104).

Table 102 Table SAAW.9.3. Pharmacokinetic Parameters in Base and Final Population Model

Parameter Description	Base Population Model		Final Population Model	
	Population Estimate (%SEE)	Interpatient Variability (%SEE)	Population Estimate (%SEE)	Interpatient Variability (%SEE)
Rate of Absorption				
Parameter for Ka(hr-1)	0.225 (24.2)	---	0.212 (17.2)	---
Clearance				
Parameter for CL/F(L/hr)	47.4 (5.76)	56.7% (18.9)	47.1 (5.39)	52.3% (18.8)
Effect of age on CL/F			-1.13 (27.9)	
Volume of Distribution				
Parameter for V/F(L)	653 (22.5)	---	768 (17.2)	61.6% (31.7)
Residual Error				
Additive (ng/mL)		7.97 (14.5)		6.08 (23.0)
Proportional (%)		26.2 (19.4)		27.6 (17.6)

Abbreviations: SEE = standard error of the estimate; Ka = absorption rate constant; CL/F = apparent clearance; V/F = apparent volume of distribution.
a CL/F = 47.1 + (AGE - 49.68) * (-1.13)

Table 103 Table SAAW.9.5. Effect of Age on Clearance Estimates

Age (years)	Population Estimate of Duloxetine Clearance (L/hr)
28 (population minimum)	71.6
36 (5th percentile)	62.6
49 (median)	47.9
63 (95th percentile)	32.0
64 (population maximum)	30.9

Table 104 Table SAAW.9.2. Descriptive Summary of Observed Plasma Duloxetine Concentrations

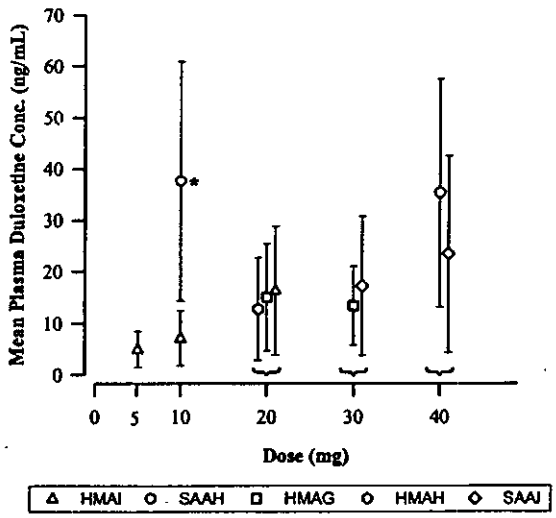
Duloxetine Dose	Mean Duloxetine Concentrations (ng/ml) (CV%)				
	Visit 3 Week 0	Visit 4 Week 4	Visit 5 Week 8	Visit 6 Week 12	Overall Steady State a
20 mg QD	11.18 (92.4)	25.07 (77.5)	25.67 (76.8)	21.44 (86.7)	23.48 (81.3)
n b	44	42	41	77	160
20 mg BID	12.72 (88.4)	44.18 (43.4)	38.61 (47.9)	38.34 (45.3)	39.93 (45.5)
n b	81	36	33	69	138
40 mg BID	—	90.21 (58.0)	106.92 (69.9)	108.75 (76.6)	103.49 (71.6)
n b	—	34	35	63	132

a The concentrations at Visit 3 (start of duloxetine treatment, Week 0) were not included because steady state was not reached.
b n = number of patients for whom quantifiable plasma concentrations, as well as sample draw times, were available.

8.11.1.3.4 SUMMpop

Descriptive statistics for mean duloxetine plasma concentrations for patients across studies HMAG, HMAH, HMAI, SAAH, and SAAI, (SUMMpop), indicate clear effects of gender and smoking status, but no clear effect of dose. Possibly, due to patient populations and other factors being inconsistent across the studies included for evaluation, (See Figure 44, Table 105, and Table 106).

Figure 44 Mean Duloxetine Concentrations by Dose (PopPK Report SUMMpop)



Some data points plotted at 20, 30, or 40 mg on the dose axis have been moved to the right or left off the grid to improve data clarity.
* See note in text (Section 9.1 Pharmacokinetic Results) regarding these data

Figure 9.1. Mean (SD) plasma concentrations (ng/ml) of duloxetine (by dose) for patients included in the pharmacokinetic analysis from studies HMAG, HMAH, HMAI, SAAH, and SAAI.

Table 105 Table 9.2. Descriptive Statistics for Duloxetine Plasma Concentrations (ng/mL) (by Gender) for Patients from Studies HMAG, HMAH, HMAI, SAAH, and SAAI. (SUMMpop)

Dose	5 mg		10 mg		20 mg		30 mg		40 mg	
Study	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
HMAG					17.1 ± 11.2 (65.3) [14.9]	12.3 ± 8.79 (71.5) [8.91]	14.1 [14.1]	12		
N					49	37	2	1		
HMAH					14.9 ± 10.9 (72.8) [12.2]	8.72 ± 6.15 (70.5) [7.0]				
N					144	80				
HMAI	5.05 ± 3.67 (72.5) [3.69]	4.56 ± 3.11 (68.2) [3.48]	7.79 ± 6.01 (77.1) [6.2]	5.68 ± 3.24 (57.1) [4.45]	17.3 ± 13.5 (78) [14.5]	14.9 ± 10.9 (73.1) [10.6]				
N	84	34	117	56	105	70				
SAAH			33.1 ± 23.4a (70.7) [28.3]	49.7 ± 22.3a (44.9) [48.9]					38.7 ± 22 (56.9) [33]	13.9 ± 5.45 (39.2) [14.3]
N			8	3					24	4
SAAI								17.2 ± 13.5 (78.6) [13.6]		23.4 ± 19.1 (81.8) [16.4]
N								92	-	37

Values are mean ± SD, (CV), range, [median]
a Data likely reflect prior doses of 40 mg

Table 106 Table 9. 3. Descriptive Statistics for Duloxetine Plasma Concentrations (ng/ mL) (by Smoking Status) for Patients from Studies HMAG, HMAH, HMAI, SAAH, and SAAI (SUMMpop)

Study	Dose									
	5 mg		10 mg		20 mg		30 mg		40 mg	
	Smoker	Non-Smoker	Smoker	Non-Smoker	Smoker	Non-Smoker	Smoker	Non-Smoker	Smoker	Non-Smoker
HMAG					9.77 ± 66 (6.46)	16.2 ± 66.6 (10.8)		13.4 ± 56.9 (7.61)		
					[7.87]	[13.3]		[[12]		
N					16	70		3		
HMAH					7.65 ± 5.69 (74.5)	14.5 ± 10.5 (72.3)				
					[6.13]	[11.6]				
N					57	167				
HMAI	**4.36 ± 2.77** (63.7)	5.17 ± 3.8 (73.4)	6.75 ± 4.13 (61.2)	7.76 ± 6.88 (88.7)	12.6 ± 6.49 (51 5)	18.3 ± 14.4 (78.7)				
	[3.39]	[3.65]	[5.97]	[5.41]	[11]	[15.4]				
N	38	80	103	67	60	115				
SAAH			29.2 ± 20.3 a (69.3)	42.4 ± 25 a (59)					28.9 ± 21.1 (73.3)	37.7 ± 22.7 (60.2)
			[28.3]	[40.5]					[22.4]	[29.9]
N			4	7					8	20
SAAI							28.5 ± 25.1 (88)	16.2 ± 11.9 (73.1)	29.4 ± 22.2 (75.4)	21.5 ± 18.1 (8.42)
							[12.8]	[13.6]	[17.9]	[15.3]
N							7	85	9	28

Values are mean ± SD, (CV), range, [median]
a According to sponsor data likely reflects prior doses of 40 mg

8.11.2 JAPANESE STUDIES

Twelve studies, examining duloxetine bioavailability and pharmacokinetics, have been conducted in Japan [redacted] No data has been submitted from these studies as it was claimed that the data has not been analyzed.

A list of these studies and the type of formulations used can be found in § 10.1 Appendix 1 Human Clinical Pharmacology and Biomaterial Studies.

9 REGULATORY ISSUES

9.1 WAIVER REQUEST

9.2 ONGOING STUDIES

The following studies were reported as ongoing in the amendment dated March 12, 2002

Study SBBN	Assessment of Pharmacodynamic Effects and Safety During Treatment with Increasing Doses of Duloxetine
Study SBAS	Duloxetine/Tolterodine Interaction Study

10 APPENDICES

10.1 APPENDIX 1 HUMAN CLINICAL PHARMACOLOGY AND BIOMATERIAL STUDIES

Table 107 Human Clinical Pharmacology and Biomaterial Studies in NDA 21427 (Duloxetine Hydrochloride for Depression)

Protocol Number	Protocol Title	NDA Vol.	Dates
Human Biomaterial Studies			
ADME Report 62:	In Vitro Protein Binding of 14C-Duloxetine in Mouse, Rat, Dog, and Human Plasma at a Concentration of 150.2 ng/mL	36	—
ADME Report 58 – Amendment 01:	In Vitro Protein Binding of 14C-Duloxetine in Plasma from American and Japanese Men and Women at a Concentration of 150.2 ng/mL	36	—
ADME Report 31:	Protein Binding of LY248686 in Rat, Dog and Human Plasma	36	—
ADME Report 45:	In Vitro Interaction of Duloxetine with Human Cytochromes P450 CYP3A and CYP2D6	36	—
ADME Report 64:	In Vitro Interaction of Duloxetine, LY248686, with Human Cytochromes P450 CYP2C9 and CYP1A2	36	—
ADME Report 72:	Identification of the Human Cytochromes P450 Responsible for the Formation of the 4-, 5-, and 6-Hydroxy Metabolites of Duloxetine (LY248686)	36	—
ADME Report 77:	Examination of CYP1A2 and CYP3A Induction by Duloxetine (LY248686) in Primary Cultures of Human Hepatocytes	36	—
ADME Report 70:	NMR Identification of 5-Hydroxy 6-Methoxy Duloxetine-O-Sulfate as a Human Metabolite of Duloxetine	36	—
Descriptive PK			
F1J-LC-HMBI	IV Absolute Bioavailability	35	Jul 2001
F1J-LC-HMAA:	LY248686 Hydrochloride (Immediate-Release) Dose-Ranging Study: Safety and Preliminary Disposition in Normal, Healthy Volunteers	41	Aug – Sept 1991
F1J-LC-HMAB.	LY248686 Hydrochloride (Enteric-Coated) Dose-Ranging Study: Safety and Preliminary Disposition in Normal, Healthy Volunteers	41 – 42	Mar – Apr 1992
F1J-LC-HMAD:	LY248686 Hydrochloride (Enteric-Coated) Multiple-Dose Dose-Ranging Study: Safety and Disposition in Normal, Healthy Volunteers	40 – 41	Jul – Aug 1992
F1J-LC-HMAP:	(LY248686) Duloxetine HCl: Oral Multiple Dose Study II	39 – 40	Apr – May 1997
F1J-BD-HMAR:	(LY248686) Duloxetine HCl: A Single-Blind, Placebo-Controlled Study to Investigate Safety and Pharmacokinetics of Dose Ranging of Duloxetine b.i.d. in Healthy Volunteers	38 – 39	Nov – Dec 1998
Mass Balance			
F1J-LC-HMAF:	LY248686 Hydrochloride (Duloxetine HCl): [14C]-Labeled LY248686 HCl Study of Absorption, Distribution, Metabolism, and Excretion in Normal Human Volunteers	37	Nov 1992
F1J-LC-SAAZ:	[14-C]-LY248686: Disposition After Oral Administration in Healthy Subjects	36 – 37	Oct – Nov 1998
Metabolite Kinetics			
F1J-LC-HMBN:	A Study Examining the Plasma Concentrations and Pharmacokinetics of Duloxetine (and Metabolites) When a Single 60-mg Dose and Multiple (Steady State) 60-mg BID and QD Doses of Duloxetine are Administered to Healthy Subjects	37 – 38	Mar – Apr 2001

Protocol Number	Protocol Title	NDA Vol.	Dates
Bioequivalence			
F1J-LC-HMAO:	Pilot Bioequivalency Study: Duloxetine HCl Enteric-Coated Tablets Compared With Capsules Containing Enteric-Coated Pellets	36	Jun – Jul 1994
F1J-LC-HMBG	Duloxetine Bioequivalence Study	35 – 36	Aug 2000
Intrinsic Factors [e.g., Age, Ethnic Groups, Organ Dysfunction, Gender, Body Size and Weight]			
F1J-LC-SAAY:	Pharmacokinetics of Duloxetine in the Elderly	42	
F1J-LC-HMBJ:	Single Dose Pharmacokinetics of Duloxetine in Subjects with End Stage Renal Disease	42 – 43	
F1J-LC-HMAX:	Single Dose Pharmacokinetics of Duloxetine in Patients with Cirrhosis Compared with Healthy Subjects	43	
Extrensic Factors [e.g., Dietary Factors, Smoking, Drug-Drug Interactions]			
F1J-LC-HMAZ:	Duloxetine/Desipramine Interaction Study	44	Nov – Dec 1999
F1J-FW-SBAG:	Evaluation of Duloxetine Paroxetine Pharmacokinetic Interaction in Healthy Subjects	44 – 45	Feb – April 2001
F1J-BD-HMBF:	A Double-Blind Cross-Over Study to Investigate the Effects of Duloxetine (LY248686) on the Pharmacokinetics of a Single IV Dose of Theophylline in Healthy Male Subjects	45 – 46	
F1J-LC-SBAA:	The Effect of Food and Bedtime Administration on the Rate and Extent of Duloxetine HCl Absorption	46	
F1J-FW-HMBB:	Evaluation of the Impact of Gastric pH and the Presence of Activated Charcoal on the Absorption of Duloxetine in Healthy Subjects	46 – 47	
POP PK			
F1J-MC- HAMQ (ab): F1J-MC-HMAU:	Population PK Study Reports \Hpbio\Hupharm\Pk\PopPk Population PK Report for F1J-MC- HAMQ (ab): and F1J-MC-HMAU:	47 – 48	
F1J-MC-SAAB	Population Pharmacokinetic Analysis of Study: F1J-MC-SAAB Duloxetine for Urinary Incontinence: A Multiple-Dose Study for Efficacy and Safety	48	
F1J-MC-SAAW	Population Pharmacokinetic Analysis of Study: F1J-MC-SAAW Duloxetine Versus Placebo in the Relief of Stress Incontinence	49	
	Combined Descriptive Summary Population PK Report	49	
Human Pharmacodynamics (PD) Study Reports			
F1J-LC-BD-O001:	A Double-Blind Placebo Controlled Comparison of the Effects of Duloxetine (LY248686) and Desipramine on the Tyramine Pressor Test in Healthy Volunteers	49 – 50	
F1J-LC-HMAE:	LY248686 Hydrochloride (Duloxetine): Influence on Mood of Normal Volunteers	50 – 51	
F1J-MC-SAAN:	Assessment of the Serotonin and Norepinephrine Reuptake Blocking Properties of Duloxetine in Healthy Subjects	51	
PD Interactions			
F1J-LC-HMBA:	Duloxetine-Ethanol Interaction Study	51	March – June 2000

Protocol Number	Protocol Title	NDA Vol.	Dates
F1J-BD-HMBD:	A Pharmacokinetic and Pharmacodynamic Evaluation of the Combined Administration of Duloxetine (LY248686) and Lorazepam in Healthy Subjects	51 – 52	April – June 2000
F1J-LC-HMAJ:	Duloxetine- Temazepam Drug Interaction Study	52 – 53	Oct – Nov 1993
	Japanese Studies		
F1J-JE-106G:	Repeated Administration Test (40 mg, 7 days)	53 – 54	
F1J-JE-107G:	Pharmacokinetic Study in the Elderly	55 – 56	
F1J-JE-1005:	Study of Effects of Meals, and Capsules Filled with Enteric-Coated Granules	57 – 58	
	Other Clinical Pharmacology Studies		
F1J-JE-1001:	Phase I Clinical Trial of LY248686 (Single- Dose Study)	58	
F1J-JE-1002:	Phase I Clinical Study (Bioavailability Comparison Test Between 10mm tablets and 7.5mm tablets)	58	
F1J-JE-1003:	Phase I Clinical Trial of LY248686 (Repeated- Dose Study)	58	
F1J-JE-1004:	LY248686 Phase I Clinical Trial (Single-Dose Study; Capsules containing enteric-coated granules)	58	
F1J-JE-1006:	Phase I Clinical Trial of LY248686: Repeated Dose Study (Capsules Filled with Enteric Coated Granules)	58	
F1J-JE-101G:	Investigation of Platelet Serotonin Uptake Inhibition in Subjects Receiving LY248686	59	
F1J-JE-103G:	Phase I Clinical Study of LY248686 (Bio- Equality (1))	59	
F1J-JE-104G:	Phase I Clinical Study of LY248686 (Bio- Equality (2))	59	
F1J-JE-105G:	LY248686 Phase I Clinical Study Protocol. Bioequivalence Study (3)	59	

10.2 APPENDIX 2 DULOXETINE FORMULATIONS USED IN HUMAN STUDIES

Table 108 Duloxetine Formulations Used in Human Studies

Protocol Number	Protocol Title	Formulation	Strength	Lot	Plant	Date Packaged
Descriptive Pharmacokinetic & Bioavailability Studies						
F1J-LC-07-24	IV Absolute Bioavailability	**EC 20% Caps** IV Solution	**60 mg** 0.8 mg in	**CT17676** CT19808	**Indianapolis** "	**07-24-00** 07-03-00
F1J-LC-HMAA	LY248686 Hydrochloride (Immediate-Release) Dose-Ranging Study: Safety and Preliminary Disposition in Normal, Healthy Volunteers	IR Cap	1 mg 5 mg 10 mg 25 mg	CT00074 CT00075 CT00076 CT00077	Indianapolis	7-11-91 " " "
F1J-LC-HMAB	LY248686 Hydrochloride (Enteric-Coated) Dose-Ranging Study: Safety and Preliminary Disposition in Normal, Healthy Volunteers	EC Tablet	5 mg 10 mg 20 mg 40 mg 60 mg	CT01090 CT01091 CT01092 CT01093 CT01094	Indianapolis	03-09-92 " " " "
F1J-LC-HMAD	LY248686 Hydrochloride (Enteric-Coated) **Multiple**-Dose Dose-Ranging Study: Safety and Disposition in Normal, Healthy Volunteers	EC Tablet	2.5 mg 5.0 mg 10.0 mg 20.0 mg 40.0 mg	CT01418 CT01090 CT01091 CT01092 CT01093	Indianapolis	03-09-92 " " " 06-08-92
F1J-LC-HMAP	(LY248686) Duloxetine HCl: Oral **Multiple** Dose Study II	EC 5% Caps EC 10% Caps	10 mg 20 mg	CT08000 CT08001	Indianapolis	03-25-97 "
F1J-BD-HMAR	(LY248686) Duloxetine HCl: A Single-Blind, Placebo-Controlled Study to Investigate Safety and Pharmacokinetics of Dose Ranging of Duloxetine **b.i.d.** in Healthy Volunteers	EC 10% Caps	20 mg	CT131116		11-05-98
Mass Balance						
F1J-LC-HMAF	LY248686 Hydrochloride (Duloxetine HCl) [14C]-Labeled LY248686 HCl Study of Absorption, Distribution, Metabolism, and Excretion in Normal Human Volunteers	EC Tablet		CT01844	Indianapolis	10-27-1994?
F1J-LC-SAAZ	[14-C]-LY248686: Disposition After Oral Administration in Healthy Subjects	EC Tablet		CT12953	Indianapolis	10-02-98
Metabolite Kinetics						
F1J-LC-HMBN	A Study Examining the Plasma Concentrations and Pharmacokinetics of Duloxetine (and Metabolites) When a Single 60-mg Dose and Multiple (Steady State) 60-mg **BID** and QD Doses of Duloxetine are Administered to Healthy Subjects	**EC 20% Caps**	**60 mg**	**CT17676**	**Indianapolis**	**07-24-00**
Bioequivalence						
F1J-LC-HMAO	Pilot Bioequivalency Study: Duloxetine HCl Enteric-Coated Tablets Compared With Capsules Containing Enteric-Coated Pellets	EC Tablet EC 5% Caps EC 10% Caps	20 mg 5 mg 20 mg	CT03155 CT03338 CT03157	Indianapolis " "	06-06-94 " "
F1J-LC-HMBG	Duloxetine Bioequivalence Study	EC 10% Caps **EC 20% Caps**	20 mg **60 mg**	CT17675 **CT17676**	Indianapolis "	**07-24-00** "
Intrinsic Factors [e.g., Age, Ethnic Groups, Organ Dysfunction, Gender, Body Size and Weight]						
F1J-LC-SAAY	Pharmacokinetics of Duloxetine in the Elderly	EC 10% Caps	20 mg	CT11439	Indianapolis	06-05-98
F1J-LC-HMBJ	Single Dose Pharmacokinetics of Duloxetine in Subjects with End Stage Renal Disease	EC 10% Caps	20 mg	CT15688	Indianapolis	11-01-99
F1J-LC-HMAX	Single Dose Pharmacokinetics of Duloxetine in Patients with Cirrhosis Compared with Healthy Subjects	EC 10% Caps	20 mg	CT15688	Indianapolis	11-01-99

Table 109 Duloxetine Formulations Used in Human Studies (Continued)

Protocol Number	Protocol Title	Formulation	Strength	Lot	Plant	Date Packaged
Extrinsic Factors [e.g., Dietary Factors, Smoking, Drug-Drug Interactions]						
F1J-LC-HMAZ	Duloxetine/Desipramine Interaction Study	EC 10% Caps	20 mg	CT15688	Indianapolis	11-01-99
F1J-FW-SBAG	Evaluation of Duloxetine Paroxetine Pharmacokinetic Interaction in Healthy Subjects	***EC 20% Caps***	***20 mg***	***CT19715***	***Indianapolis***	***03-14-01***
F1J-BD-HMBF	A Double-Blind Cross-Over Study to Investigate the Effects of Duloxetine (LY248686) on the Pharmacokinetics of a Single IV Dose of Theophylline in Healthy Male Subjects	EC 10% Caps	20 mg	00340647	—	10/31/00
F1J-LC-SBAA	The Effect of Food and Bedtime Administration on the Rate and Extent of Duloxetine HCl Absorption	EC 10% Caps	20 mg	CT11439	Indianapolis	06-05-98
F1J-FW-HMBB	Evaluation of the Impact of Gastric pH and the Presence of Activated Charcoal on the Absorption of Duloxetine in Healthy Subjects	EC 10% Caps	20 mg	CT16508	Indianapolis	03-07-00
Population Pharmacokinetics						
F1J-MC- HAMQ (ab): F1J-MC-HMAU	Population PK Study Reports \Hpbio\Hupharm\Pk\PopPk Population PK Report for F1J-MC- HAMQ (ab): and F1J-MC-HMAU:					
F1J-MC-SAAB	Population Pharmacokinetic Analysis of Study. F1J-MC-SAAB Duloxetine for Urinary Incontinence: A Multiple-Dose Study for Efficacy and Safety	EC 5% Caps EC 10% Caps		CT05939 CT04363	Indianapolis	03-21-96 05-08-95
F1J-MC-SAAW	Population Pharmacokinetic Analysis of Study: F1J-MC-SAAW Duloxetine Versus Placebo in the Relief of Stress Incontinence	EC 5% Caps EC 10% Caps		CT11469 CT11755 CT11612 CT12646		06-09-98 08-05-98 05-13-98 10-02-98
	Combined Descriptive Summary Population PK Report					
Human Pharmacodynamics (PD) Study Reports						
F1J-LC-BD-O001	A Double-Blind Placebo Controlled Comparison of the Effects of Duloxetine (LY248686) and Desipramine on the Tyramine Pressor Test in Healthy Volunteers	EC 10% Caps		99340437 99340900	—	07-15-99 11-30-99
F1J-LC-HMAE	LY248686 Hydrochloride (Duloxetine): Influence on Mood of Normal Volunteers	EC Tablet		CT01090 CT01092	Indianapolis	03-09-92 09-09-92
F1J-MC-SAAN	Assessment of the Serotonin and Norepinephrine Reuptake Blocking Properties of Duloxetine in Healthy Subjects	EC 5% Caps EC 10% Caps		CT08071	Indianapolis	05-01-97
Pharmacodynamic Drug Interaction Studies						
F1J-LC-HMBA	Duloxetine-Ethanol Interaction Study	EC10% Caps		CT15688	Indianapolis	11-01-99
F1J-BD-HMBD	A Pharmacokinetic and Pharmacodynamic Evaluation of the Combined Administration of Duloxetine (LY248686) and Lorazepam in Healthy Subjects	EC 10% Caps		00340027 00330030	—	03-14-00
F1J-LC-HMAJ	Duloxetine- Temazepam Drug Interaction Study	EC Tablet		CT01092	Indianapolis	03-09-92
Efficacy Studies						
MC-HMAQ A & B		EC 5% Caps EC 10% Caps		CT13506 CT13534 CT14378 CT14381 CT15917 CT16312 CT16332 CT17067	Indianapolis " " " " " " "	01-22-99 " 05-03-99 " 12-10-99 01-31-00 03-03-00 06-02-00
MC-HMAT A & B		EC 10% Caps		CT16423 CT16744 CT17335 CT17968	Indianapolis " " "	02-15-00 05-12-00 07-12-00 11-07-00
MC-HMBH A & B		EC 10% Caps		CT18124	Indianapolis	11-01-00

Table 110 Duloxetine Formulations Used in Human Studies (Continued)

Protocol Number	Protocol Title	Formulation	Strength	Lot	Plant	Date Packaged
Safety Studies						
		EC10% Caps		CT15828	Indianapolis	12-06-99
				CT16299	"	03-23-00
				CT16518	"	05-19-00
				CT16745	"	06-09-00
				CT17204	"	07-05-00
				CT17610	"	07-05-00
				CT17617	"	08-01-00
				CT18409	"	12-07-00
				CT18923	"	02-16-01
				CT19092	"	03-01-01
				CT19093	"	01-30-01
				CT19098	"	01-30-01
				CT19109	"	03-06-01
				CT20489	"	04-018-01
Japanese Studies						
F1J-JE-106G	Repeated Administration Test (40 mg, 7 days)	Caps	20 mg	CP6015		≤ Apr 96
F1J-JE-107G	Pharmacokinetic Study in the Elderly	Caps	10 mg	CF6014		≤10-08-96
F1J-JE-1005	Study of Effects of Meals, and Capsules Filled with Enteric-Coated Granules	EC Granule Caps	10 mg	CP3001		≤03-18-93
Other Clinical Pharmacology Studies						
F1J-JE-1001	Phase I Clinical Trial of LY248686 (Single- Dose Study)	EC Tabs 10 mm ?	2.5 mg 5 mg 10 mg 20 mg 40 mg 60 mg			≤ June 92
F1J-JE-1002	Phase I Clinical Study (Bioavailability Comparison Test Between 10mm tablets and 7.5mm tablets)	EC Tab 7.5 mm EC Tab 10 mm	20 mg 20 mg			≤ Oct 92
F1J-JE-1003	Phase I Clinical Trial of LY248686 (Repeated- Dose Study)	EC Tab 7.5 mm	20 mg			≤ Dec 92
F1J-JE-1004	LY248686 Phase I Clinical Trial (Single-Dose Study; Capsules containing enteric-coated granules)	EC Tab 7.5 mm EC Granule Caps	20 mg 10 mg			≤ Feb 93
F1J-JE-1006	Phase I Clinical Trial of LY248686: Repeated Dose Study (Capsules Filled with Enteric Coated Granules)	EC Granule Caps	10 mg			≤ Apr 93
F1J-JE-101G	Investigation of Platelet Serotonin Uptake Inhibition in Subjects Receiving LY248686	EC Granule Caps	10 mg			≤ Sept 94
F1J-JE-103G	Phase I Clinical Study of LY248686 (Bio- Equality (1))	EC Granule Caps EC Granule Caps	10 mg 10 mg		[redacted] Lilly	≤ Nov 94
F1J-JE-104G	Phase I Clinical Study of LY248686 (Bio- Equality (2))	EC Granule Caps EC Granule Caps	10 mg 20 mg		Lilly Lilly	≤ Aug 95
F1J-JE-105G	LY248686 Phase I Clinical Study Protocol: Bioequivalence Study (3)	EC Granule Caps EC Granule Caps	5 mg 10 mg		Lilly Lilly	≤ Aug 95

10.3 APPENDIX 3 BIOANALYTIC ASSAY METHODS USED IN CLINICAL STUDIES

Table 111 Duloxetine Bioanalytic Assay Methods Used in Clinical Studies

Assay #	Analyte	Method Description	Matrix	Range	Studies	Comment
5NJ- 18, Rev. 3	Parent		Plasma	ng/ mL	F1J-LC-HMAA	**Unacceptable** bias and variability
5NJ- 18, Rev. 4,	Plasma		Plasma	ng/ mL	F1J-LC-HMAB	"
6204- 122, [redacted] b	Parent		Plasma	ng/ mL	F1J-MC-SAAB F1J-MC-SAAH F1J-MC-SAAI F1J-MC-SAAL F1J-MC-SAAN F1J-MC-HMAH	**Unacceptable** potential interfering endogenous substance
[redacted] -004- 01	Parent	LC/ MS/ MS	Plasma	ng/ mL	F1J-MC-SAAW F1J-LC-SAAY F1J- LC- SAAZ F1J- LC- SBAA	**Acceptable.**
138371_ R2 f	Parent	LC/ MS/ MS	Plasma	ng/ mL	F1J-FW-SBAG F1J-MC-HMAQ F1J-BD-HMAR F1J-MC-HMAU F1J-LC-HMAX F1J-LC-HMAZ F1J-LC-HMBA F1J-FW-HMBB F1J-BD-HMBD F1J-BD-HMBF F1J-LC-HMBG F1J-LC-HMBI F1J-LC-HMBJ F1J-LC-HMBN F1J-BD-O001	**Acceptable. Very good.**
LC- F1J- P- PL- July 1992, [redacted]	Parent		Plasma	ng/ mL	F1J-LC-HMAD F1J-LC-HMAE F1J-LC-HMAF	**Biased.**
LC- F1J- PM- PL- 21Jan94,	Parent		Plasma	ng/ mL ng/ mL	F1J-MC-HMAG F1J-LC-HMAO	**Biased.** Potential Interference with Internal Standard.
3MAN009- V01	Parent e		Plasma	ng/ mL	F1J-MC-HMAI	
6204- 122, [redacted] b	Parent e		Plasma	ng/ mL	F1J-LC-HMAJ F1J-LC-HMAP	
6204- 130, [redacted] b	Parent		Urine	ng/ mL	F1J-LC-HMAJ	

Table 112 Duloxetine Metabolite and Bioanalytic Assay Methods and Methods for other Drugs Used in Clinical Studies

Assay #	Analyte	Method Description	Matrix	Range	Studies
5NJ - 18, Rev. 3	LY292117 d		Plasma	Detection limit: Approximately / mL	F1J-LC-HMAA
012684 - 1,	Dextromethorphan Dextrophan	LC/ MS/ MS	Urine	µg/ mL	F1J-FW-SBAG F1J-LC-HMAX
Naphthol, Rev. 1,	Total Naphthol		Plasma	ng/ mL	F1J-LC-HMAA
Naphthol, Rev. 2,	Total Naphthol		Urine	µg/ mL	F1J-LC-HMAA
No method Number,	Free and Total Naphthol		Urine	µg/ mL	F1J LC-HMAB
6204 - 126,	Temazepam		Plasma	ng/ mL	F1J LC-HMAJ
6204 - 129,	Temazepam		Urine	ng/ mL	F1J-LC-HMAJ
906DM - 196- 01	LY550408 LY581920 (metabolites)	LC/ MS/ MS	Plasma	ng/ mL	F1J-LC-HMAX F1J-LC-HMBI F1J-LC-HMBJ F1J-LC-HMBN
906DM - 187- 03	LY550408 (metabolite)	LC/ MS/ MS	Plasma	ng/ mL	F1J-LC-HMBJ
GC78.	Desipramine		Plasma	ng/ mL	F1J-LC-HMAZ F1J-BD-O001
CP005086,	Lorazepam		Plasma	ng/ mL	F1J-BD-HMBD
013331 - 1,	Theophylline	LC/ MS/ MS	Plasma	µg/ mL	F1J-BD-HMBF
012972 - 2,	Theophylline 1-Methylxanthine 3-Methylxanthine 1, 3-Dimethyluric acid	LC/ MS/ MS	Urine	µg/ mL	F1J-BD-HMBF

Abbreviations:
Parent = Duloxetine
LY550408 = Glucuronide conjugate of 4- hydroxy duloxetine
LY581920 = Sulfate conjugate of 5- hydroxy, 6- methoxy duloxetine

a = Methods were developed at Eli Lilly unless otherwise noted

d = Acid catalyzed degradation product of duloxetine
e = Desmethyl duloxetine was validated with this method but sample results were not used

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10.6 APPENDIX 6 COMMON ADVERSE EVENTS OBSERVED IN PHASE I AND II STUDIES

Table 117 Number of Common Adverse Events Observed in Phase I and II Studies

Study	HMBG		HMBN		HMAR *Gender Effect Female vs. Male different AEs*							HMAP		HMAD					HMAB					SAAY elderly Females	HMBJ ESRD	HMAX	Subjects with cirrhosis possible & probable AEs	HMAZ		SBAG	HMBF	SBAA	HMBB	HMAE		HMBA	HMBD
Dose (mg)	60		60	60	pbo	20	40	60	80	M	F	20 – 40		2.5	5	10	20	40	10	20	40	60	80	40	60	20		40		40	20	40	40	5	20	60 mg	60 mg
Regimen	SD		SD	BID	BID							BID		SD					SD					SD	SD	SD		BID		QD	SD	SD	SD	QD	QD	SD	BID
n	5 M	20 F								7	7	8	8													6		7 M	9 F			13		11 M	11 M	13 m/f	8/8/ M/F
Abdominal pain		2	4													¾										1							2		1			
Abnormal Dreams											4		4					1											2				1		1	1		
Abnormal Ejaculation																												1							1		
Abnl Thinking																																1					
Abnormal Vision																													1								
Accidental Injury																																2					
Alopecia																																		1	1		
Amblyopia																												1				2					
Anorexia		2	3												1/4			2/4										2				2					
Asthenia	1	2	6			1				1													1			2		2	1			1	4	2		
Constipation							3			1	2																	2					2				
Cough																																		2			
Diarrhea	3	10	7												¼	3/4						1		4 middle aged	4/12	4	3			1		4	25	2		4	
Diplopia		1																																			
Dizziness		6	4													1/4		¼				2	1	4 esp eld	1/12	5	4	1	2	1		6	1	1	3		
Dry Mouth		2									3	2																	2	1		2		3			
Dry skin																																		1			
Dysmenorrhea																								2								1					
Ecchymoses																																					
Edema			3																															1			
Epistaxis																																		2			
Eructation																																			1		
Euphoria																												1								
Fever																																		1			
Headache	1	6	21	6		2	1		1		28	4	1	3/4	½	1/4		4/4				1		11		3	2	1	9		1	16		13	11		
Hostility																																		1	1		
Hypertension																		1/4						3													
Hypotension orthostatic										1	2																										
Insomnia		2	22	11	2	0	3	7	17	0	30		4																2			2				
Libido decreased																												1	1								
Migraine		1																																			
Mydriasis											3																					2				1	
N/ dyspepsia fx	2	12	22	5	1	2	2	1	1		16	2										1	0	12/24	4/12	9	7	2	5	1	2	35	6	1	2	5	

Study	HMBG		HMBN		HMAR *Gender Effect Female vs. Male different AEs*							HMAP		HMAD					HMAB					SAAY elderly Females	HMBJ ESRD	HMAX	Subjects with cirrhosis possible & probable AEs	HMAZ		SBAG	HMBF	SBAA	HMBB	HMAE		HMBA	HMBD
Nervousness														5/4	2/4	¼													9	1							
Pain			2																																		
Paresthesia			4	2														3/4																			
Pharyngitis																																		2			
Pruritis																																		1	1		
Rash					1		3				4				2/4																			4	1	1		
Rhinitis		1																												1	2		3	2			
Somnolence	1	5	3								1	4									1				1		1	2	3	12		23			2		
Sleep disorder											3																										
Syncope																																	1				
Tachycardia								2																						3				1			
Taste Perversion																																2		1		1	
Thrombocytopenia												1.~50 k had not resolved at 2 moths																									
Tremor/Twitching														1/4	1/4	2/4	¼												1	2					1		
Urinary Frequency Polyuria																				2													4				
Urine problems																				2			1						1	1							
Urinary Retention																			1	2		1	3														
UTI											1																										
Urgency																																	4				
Vasodilation		1	4																																1		
Vertigo								3	2		5																										
Vomiting	1	1	8	2		2					1																		2	3/12	9	6	10		5			

10.7 APPENDIX 7 SUMMARY OF SINGLE DOSE PHARMACOKINETIC METRICS ACROSS STUDIES

Table 118 Summary of Pharmacokinetic Metrics from Single Dose Studies

Study	Date	Design	Assay	N	Gender	Age (years)	Weight (Kg)	Race C/B/A/NatAmer	Tabacco (PPD)	2D6 Genotype	Formulation	Dose (mg) & Administration	Tlag (hours)	Cmax (ng/ml)	Tmax (hours)	AUC (ng/ml x hr^{-1})	t1/2 (hours)	Cl/F (L/hr)	Cl/F (L/hr x kg^{-1})	Vβ/F (L)	Vβ/F (L/kg)		Comments
HMAA	Aug - Sep 1991	Single Rising Dose		4	Male	34 8 ± 2 6 (7 6) 32 - 37	70 3 ± 9 0 (12 8) 58 2 - 78 2	3/0/0/1	NR	NR	IR Capsules	60 mg fed		54 7	4 17 ± 1 8 [redacted]	417 ± 331 [redacted]	9 5 ± 5 8 [redacted]						
												60 mg fasted		29 1	3 17 ± 0 8 [redacted]	360 ± 320 [redacted]	3 7 ± 1 3 [redacted]						
															2 5 – 6 0		2 4 – 13 7		214 ± 149 L/hr		23 9 ± 9 4		Reported in HMAF
HMAB	Mar – Apr 1992	Single Rising Dose		6	Male	37 5 ± 10 5 (28 1) 26 0 - 55 0	77 7 ± 8 4 (8 2) 67 7 - 85 0																
				4							EC Tablets	10 mg		4 15 ± 1 06 [redacted]	5 0 ± 1 41 [redacted]	76 8 ± 16 5 [redacted]	13 8 ± 1 5 [redacted]		1 64 ± 0 47 [redacted]		32 2 ± 5 8 [redacted]		
				4								20 mg		17 6 ± 9 5 [redacted]	3 0 ± 0 0 (0 0)	247 ± 169 [redacted]	12 1 ± 5 3 [redacted]		1 79 ± 1 75 [redacted]		25 1 ± 16 9 [redacted]		
				4								40 mg		38 8 ± 9 0 [redacted]	6 75 ± 3 77 [redacted]	632 ± 307 [redacted]	14 1 ± 6 2 [redacted]		0 95 ± 0 40 [redacted]		17 8 ± 6 1 [redacted]		-
				4								60 mg		46 3 ± 16 1 [redacted]	4 75 ± 1 5 [redacted]	789 ± 601 [redacted]	14 2 ± 8 8 [redacted]		1 40 ± 0 75 [redacted]		22 5 ± 4 7 [redacted]		
				4								80 mg		43 3 ± 18 7 [redacted]	4 0 ± 1 41 [redacted]	622 ± 333 [redacted]	12 1 ± 1 2 [redacted]		1 85 ± 0 79 [redacted]		33 1 ± 15 3 [redacted]		
HMAF	Nov-92	SD OL Radio-labeld Mass Balance	[redacted]	4	Male	35 ± 5 8 (16 5) 30 – 40	77 3 ± 6 4 8 3 (71 7 –86 6)	2/1/0/1	3 smokers		50 µCi Radiolabeled 20 mg EC Tablets	20 mg po Fasting		13 5 ± 5 9 (43 6) [redacted]	5 8 ± 1 0 (16 7) [redacted]	226 0 ± 116 9 (52 6) [redacted]	14 4 ± 5 3 (36 9) [redacted]	103 3 ± 38 3 (37 0) [redacted]	1 33 ± 0 5 (37 5) [redacted]	2188 3 ± 1281 5 (58 6) [redacted]	28 3 ± 17 0 (60 0) [redacted]		
HMAO	Jun – Jul 1994	SD BE Study	[redacted]	7	Male	NR	71 2 ± 4 7 (6 1) 62 0 – 78 2	NR	NR	NR	20 mg Capsule EC Pellets	20 mg Fasting		10 7 ± 5 4 (50 5) [redacted]	5 6 ± 1 0 (17 8) [redacted]	142 0 ± 85 6 (60 4) [redacted]	9 0 ± 4 2 (46 7) [redacted]	204 7 ± 146 3 (71 5) [redacted]		1999 ± 568 (28 4) [redacted]			
												20 mg Fed		9 0 ± 3 3 (36 7) [redacted]	8 7 ± 2 4 (27 6) [redacted]	167 7 ± 63 6 (37 9) [redacted]	10 3 ± 2 6 (25 2) [redacted]	132 0 ± 41 4 (31 4) [redacted]		1890 ± 471 (24 9) [redacted]			
											4 x 5 mg Capsules EC Pellets	20 mg Fasting		10 2 ± 4 3 (42 2) [redacted]	4 7 ± 0 8 (17 0) [redacted]	135 6 ± 75 5 (55 3) [redacted]	8 3 ± 3 2 (38 6) [redacted]	190 9 ± 106 1 (55 6) [redacted]		1983 ± 709 (35 8) [redacted]			
												20 mg Fed		9 1 ± 4 0 (44 0) [redacted]	8 8 ± 3 5 (40 7) [redacted]	162 9 ± 60 1 (36 9) [redacted]	9 7 ± 1 3 (13 4) [redacted]	136 6 ± 46 5 (34 0) [redacted]		1898 ± 627 (33 0) [redacted]			
SAAZ a ?	Oct – Nov 1998	SD OL Radio-labeled Mass Balance	Lilly UK	4	3M/1F	45 5 ± 1 9 (4 2) 44 - 48	74 0 ± 7 0 (9 5) 66 7 – 83 5	3/1/0/0	NR	EM	EC Tablet 100 6 µCi	20 2 mg po Fasted	2 5 ± 1 0 (40 0) 2 - 4	23 5 ± 14 0 (60) [redacted]	6 0 4.0 – 16 0	257 3 ± 181 8 (71) [redacted]	11 2 ± 3 1 (24 4) [redacted]	119 0 ± 80 7 (68) [redacted]	1 59 ± 1 08 (68) [redacted]	Vss/F 1898 6 ± 1468 2 (77) [redacted]	25 9 ± 20 7 (80) [redacted]		
				3	3M	44 7 ± 1 2 (2 6) 44 0 – 46 0	76 4 ± 6 3 (8 2) 71 7 - 83 5	2/1/0/0	NR	EM			2 7 ± 1 2 (43 3) 2 - 4	19 4 ± 14 1 (72 5) [redacted]	8 7 ± 6 4 (74 2) 6 0 [redacted]	181 6 ± 123 3 (67 9) 127 2 [redacted]	10 7 ± 3 8 (33 4) [redacted]	144 8 ± 76 1 (52 6) 158 6 [redacted]	1 9 ± 1 1 (55 8) [redacted]	Vss/F 2245 0 ± 1585 5 (70 6) 1364 2 [redacted]	30 2 ± 23 1 (76 4) 17 5 [redacted]		
				1	1F	46	66 7	1/0/0/0	NR	EM			2 0	32 9	6 0	484 3	12 5	41 7	0 83	859 6	12 9		

Study	Date	design	Assay	N	Gender	Age (years)	Weight (Kg)	Race C/B/A/NatAmer	Tabacco (PPD)	2D6 Genotype	Formulation	Dose (mg) & Administration	Tlag (hours)	Cmax (ng/ml)	Tmax (hours)	AUC (ng/ml x hr^{-1})	t1/2 (hours)	Cl/F (L/hr)	Cl/F (L/hr x kg^{-1})	Vβ/F (L)	Vβ/F (L/kg)		Comments
HMBI a b	Aug-2000	SD Absolute BA		12	1M / 1F	NR	NR	NR	NR	NR	60 mg Cap po	60 mg po		59 3 ± 23 2 (39 1)	6 5 ±1.4 (28 3)	910 5 ± 320.3 (35.2)	11 45 ± 0 2 (1 9)	70.26 ± 24.7 (35.1)		1157.5 ± 386.8 (33.4)		0.0745 ± 0.5 (65 9)	
											IV Soln	0 8 mg IV over 30 minutes		2 05 ± 1 2 (58 6)	0 5	13 35 ± 3 0 (22 8)	7.08 ± 2 4 (34 4)	61 6 ± 14 1 (23 0)		604 ± 72 1 (11 9)		—	
HMBG a b	Jul 2001	SD BE TBM vs CTF		25	M/F	41 4 ± 10 6 (25 5) 22 - 66 [39]	71 7 ± 13.5 (18 8) 48.7 - 93 3 [39]	19/4/2/0	NR	NR	20 mg caps 10% EC pellets CTF	60 mg po Fasted (3 x 20 mg)	1 8 ± 0 8 (47 2) 2 0	52 8 ± 20 9 (39 7) 50 9	6 5 ± 1 0 (16.1) 6 0	921.4 ± 403 1 (43 8) 862 9	11 9 ± 2 3 (19 2) 11 7	82 2 ± 51.7 (62 9) 69 5	1.1 ± 0 6 (52 4) 0 9	1334 5 ± 674 8 (50 6) 1159 3	18 8 ± 8 9 (47 0) 17.1		
											60 mg caps 20% EC pellets TBM	60 mg po Fasted	2 0 ± 0 9 [45 3] 2.0	54.1 ± 23.1 [42 7] 46 5	6 3 ± 1.1 [17 5] 6 0	944 7 ± 446 7 [47 5] 897 2	12.1 ± 1 9 [15 7] 12.0	81.0 ± 51 2 [62 6] 66 9	48 5 ± 30 4 [62.6] 44 7	1362.1 ± 713.6 [52 4] 3254 1	18 9 ± 8.3 [43.9] 18.0		
				20	F/A	40 8 ± 10 3 (25 4) 22 - 65 [40]	66 8 ± 12 3 (17.9) 48.6 - 93 3 [66 6]	14/4/2/0	NR	NR	20 mg caps 10% EC pellets CTF	60 mg po Fasted (3 x 20 mg)	1 7 ± 0 7 (43 1) [2 0]	55 0 ± 22 7 (41 3) [52 6]	6 5 ± 0 9 (14 2) [6 0]	969 1 ± 431 6 (44 5) [886 5]	11 9 ± 2 4 (20 5) [11 6]	81 1 ± 57.1 (70 4) [67 7]	1 2 ± 0 7 (56 4) [0 9]	1312.6 ± 751 6 (57 3) [1077 6]	19 2 ± 9 7 (50 8) [17 2]		
											60 mg caps 20% EC pellets TBM	60 mg po Fasted	2 0 ± 1 0 (51 2) [2 0]	57.8 ± 24 2 (41 8) [52 6]	6 4 ± 1.0 (16 3) [6 0]	1010 4 ± 473.0 (46 8) [1066.1]	12 0 ± 1 8 (15 8) [12 0]	78 7 ± 55 6 (70 6) [65 5]	48.9 ± 33.4 (68.4) [44 6]	1298 4 ± 761 8 (58 8) [932.9]	18.6 ± 8 9 (47.8) [15 5]		
				20	M	44 2 ± 12 2 (27 5) 32 - 62 [39]	83 4 ± 12.4 (14 9) 64 2 - 98 2 [87.1]	5/0/0/0	NR	NR	20 mg caps 10% EC pellets CTF po Fasted	60 mg po Fasted (3 x 20 mg)	2 0 ± 1 2 (61 2) [2 0]	43 8 ± 7 4 (16 9) [40 2]	6 0 ± 1.4 (23 6) [6 0]	730 4 ± 182 5 (25 0) [685 0]	11 7 ± 1.7 (14 8) [12 4]	96 6 ± 23 0 (26 6) [87 6]	1 1 ± 0 3 (30 2) [1 2]	1423 5 ± 191 9 (13 5) [1462 4]	17 5 ± 4 2 (24 1) [17 0]		
											60 mg caps 20% EC pellets TBM	60 mg po Fasting	2 0 ± 0 0 (0,0) [2.0]	39 3 ± 8 6 (22 0) [43 5]	6 0 ± 1.4 (23.6) [6 0]	681.9 ± 193.5 (28.4) [715.6]	12.2 ± 2.1 (16 9) [12 0]	94 6 ± 29 2 (30 9) [83 8]	47.3 ± 14 6 (30 9) [41 9]	1624 9 ± 437.1 (26 9) [1400 0]	19 8 ± 5 6 (29 3) [19 5]		
HMAO a c?	Jun – Jul 1994	SD XO pilot BE	Lilly	7	M	NR	71 2 ± 4 7 (6 5) 71 0 62 0 - 76 2	NR	NR	NR	20 mg 10% EC pellet Capsule	20 mg AM Fasting	3 3 ± 1 2 (35 1) [3]	10 7 ± 5 4 (50 7) 9 2	5 6 ± 1 0 (17 5) 5 0	142 0 ± 65 8 (60 4) 110 9	9 0 ± 4 2 (46 7) 9 3	204 7 ± 146 3 (71 5) 180 3	2 9 ± 2 0 (70 7) 2 4	1999 0 ± 567.7 (28 4) 1759 0	28 5 ± 9 9 (34 9) 24 4		Abbreviated Reports
				7	M	NR	71 7 ± 4 9 (6 8) 72 3 63 3 - 78 4	NR	NR	NR	5 mg EC pellet Capsule	20 mg AM Fasting		10 2 ± 4 3 (41 9) 9 1	4.7 ± 0 8 (16 0) 5 0	136 8 ± 75 6 (55 3) 117 0	8 3 ± 3 2 (38 3) 7 3	190 9 ± 106 1 (55 6) 171 0	2 7 ± 1 5 (54 9) 2 4	1983 0 ± 709 5 (35 8) 1808 0	27 8 ± 9 9 (35 7) 23 1		
				7	M	NR	70 8 ± 4 2 (6 0) 69 5 63 8 - 75 0	NR	NR	NR	20 mg 10% EC pellet Capsule	20 mg AM Fed	6 3 ± 2 5 (39 0) [7]	9 0 ± 3 3 (36 0) 7.4	8 7 ± 2 4 (27.1) 7 0	167 6 ± 63 6 (37 9) 164 6	10 3 ± 2 6 (25 3) 9 3	116 9 ± 61 8 (52 9) 121 5	1.7 ± 0 9 (55 7) 1 6	1890 3 ± 471 1 (24 9) 1942 0	26 7 ± 6 8 (25 4) 28 2		
				7	M	NR	71 6 ± 4 6 (6 5) 71 5 64 4 - 77 1	NR	NR	NR	5 mg EC pellet Capsule	20 mg AM Fed	5 6 ± 2 4 (43 9) [6]	9 1 ± 4 0 (44 5) 7 4	8 6 ± 3 5 (40 9) 7 0	162 9 ± 60 1 (36 9) 148 5	9 7 ± 1 3 (13 7) 10 1	135 6 ± 45 5 (34 0) 134 7	1 9 ± 0 7 (37 3) 1 9	1898 3 ± 627 0 (33 0) 1801 0	26 7 ± 9 5 (35 6) 24 7		
				6	M	NR	76 6 ± 5 9 (7 7) 75 6 69 8 - 86 2	NR	NR	NR	20 mg 10% EC pellet Capsule	20 mg AM Fasting	3 4 ± 1 4 (39 7) [3]	9 3 ± 2 2 (23 3) 9 7	6 0 ± 1 1 (18 3) 6 0	150 1 ± 55 3 (36 8) 145 8	10 1 ± 1 5 (15 3) 10 6	150 1 ± 57 9 (38 6) 142 1	2 0 ± 0 8 (41 3) 1 8	2100 8 ± 531 0 (25 3) 1997 0	27 6 ± 7 6 (28 2) 24 7		
				6	M	NR	76 3 ± 6 8 (8 9) 68 - 87 2	NR	NR	NR	20 mg EC Tablet	20 mg AM Fasting	3 7 ± 1 0 (28 2) [3]	10 9 ± 4 7 (43 3)	5 ± 0 (0) 5	145 5 ± 58 1 (39 9)	10 3 ± 5 8 (56 2)	158 7 ± 65 3 (41.1)	2 1 ± 0 9 (44 1) 1 9	2090 ± 840 (40 2)	27 5 ± 10 8 (39 3) 24 8		
				6	M	NR	76 2 ± 5 7 (7 5) 75 9 69 1 - 85 1	NR	NR	NR	20 mg EC Tablet	20 mg PM Fasting	6 3 ± 1 6 (25 6) [6]	6 2 ± 1 9 (31 1) 6 5	8 3 ± 2 1 (24 8) 9 0	9 8 ± 3 9 (39 5) 9 1	68 4 ± 30 7 (44 9) 65 6	218 5 ± 87 5 (40 0) 205 3	2 9 ± 1 2 (40 8) 2 5	2944 8 ± 1451 8 (49 3) 2469 0	38 9 ± 19 6 (50 4) 33 3		

Study	Date	design	Assay	N	Gender	Age (years)	Weight (Kg)	Race C/B/A/NatAmer	Tabacco [redacted])	2D6 Genotype	Formulation	Dose (mg) & Administration	Tlag (hours)	Cmax (ng/ml)	Tmax (hours)	AUC (ng/ml x hr^{-1})	t1/2 (hours)	Cl/F (L/hr)	Cl/F (L/hr x kg^{-1})	Vβ/F (L)	Vβ/F (L/kg)		Comments
HMBN	Mar – Apr 2001 [2]	OL SD & MD PK	[redacted]	12	6 F 6 M	36.9 ± 11.2 (28.7) 36 [36.5] 23.0 - 61.0	80.3 ± 15.1 (18.9) 72.8 [72.8] 66.2 - 113.4	[redacted] 9/3/1/0	Mixed	11 EM 1 PM	60 mg caps 20% EC pellets TBM	60 mg po 2 hour p.a light breakfast	[redacted]	56.1±26.8 (48) 45.2 [redacted]	5.3±1.3 (24.4) 5.0 [redacted]	845.3±473.6 (56) 680.7 [redacted]	10.9 ± 1.8 (16.5) 11.3 [redacted]	93.8±51.7 (55) 80.0 [redacted]	1.2±0.7 (58.2) 1.1 [redacted]	1390.9±834.046 [redacted] 1318.6 [redacted]	17.6±8.2 (46.7) 15.2 [redacted]	[redacted]	[redacted]
				6	M	38.7 ± 5.2 (13.5) 39.5 29.0 - 44.0	87.3 ± 15.9 (18.2) 87.4 66.5 - 113.4	4/2/0/0	NS	5 EM 1 PM				69.5±30.0 (43.2) 60.0 [redacted]	5.7±0.8 (14.4) 6.0 [redacted]	612.1±385.8 (63.0) 503.9 [redacted]	10.2 ± 2.2 (21.3) 9.0 [redacted]	123.7±56.1 (45.3) 119.9 [redacted]	1.6±0.9 (57.0) 1.2 [redacted]	[redacted] (39.6) 1646.5 [redacted]	20.6±9.7 (46.9) 19.9 [redacted]	[redacted]	[redacted]
				6	F	39.2 ± 15.8 (40.2) 34.0 23.0 - 61.0	73.2 ± 11.0 (15.1) 69.9 [redacted] 56.2 - 95.3	[redacted] 5/0/1/0	Mixed	EM				42.7±15.5 (36.4) 40.0 [redacted]	5.0±1.7 (33.9) 5.0 [redacted]	1078.5±462.6 (42.9) 951.4 [redacted]	11.6 ± 1.1 (9.8) 11.6 [redacted]	63.8±24.0 (37.7) 63.7 [redacted]	0.9±0.4 (47.4) 0.8 [redacted]	1050.9±368.8 (35.1) 1042.4 [redacted]	14.6±5.8 (39.7) 13.1 [redacted]	[redacted]	[redacted]
				6	M	36.7 ± 6.8 (18.6) 39.0 29.0 - 42.0	78.0 ± 11.8 (16.1) 74.4 68.5 - 91.2	[redacted] 2/1/0/0	Smokers	EM				34.7±11.0 (31.8) 36.3 [redacted]	4.0±2.0 (50.0) 4.0 [redacted]	433.8±188.0 (38.9) 402.2 [redacted]	8.9 ± 0.3 (2.9) 9.0 [redacted]	152.9±57.5 (37.6) 149.2 [redacted]	2.0±0.9 (44.3) 2.2 [redacted]	1941.6±676.1 (34.8) 1930.6 [redacted]	25.6±10.9 (42.1) 28.2 [redacted]	[redacted]	[redacted]
				2	M	41.0 ± 4.2 (10.3) 41.0 39.0 - 44.0	98.6 ± 21.1 (21.5) 98.6 83.5 - 113.4	[redacted] 1/1/0/0	NS	EM				41.3±6.0 (14.6) 41.3 [redacted]	6.0 [redacted]	503.9±58.4 (11.6) 503.9 [redacted]	10.6 ± 2.8 (26.4) 10.6 [redacted]	119.8±13.9 (11.6) 119.8 [redacted]	1.2±0.1 (10.0) 1.2 [redacted]	1859.0±696.9 (37.5) 1859.0 [redacted]	18.6±3.1 (16.7) 18.6 [redacted]	[redacted]	[redacted]
				1	M	40	93	1/0/0/0	NS	PM				[redacted]									
SAAY	Aug – Sep 1998	OL SD PK Parallel	Lilly [redacted]	12	F	68.6 ± 4.1 (6.0) 67.0 65.0 - 77.0	66.0 ± 7.6 (11.6) 66.0 52.2 - 80.7	Elderly All	NS		CT11439	2 x 20 mg EC Capsules 2 hours before breakfast	2.2 ± 1.2 (55.1) 2.0 [redacted]	49.4 ± 15.9 (32.2) 52.6 [redacted]	4.8 ± 1.5 (32.5) 5.0 [redacted]	866.9 ± 335.2 (38.7) 912.4 [redacted]	15.0 ± 4.6 (30.7) 13.3 [redacted]	52.9 ± 20.2 (38.2) 44.1 [redacted]	0.82 ± 0.4 (45.6) 0.7 [redacted]	1099.9 ± 377.5 (34.3) 1033.8 [redacted]	17.2 ± 8.0 (46.6) 15.2 [redacted]	[redacted]	V is Vss
				6	F	67.0 ± 2.8 (4.1) 65.5 65.0 - 71.0	63.7 ± 8.0 (12.5) 65.1 52.2 - 73.0	Elderly Hispanic					2.2 ± 1.0 (45.4) 2.0 [redacted]	50.8 ± 19.5 (38.3) 54.0 [redacted]	4.2 ± 1.8 (44.0) 4.0 [redacted]	813.4 ± 257.9 (31.7) 912.4 [redacted]	13.7 ± 2.1 (15.7) 13.3 [redacted]	54.8 ± 20.9 (38.3) 44.1 [redacted]	0.89 ± 0.4 (47.9) 0.7 [redacted]	1120.1 ± 486.9 (43.5) 962.1 [redacted]	18.3 ± 10.5 (57.3) 15.0 [redacted]	[redacted]	
				5	F	71.2 ± 4.7 (6.5) 70.0 66.0 - 77.0	68.3 ± 8.1 (11.9) 66.2 58.5 - 80.7	Elderly Caucasian					2.4 ± 1.5 (63.2) 2.0 [redacted]	46.7 ± 14.4 (29.6) 51.7 [redacted]	5.2 ± 1.1 (21.1) 6.0 [redacted]	869.3 ± 444.7 (51.2) 700.8 [redacted]	14.3 ± 3.9 (27.5) 12.8 [redacted]	54.8 ± 21.9 (40.2) 57.1 [redacted]	0.81 ± 0.4 (44.4) 0.8 [redacted]	1054.4 ± 299.3 (28.4) 1056.2 [redacted]	15.8 ± 5.8 (37.0) 15.0 [redacted]	[redacted]	
				12	F	41.6 ± 5.7 (13.7) 41.0 32.0 - 50.0	71.4 ± 11.7 (16.3) 71.5 44.5 - 85.7	Middle Aged All					1.8 ± 0.8 (45.5) 2.0 [redacted]	49.8 ± 18.9 (37.9) 47.7 [redacted]	3.7 ± 0.8 (21.2) 4.0 [redacted]	699.3 ± 341.9 (48.9) 631.0 [redacted]	10.4 ± 2.8 (27.2) [redacted] 6.9 - 14.7	70.3 ± 33.9 (48.3) 63.4 [redacted]	1.0 ± 0.5 (51.6) 0.9 [redacted]	1083.5 ± 364.9 (33.7) 962.2 [redacted]	15.5 ± 5.8 (37.4) 13.7 [redacted]	[redacted]	
				10	F	41.1 ± 5.9 (14.3) 41.0 32.0 - 50.0	71.1 ± 11.8 (16.4) 71.5 44.5 - 85.7	Middle Aged Excluding Outliers					1.8 ± 0.9 (51.1) 2.0 [redacted]	54.2 ± 17.3 (32.0) 52.1 [redacted]	3.8 ± 0.8 (23.4) 4.0 [redacted]	779.5 ± 316.1 (40.6) 646.2 [redacted]	10.9 ± 2.9 (26.3) [redacted] 6.9 - 14.7	57.5 ± 17.8 (31.0) 61.9 [redacted]	0.8 ± 0.3 (40.6) 0.8 [redacted]	950.7 ± 212.4 (22.3) 939.4 [redacted]	13.7 ± 3.9 (28.3) 13.3 [redacted]	[redacted]	
				2	F	44.0 ± 5.7 (12.9) 44.0 40.0 - 48.0	72.8 ± 16.4 (22.5) 72.8 61.2 - 84.4	Middle Aged Outliers (Hispanic)					2.0 ± 0.0 (0.0) 2.0 [redacted]	27.4 ± 1.2 (4.4) 27.4 [redacted]	4.0 ± 0.0 (0.0) 4.0 [redacted]	298.1 ± 5.6 (1.9) 298.1 [redacted]	8.0 ± 0.5 (6.2) [redacted] 7.6 - 8.3	134.2 ± 2.5 (1.9) 134.2 [redacted]	1.9 ± 0.4 (20.7) 1.9 [redacted]	1747.5 ± 26.8 (1.5) 1747.5 [redacted]	24.7 ± 5.9 (24.0) 24.7 20.5 - 28.9	[redacted]	
				9	F	41.1 ± 6.2 (15.2) 41.0 32.0 - 50.0	70.2 ± 12.0 (17.0) 71.2 44.5 - 85.7	Middle Aged Hispanic Only Excluding Outliers					1.6 ± 0.5 (33.9) 2.0 [redacted]	54.3 ± 18.4 (33.8) 50.9 [redacted]	3.6 ± 0.9 (24.8) 4.0 [redacted]	781.2 ± 329.8 (43.3) 843.9 [redacted]	10.7 ± 3.0 (27.9) [redacted] 6.9 - 14.7	59.2 ± 18.0 (30.5) 62.1 [redacted]	0.9 ± 0.3 (38.3) 0.9 [redacted]	968.4 ± 217.3 (22.4) 946.3 [redacted]	14.1 ± 3.9 (27.4) 13.4 [redacted]	[redacted]	
				1	F	41	79.4	Middle Aged Caucasian					[redacted]										
HMAX Cirrhosis		OL SD PK		6	5 M 1 F	45.7 ± 15.7 (34.5) 24 - 63 [46.5]	80.4 ± 10.5 (13.1) 82.8 - 93.9 [81.8]	6/0/0/0	Mixed	EM		20 mg		13.8 ± 10.9 (79.1) [redacted] [12.0]	3.8 ± 1.2 (30.5) [redacted] [3.5]	370.1 ± 605.2 (163.5) [redacted] [126.0]	18.3 ± 15.2 (82.9) [redacted] [12.9]	160.2 ± 100.6 (62.8) [redacted] [159.7]	1.9 ± 1.2 (61.6) [redacted] [2.1]	2908.6 ± 1714.8 (59.0) [redacted] [2298.0]	35.3 ± 19.3 (54.6) [redacted] [29.5]	[redacted]	does not include PM
				4	3 M 1 F	47.3 ± 17.7 (37.6) 24 - 63 [51.0]	81.7 ± 13.3 (16.3) 82.8 - 93.9 [85.0]	4/0/0/0	NS					14.8 ± 13.8 (93.5) [redacted] [10.2]	4.3 ± 1.3 (29.6) [redacted] [4.0]	492.1 ± 742.2 (150.8) [redacted] [147.5]	22.4 ± 17.7 (79.2) [redacted] [13.9]	160.5 ± 129.5 (80.7) [redacted] [177.0]	1.9 ± 1.5 (81.3) [redacted] [2.0]	3213.9 ± 2125.3 (66.1) [redacted] [3446.1]	38.2 ± 24.2 (63.5) [redacted] [39.2]	[redacted]	
				3	3 M	43.3 ± 19.5 (45.0) 24 63 43.0	87.9 ± 5.3 (6.0) 84 93.9 85.9	3/0/0/0	NS					8.3 ± 5.8 (69.7) 4.5 [redacted] 5.4	3.7 ± 0.6 (15.7) 3 [redacted] 4.0	122.5 ± 83.4 (68.1) 72.6 [redacted] 78.2	13.5 ± 1.0 (7.6) 12.8 [redacted] 13.1	209.8 ± 102.7 (49.0) 91.4 [redacted] 282.8	2.4 ± 1.3 (52.2) 1.0 [redacted] 3.1	3990.9 ± 1775.5 (44.5) 1942.2 [redacted] 4950.0	48.3 ± 22.2 (48.0) 20.7 [redacted] 57.6	[redacted]	
				2	2 M	42.5 ± 16.3 (38.3) 42.5 - 31 [54]	78.0 ± 2.2 (2.8) 78.0 - 78.4 [79.5]	2/0/0/0	Smokers					12.0 ± 4.0 (33.7) [redacted] [14.8]	3.0 ± 0.0 (0.0) [redacted] [3]	492.1 ± 742.2 (150.8) [redacted] [147.5]	10.1 ± 1.9 (19.0) [redacted] [11.44]	160.5 ± 129.5 (80.7) [redacted] [177.0]	1.9 ± 1.5 (81.3) [redacted] [2.0]	3213.9 ± 2125.3 (66.1) [redacted] [3446.1]	38.2 ± 24.2 (63.5) [redacted] [39.2]	[redacted]	
				1	1 F	59	62.8	1/0/0/0	NS					[redacted]									
				1	1 M	38	88.5	1/0/0/0	NS	PM				[redacted]									

Study	Date	design	Assay	N	Gender	Age (years)	Weight (Kg)	Race C/B/A/NatAmer	Tabacco ([redacted])	2D6 Genotype	Formulation	Dose (mg) & Administration	Tlag (hours)	Cmax (ng/ml)	Tmax (hours)	AUC (ng/ml x hr $^{-1}$)	t1/2 (hours)	Cl/F (L/hr)	Cl/F (L/hr x kg $^{-1}$)	Vβ/F (L)	Vβ/F (L/kg)		Comments
HMBJ ESRD		SD	LC/MS/MS	12	Mix	38 9 ± 13 2 (33 8) 19 0 - 61 0 [39 5]	81 3 ± 16 5 (20 2) 62 1 - 112 9 [74 8]	7/5/0/0	Mixed			60 mg	2 5 ± 0 9 (36 2) [redacted] [2 0]	34 4 ± 18 3 (53 3) [redacted] [33 9]	5 0 ± 1 3 (27 0) [redacted] [4 0]	672 2 ± 615 9 (91 6) [redacted] [469 5]	13 8 ± 4 6 (33 3) [redacted] [13 1]	122 8 ± 61 7 (50 2) [redacted] [120 3]	1 6 ± 1 0 (62 7) [redacted] [1 3]	2354 6 ± 1262 3 (53 6) [redacted] [1794 6]	30 0 ± 19 1 (63 5) [redacted] [22 5]		
				2	F	48 0 ± 5 7 *(46.0)* 42 0 - 50 0 12 3	70 0 ± 6 8 9 7 65 2 - 74 8	2/0/0/0	Mixed				3 0 ± 1 4 47 1 [redacted]	49 0 ± 51 4 105 0 [redacted]	5 0 ± 1 4 28 3 [redacted]	1389 8 ± 1664 3 119 7 [redacted]	19 8 ± 9 2 48 4 [redacted]	152 5 ± 182 6 119 7 [redacted]	2 3 ± 2 8 122 3 [redacted]	3146 2 ± 3196 4 101 6 [redacted]	47 4 ± 50 3 106 1 [redacted]		
				10	M	37.5 ± 14 0 (37 2) 19 0 - 61 0 [38 0]	83 6 ± 17 1 (20 4) 62 1 - 112 9 [82 8]	5/5/0/0	Mixed				2 4 ± 0 8 (35 1) [redacted] [2 0]	31 5 ± 7 8 (24 7) [redacted] [33 9]	5 0 ± 1 4 (28 3) [redacted] [4 0]	528 6 ± 136 4 (25 8) [redacted] [489 5]	12 6 ± 2 6 (20 9) [redacted] [12 6]	116 9 ± 26 7 (22 6) [redacted] [120 3]	1 4 ± 0 4 (28 6) [redacted] [1 3]	2198 2 ± 803 1 (36 6) [redacted] [1784 8]	26 8 ± 9 2 (34 5) [redacted] [22 5]		
				8	M	36 0 ± 15 3 (42 5) 19 0 - 61 0 [38 5]	84 1 ± 17 9 (21 3) 62 1 - 112 9 [82 8]	4/4/0/0	NS				2 5 ± 0 9 (37 0) [redacted] [2 0]	33 9 ± 6 1 (17 9) [redacted] [34 1]	5 0 ± 1 5 (30 2) [redacted] [4 0]	563 3 ± 130 5 (23 2) [redacted] [532 1]	12 2 ± 2 8 (23 2) [redacted] [11 9]	107 7 ± 20 8 (19 2) [redacted] [106 0]	1 3 ± 0 3 (26 4) [redacted] [1 2]	1959 0 ± 711 4 (36 3) [redacted] [1677 0]	23 3 ± 6 1 (26 2) [redacted] [21 3]		
				2	M	37 2 ± 14 7 (39 5) 15 3 - 61 0 [38 3]	68 0 ± 33 7 (49 6) 17 9 - 112 9 [75 2]	1/1/0/0	Smokers				6 6 ± 12 3 (186 2) [redacted] [2 0]	25 0 ± 11 7 (46 7) [redacted] [24 8]	7 8 ± 9 2 (117 8) [redacted] [4 5]	400 5 ± 235 4 (58 8) [redacted] [406 1]	13 1 ± 5 9 (45 3) [redacted] [13 1]	98 8 ± 53 5 (55 4) [redacted] [107 8]	4 5 ± 8 9 (196 9) [redacted] [1 5]	1961 7 ± 1260 6 (64 3) [redacted] [1816 0]	26 2 ± 12 2 (46 4) [redacted] [24 8]		
				4	M	47 3 ± 11 8 (24 9) 46 0 - 35 0 [61 0]	94 6 ± 16 1 (17 1) 95 5 - 74 4 [112 9]	4/0/0/0	NS				2 0 ± 0 0 (0 0) [redacted] [2 0]	34 5 ± 8 9 (25 8) [redacted] [42 4]	4 0 ± 0 0 (0 0) [redacted] [4 0]	583 2 ± 155 1 (27 5) [redacted] [758 9]	14 0 ± 2 6 (18 7) [redacted] [17 3]	105 1 ± 21 8 (20 5) [redacted] [129 2]	1 1 ± 0 2 (16 8) [redacted] [1 3]	2306 3 ± 905 5 (39 3) [redacted] [3695 7]	24 3 ± 8 0 (32 8) [redacted] [36 0]		
				4	M	24 8 ± 8 3 (33 7) 21 5 - 19 0 [37 0]	73 7 ± 14 0 (18 90 69 7 - 62 1 [93 4]	0/4/0/0	NS				3 0 ± 1 2 (38 5) [redacted] [4 0]	33 3 ± 2 3 (6 9) [redacted] [35 3]	6 0 ± 1 6 (27 2) [redacted] [8 0]	563 3 ± 125 3 (922 2) [redacted] [729 7]	10 4 ± 1 8 (16 9) [redacted] [13 0]	110 3 ± 22 8 (20 5) [redacted] [130 6]	1 5 ± 0 4 (24 5) [redacted] [2 0]	1611 8 ± 198 3 (12 3) [redacted] [1877 0]	22 4 ± 4 6 (20 8) [redacted] [28 5]		
				1	M	40	67 6	1/0/0/0	Smoker														
				1	M	47	95	0/1/0/0	Smoker														
				1	F	50	65 2	1/0	Smoker														
				1	F	42	74 8	1/0	NS														
HMBB		SD		14	M	24 4 ± 4 2 (17 3) 21 0 - 38 0 [24 0]	68 9 ± 8 6 (9 5) 59 0 - 79 8 [68 8]	0 / 0 / 14 / 0	NR	NR		40 mg SD	2 4 ± 1 1 (44 9) [redacted] [2 0]	22 0 ± 12 6 (57 6) [redacted] [19 9]	7 3 ± 1 7 (23 1) [redacted] [8]	447 ± 408 (91 2) [redacted] [369]	10 3 ± 3 15 (30 6) [redacted] [9 54]	137 ± 88 6 (64 6) [redacted] [108]	2 01 ± 1 3 (65 8) [redacted] [1 56]	1847 ± 1073 (58 1) [redacted] [1547]	18 4 ± 4 9 (26 6) [redacted] [17 3]		
				11		24 3 ± 4 8 (19 7) 21 0 - 38 0 [23 0]	69 4 ± 8 0 (8 7) 59 1 - 79 8 [70 5]	Chinese					2 7 ± 1 0 (37 0) [redacted] [2 0]	22 3 ± 13 2 (59 4) [redacted] [19 9]	7 3 ± 1 3 (18 5) [redacted] [8 0]	465 0 ± 451 9 (97 2) [redacted] [360 0]	10 2 ± 3 4 (33 1) [redacted] [9 4]	135 7 ± 90 2 (66 5) [redacted] [111 0]	2 0 ± 1 4 (70 7) [redacted] [1 6]	1829 9 ± 1183 2 (63 0) [redacted] [1539 0]	26 9 ± 18 2 (67.7) [redacted] [20 1]		
				3		24 7 ± 1 2 (4 7) 24 0 - 26 0 [24 0]	67 1 ± 9 6 (14 3) 59 0 - 77 7 [64 5]	Malay					1 3 ± 0 6 (43 3) [redacted] [1 0]	21 2 ± 12 7 (59 7) [redacted] [19 8]	7 3 ± 3 1 (41 7) [redacted] [5 0]	382 7 ± 229 0 (59 9) [redacted] [378 0]	10 4 ± 2 6 (25 1) [redacted] [10 2]	142 3 ± 100 6 (70 6) [redacted] [106 0]	2 0 ± 1 1 (56 6) [redacted] [1 6]	1906 0 ± 908 3 (47 6) [redacted] [1554 0]	27 6 ± 9 0 (32 7) [redacted] [24 1]		

Study	Date	design	Assay	N	Gender	Age (years)	Weight (Kg)	Race C/B/A/NatAmer	Tabacco [redacted]	2D6 Genotype	Formulation	Dose (mg) & Administration	Tlag (hours)	Cmax (ng/ml)	Tmax (hours)	AUC (ng/ml x hr^{-1})	t1/2 (hours)	CL/F (L/hr)	CL/F (L/hr x kg^{-1})	VB/F (L)	VB/F (L/kg)		Comments
SBAA		SD				36 2 ± 10 7 (29 6) 18 - 50 [37]	65 2 ± 11 3 (17 3) 49 9 - 85 7 [61 45]		Mixed		10% Caps	20 mg Fasting		26 7 ± 9 3 (34 9) [28 55]	5 4 ± 2 3 (42 0) [6]		11 7 ± 2 3 (19 8) [11 4]					
						38 0 ± 10 9 (28 7) 21 - 50 [38 5]	63 8 ± 12 1 (19 0) 49 9 - 81 2 [61]		Smokers					23 8 ± 12 5 (52 6) [27 85]	5 2 ± 3 0 (58 0) [5]		12 6 ± 2 4 (18 8) [12 8]		2 65 ± 2 89 (108 76) [1 37]	3006 1 ± 2755 9 (91 7) [1660 485]	53 7 ± 58 7 (109 4) [26 8]		
						30 8 ± 9 7 (31 5) 18 - 44 [30]	66 8 ± 11 3 (17 0) 53 5 - 85 7 [64 85]		NS					29 6 ± 3 7 (12 5) [29 09]	5 7 ± 1 5 (26 6) [6]		10 8 ± 2 1 (19 2) [11 1]		1,40 ± 0 71 (50 49) [1 18]	1519 3 ± 359 2 (23 6) [1360 77]	23 3 ± 6 6 (28 4) [21 5]		
						36 2 ± 10 7 (29 6) 18 - 50 [37]	65 2 ± 11 3 (17 3) 49 9 - 85 7 [61 45]		Mixed			20 mg Fast 2 SD		27 5 ± 8 3 (30 3) [27 75]	6 7 ± 1 6 (23 4) [6]	464 3 ± 146 9 (32 1) [470 5]	12 5 ± 2 9 (23 4) [12 05]	97 8 ± 44 0 (45 0) [85 02]	1 61 ± 0 99 (61 56) [1 35]	1935 4 ± 1222 1 (63 1) [1629 95]	32 3 ± 28 7 (82 6) [27 0]		
						34 9 ± 11 2 (32 0) 18 - 49 [36]	65 6 ± 11 9 (18 1) 49 9 - 85 7 [64 85]		NS					28 9 ± 10 0 (34 6) [29 9]	6 8 ± 1.0 (15 3) [6]	465 2 ± 171 0 (35 2) [490 64]	12 5 ± 3 5 (28 3) [11 65]	97.2 ± 52 8 (54 30 [81 71]	1,61 ± 1,19 (73 71) [1 17]	1930 7 ± 1524 8 (79 0) [1507 0]	32 9 ± 33 1 (100 6) [24 4]		
						36 5 ± 11 8 (31 8) 21 - 48 [36 5]	64 4 ± 11 8 (18 1) 54 4 - 81,2 [61]		Smokers					24 9 ± 2 4 (9 7) [24 4]	6 5 ± 2 5 (38 7) [6]	422 5 ± 97 8 (23 2) [427 9]	12 5 ± 1 5 (11 9) [12 55]	98 9 ± 24 3 (24 6) [94 6]	1 59 ± 0 54 (33 69) [1 68]	1944 9 ± 225 1 (11 6) [1901 5]	31 1 ± 7 1 (22 9) [33 2]		
						36 2 ± 10 7 (29 6) 18 - 50 [37]	65 2 ± 11 3 (17 3) 49 9 - 85 7 [61 45]		Mixed			20- mg SD Fed		19 6 ± 6 8 (34 7) [21 85]	9 8 ± 3 1 (31 5) [10]		11 2 ± 2 1 (18 6) [11 1]	142 3 ± 119 8 (84,1) [94 7]	2 41 ± 2 52 (104 59) [1 29]	3078 1 ± 2844 0 (92 4) [2013 175]	52 4 ± 59 9 (114 3) [30 8]		
						34 9 ± 11 2 (32 0) 18 - 49 [36]	66 8 ± 11 3 (17 0) 53 5 - 85 7 [64 85]		NS					21 6 ± 4 4 (20 4) [21 85]	8 3 ± 2 3 (28 1) [9]		10 5 ± 1 6 (15 4) [10 9]	101 8 ± 42,7 (42 0) [87 9]	1 57 ± 0 73 (46 68) [1 26]	2063 1 ± 667 5 (32 4) [1868 205]	31,7 ± 11 7 (36 9) [28 3]		
						38 0 ± 10 9 (28 7) 21 - 50 [38 5]	63 8 ± 12.1 (19 0) 49 9 - 81 2 [61]		Smokers					17 6 ± 8 5 (48 4) [20 9]	11 3 ± 3 2 (28 3) [11 5]		11 9 ± 2 4 (20 1) [11 15]	182 9 ± 160 4 (87,7) [122 8]	3 25 ± 3 42 (105 26) [1 83]	4093 1 ± 3857 0 (94 2) [2502 87]	73 1 ± 82 0 (112 2) [36 7]		
						36 2 ± 10 7 (29 6) 18 - 50 [37]	65 2 ± 11 3 (17 3) 49 9 - 85 7 [61 45]		Mixed			20 mg Bed		19 6 ± 6 8 (34 7) [21 85]	9 8 ± 3 1 (31 5) [10]		11 2 ± 2 1 (18 6) [11 1]	142 3 ± 119 8 (84 1) [94 7]	2 41 ± 2 52 (104 59) [1 29]	3078 1 ± 2844 0 (92 4) [2013 175]	52 4 ± 59 9 (114 3) [30 8]		
						34 9 ± 11 2 (32 0) 18 - 49 [36]	66 6 ± 11 3 (17 0) 53 5 - 85 7 [64 85]		NS					21 6 ± 4 4 (20 4) [21 85]	8 3 ± 2 3 (28 1) [9]		10 5 ± 1 6 (15 4) [10 9]	101 8 ± 42 7 (42 0) [87 9]	1 57 ± 0 73 (46 68) [1 26]	2063 1 ± 667 5 (32 4) [1868 205]	31 7 ± 11.7 (36 9) [28 3]		
						38 0 ± 10 9 (28 7) 21 - 50 [38 5]	63 8 ± 12.1 (19 0) 49 9 - 81 2 [61]		Smokers					17 6 ± 8 5 (48 4) [20 9]	11 3 ± 3 2 (28 3) [11 5]		11 9 ± 2 4 (20 1) [11 15]	182 9 ± 160 4 (87.7) [122 8]	3 25 ± 3 42 (105 26) [1 83]	4093 1 ± 3857 0 (94 2) [2502 87]	73.1 ± 82 0 (112 2) [36 7]		

10.8 APPENDIX 8 SUMMARY OF MULTIPLE DOSE PHARMACOKINETIC METRICS ACROSS STUDIES

Table 119 Duloxetine Pharmacokinetic Summary Data from Multiple Dose Studies

Study	Date	Design	Assay	N	Gender	Age (years)	Weight (Kg)	Race C/B/A/H/NA	Tabacco ([redacted])	Xanthines	2D6 Genotype	Formulation	Dose	Tlag (hours)	Cmin (ng/ml)	Cmax (ng/ml)	Tmax (hours)	AUC (ng/ml x hr $^{-1}$)	Cav (ng/ml)	% Fluctuation	Cl/F (L/hr^{-1})	Cl/F (L/hr x kg $^{-1}$)	Vβ/F (L)	Vβ/F (L/kg)	t/12 (hours)	Comment
HMAD	Jul – Aug 1992	MD qAM x 15 days		24	M	37 2 ± 8 0 (21 6) 25 - 51	73 7 ± 7 0 (9 5) 52 7 – 83 2	23/1/0/0				EC Tablets	6 grps of 4 2 5 5 qd x 14 days a breakfast 10 20 40 15th dose fasted				PK Not reported as Assay was not reliable									Graphs Reported in HMAF
HMAP	April – May 1997	Mult PO	[redacted]	8	M	37 5 ± 11 0 (29 3) [35 5] 22 0 - 53 0	74 6 ± 9 9 (13 3) [73 7] 61 7 - 88 9	5/1/0/2/0				CTO8001 20 mg caps	40mg bid (7 AM & 4 PM) x 6 5 days (total administration is 3 weeks with the first 2 weeks at lower dosages)		30 2 ± 19 4 (64 1) [26 4] [redacted]	43 0 ± 26 9 (62 6) [37 3] [redacted]	7 3 ± 2 5 (34 4) [9 0] [redacted]				1 5 ± 0 7 (45 9) [1 3] [redacted]		29 9 ± 19 9 (66 6) [22 5] [redacted]	12 5 ± 3 4 (27 4) [11 1] [redacted]	Meal 1 hours post dosing PK/PD AEs W/D 1 d/c 2° to AE Cmin at lower doses with Dose Linearity can t find data
				2		30 0 ± 5 7 [28 9] [30 0] 25 0 - 34 0	72 2 ± 1 9 (2 6) [72 2] 70 8 - 73 6	Hispanic	N						57 1 ± 18 3 (32 1) [57 1] [redacted]	63 2 ± 8 0 (9 6) [63 2] [redacted]	6 0 ± 4 2 (70 7) [6 0] [redacted]				0 7 ± 0 1 (20 3) [0 7] [redacted]		13 9 ± 4 3 (30 6) [13 9] [redacted]	14 2 ± 7 0 (49 5) [14 2] [redacted]	
				6		40 0 ± 11 5 (28 8) [39 5] 22 0 - 53 0	75 4 ± 11 6 (15 3) [75 8] 61 7 - 88 9		Y						21 3 ± 8 7 (40 6) [24 4] [redacted]	29 6 ± 11 8 (40 0) [34 0] [redacted]	7 7 ± 2 1 (25 9) [9 0] [redacted]				1 7 ± 0 6 (33 5) [1 6] [redacted]		35 2 ± 20 4 (57 9) [29 7] [redacted]	11 9 ± 2 3 (18 9) [11 1] [redacted]	
HMAR	Nov – Dec 1998	Sequential Escalating Dose	[redacted]	12	6 M 6 F	31 23 - 43	68 52 – 88	12/0/0/0/0	Mixed	9 x 1- 3 cpd		20 mg Caps CT 131116	40 mg q12h		35 3 ± 21 8 (62) [28 2] [redacted]	54 ± 28 7 (49) [45 5] [redacted]	6 8 ± 2 (30) [6] [redacted]	482 ± 267 (55) [409] [redacted]			104 ± 48 (46) [98] [redacted]		645 ± 293 (45) [643] [redacted]			Xanthines excluded during study Smokers > 1 ppd excluded
													60 mg q12h		56 7 ± 44 6 (79) [45 2] [redacted]	85 3 ± 42 4 (49) [73 7] [redacted]	6 8 ± 2 4 (35) [5] [redacted]	759 ± 392 (52) [625] [redacted]			94 ± 35 (37) [97] [redacted]		580 ± 222 (38) [567] [redacted]			
													80 mg q12h		93 7 ± 60 9 (65) [71 6] [redacted]	140 9 ± 81 2 (58) [110 4] [redacted]	6 8 ± 2 1 (30) [6] [redacted]	1322 ± 819 (62) [904] [redacted]			82 ± 43 (53) [89] [redacted]		499 ± 267 (54) [530] [redacted]		11 6 ± 1 5 (13) [11 7] [redacted]	
				6	M	33 24 - 43	73 65 - 88	18/0/0/0/0	2 x 0 5 ppd 1 x 0 5-1 ppd	1 x 0			40 mg q12h		21 6 ± 7 3 (34)	41 5 ± 12 4 (30)	5 8 ± 0 4 (7)	335 ± 103 (31)			131 ± 46 (35)		804 ± 278 (35)			
													60 mg q12h		38 2 ± 10 8 (28)	56 8 ± 20 7 (31)	6 7 ± 1 (15)	544 ± 122 (22)			115 ± 27 (24)		722 ± 177 (35)			
													80 mg q12h		54 8 ± 16 (29)	97 2 ± 34 6 (36)	6 2 ± 1 5 (24)	845 ± 169 (34)			105 ± 40 (38)		640 ± 252 (39)		11 1 ± 1 3 (12)	
				6	F	30 23 - 43	63 52 - 77	6/0/0/0/0	4 x 0 5 ppd	2 x 0			40 mg q12h		49 ± 23 4 (48)	86 5 ± 32 2 (49)	7 7 ± 2 6 (34)	628 ± 308 (49)			77 ± 35 (45)		486 ± 225 (46)			
													60 mg q12h		75 2 ± 58 6 (78)	105 8 ± 51 1 (48)	6 8 ± 3 4 (49)	974 ± 450 (47)			73 ± 31 (42)		436 ± 170 (39)			
													80 mg q12h		132 8 ± 65 4 (49)	164 5 ± 93 3 (51)	7 5 ± 2 5 (33)	1798 ± 921 (51)			58 ± 34 (58)		358 ± 213 (60)		12 ± 1 7 (14)	
HMAZ Desip Interxn Study	Nov – Dec 1999	MD	[redacted]	14	7 M 7 F	42 4 ± 13 4 (31 6) 21 0 – 63 0 [43 0]	71 5 ± 12 8 (17 9) 46 5 - 100 7 [71 2]	13/0/1/0/0	NR	NR	EM	20 mg Caps 10% EC Pellets	60 mg po q12h Fed	NR	81 3 ± 49 2 (60 5) [redacted] [71 0]	128 5 ± 68 9 (53 6) [redacted] [117 1]	5 1 ± 1 7 (34 1) [redacted] [5 0]	1195 6 ± 666 2 (55 7) [redacted] [1054 7]	995 ± 555 (55 7) [redacted] [87 9]	NR	72 6 ± 46 5 (64 0) [redacted] [65 0]	1 0 ± 0 6 (57 8) [redacted] [0 84]				
				7	M	47 4 ± 13 7 (29 0) 28 0 - 63 0 [43 0]	75 2 ± 13 3 (17 6) 64 4 - 100 7 [87 1]	7/0/0/0/0							68 8 ± 66 8 (75 1) [redacted] [64 0]	133 1 ± 92 8 (69 8) [redacted] [94 7]	4 6 ± 1 4 (30 6) [redacted] [4 0]	1271 5 ± 911 6 (71 7) [redacted] [921 6]	105 9 ± 76 0 (71 7) [redacted] [76 7]		86 4 ± 61 8 (71 5) [redacted] [65 6]	1 1 ± 0 8 (68 1) [redacted] [1 0]				
				7	F	37 3 ± 11 6 (31 7) 21 0 - 53 0 [35 0]	67 7 ± 12 0 (17 8) 46 5 - 78 5 [71 7]	6/0/1/0/0							73 7 ± 25 4 (34 5) [redacted] [77 9]	123 9 ± 40 1 (32 4) [redacted] [130 1]	5 6 ± 2 0 (35 7) [redacted] [6 0]	1119 7 ± 342 2 (30 6) [redacted] [1184 7]	93 3 ± 28 5 (30 6) [redacted] [98 7]		58 8 ± 20 4 (34 7) [redacted] [50 6]	0 9 ± 0 3 (36 1) [redacted] [0 83]				

Study	Date	Design	Assay	N	Gender	Age (years)	Weight (Kg)	Race C/B/A/H/NA	Tobacco	Xanthines	2D6 Genotype	Formulation	Dose	Tlag (hours)	Cmin (ng/ml)	Cmax (ng/ml)	Tmax (hours)	AUC (ng/ml x hr^{-1})	Cav (ng/ml)	% Fluctuation	Cl/F (L/hr^{-1})	CL/F (L/hr x kg^{-1})	Vβ/F (L)	Vβ/F (L/kg)	t1/2 (hours)	Comment
HMAJ Temazepam Interxn Study		MD		11		32 ± 9 (28.1) 20 - 49	62.3 ± 9.1 (5.0) 64.5 – 93.6	9 / 2 / 0 / 0						5.1 ± 1.9 (36.7) [5]	3.6 ± 3.0 (83.9)	14.2 ± 6.3 (44.6)	6 ± 3 (39)	206.5 ± 112.9 (54.7)	8.6 ± 4.7 (54.7)	1.4 ± 0.4 (30.9)						
				9				9 / 0 / 0 / 0																		
				2				0 / 2 / 0 / 0																		
SBAG Paroxetine Interxn Study		MD		9		23.4 ± 1.9 (7.7) 21.0 - 27.0 [23.0]	67.7 ± 6.9 (10.2) 57.7 – 81.4 [66.5]	1/0/8/0/0							0.9 ± 5.9 (56.9) [7.6]	34.5 ± 8.6 (24.8) [33.9]	6.2 ± 1.9 (29.8) [6.0]	459.7 ± 173.1 (35.3) [469.3]	20.4 ± 7.2 (35.3) [19.6]	132.9 ± 32.8 (24.7) [135.1]	90.3 ± 28.8 (31.9) [85.2]	1.3 ± 0.4 (32.5) [1.3]	1281.6 ± 282.9 (22.1) [1168.1]	19.2 ± 5.0 (26.1) [19.4]	10.3 ± 2.1 (19.9) [9.3]	
				8	M	23.4 ± 1.9 (8.2) 21.0 - 27.0 [23.0]	69.0 ± 8.2 (9.0) 61.9 – 81.4 [66.8]	Asian 1							10.2 ± 5.9 (58.3) [8.4]	34.3 ± 9.1 (26.6) [33.2]	6.0 ± 1.9 (30.9) [6.0]	491.0 ± 185.0 (37.7) [480.7]	20.5 ± 7.7 (37.7) [19.2]	131.0 ± 34.5 (26.4) [132.8]	91.1 ± 30.8 (33.8) [86.9]	1.3 ± 0.5 (34.9) [1.3]	1301.6 ± 295.6 (22.7) [1309.8]	19.2 ± 5.4 (27.9) [19.4]	10.4 ± 2.2 (20.7) [10.5]	
				4	M	24.5 ± 1.9 (7.8) 23.0 - 27.0 [24.0]	69.5 ± 8.3 (11.9) 63.2 – 81.4 [66.8]	Malay	NR	NR	EM		40 mg QD		12.3 ± 5.2 (42.0) [11.3]	37.3 ± 8.9 (16.8) [34.6]	5.0 ± 2.0 (40.0) [6.0]	542.1 ± 155.4 (28.7) [470.9]	22.6 ± 6.5 (28.7) [19.7]	118.0 ± 27.5 (23.3) [117.3]	77.5 ± 17.3 (22.4) [85.0]	1.1 ± 0.3 (24.5) [1.2]	1258.6 ± 301.8 (24.0) [1295.9]	18.5 ± 5.9 (31.9) [18.3]	11.3 ± 1.8 (14.5) [11.9]	
				14		22.3 ± 1.3 (5.7) 21.0 - 24.0 [22.0]	68.4 ± 4.6 (6.7) 61.9 – 71.9 [69.9]	Chinese							8.1 ± 6.8 (81.9) [5.2]	31.3 ± 11.1 (35.3) [27.6]	7.0 ± 1.2 (16.5) [7.0]	439.9 ± 220.8 (50.2) [350.9]	19.4 ± 9.2 (50.2) [14.7]	144.0 ± 39.7 (27.6) [153.1]	104.8 ± 37.3 (35.6) [114.5]	1.5 ± 0.6 (36.4) [1.7]	1346.5 ± 327.7 (24.3) [1369.4]	19.9 ± 5.6 (28.0) [19.4]	9.5 ± 2.4 (25.6) [8.7]	
				13		24.1	57.7	Indian 1																		
HMBN	Mar – Apr 2001	qAM x 8 days w/ food	LC/MS/MS per Lilly	11	5 M 6 F	38.8 ± 11.7 (30.2) 23.0 – 61.0	79.1 ± 15.1 (19.2) [71.2] 66.2 – 113.4	8/3/1/0/0	Mixed			60 mg Cap 20% EC Pellets + TBM	60 mg po qAM 2 hours after a light breakfast		27.0 ± 17.3 (64.1) 24.4	89.5 ± 35.6 (39.8) 94.1	5.6 ± 1.2 (21.4) [6.0]	1175.6 ± 576.7 (49.1) 1080.5	49.0 ± 24.0 (49.0) 45.0	139.3 ± 34.6 (24.9) 143.2	64.0 ± 31.0 (48.4) 55.5			0.36 ± 0.08 (19.8) 0.34		
				5	M	38.4 ± 5.8 (15.0) [39.0] 29.0 – 44.0	86.2 ± 17.5 (20.3) [83.5] 66.5 – 113.4	3/2/0/0/0	Mixed						13.3 ± 6.7 (50.3) 11.2	61.9 ± 20.0 (32.3) 58.2	5.2 ± 1.1 (21.1) [6.0]	705.8 ± 218.6 (31.0) 640.2	29.4 ± 9.1 (30.9) 26.7	166.2 ± 28.7 (17.3) 166.3	90.4 ± 22.5 (24.9) 93.7			0.42 ± 0.08 (19.0) 0.41		
				6	F	39.2 ± 15.8 (40.2) [34.0] 23.0 – 61.0	73.2 ± 11.0 (15.1) [69.9] 66.2 – 95.3	5/0/1/0/0	NS		EM				38.5 ± 14.7 (38.3) 37.8	112.5 ± 28.8 (25.6) 112.8	5.0 ± 1.3 (21.1) [6.0]	1567.1 ± 471.3 (30.1) 1508.9	65.3 ± 19.8 (30.1) 66.7	116.9 ± 20.4 (17.4) 112.6	42.0 ± 15.4 (36.6) 37.9			0.35 ± 0.06 (18.2) 0.33		
				3	M	39.7 ± 9.8 (18.6) [39.0] 29.0 – 42.0	78.0 ± 11.8 (15.1) [74.4] 68.5 – 91.2	2/1/0/0/0	Smokers						9.4 ± 2.3 (23.9) 10.2	53.1 ± 12.0 (22.6) 54.3	5.3 ± 1.2 (21.7) [6.0]	591.4 ± 72.6 (12.3) 625.9	24.7 ± 3.0 (12.2) 26.1	174.7 ± 37.1 (21.2) 165.3	102.6 ± 13.5 (13.2) 95.8			0.38 ± 0.0 (13.0) 0.37		
				2	M	41.0 ± 4.2 (10.3) [41.0] 38.0 – 44.0	98.5 ± 21.1 (21.5) [98.5] 83.5 – 113.4	1/1/0/0/0	NS						19.0 ± 7.6 (40.2) 19.0	75.3 ± 26.9 (35.8) 75.3	5.0 ± 1.4 (28.3) [6.0]	877.5 ± 287.0 (32.7) 877.5	35.6 ± 12.0 (32.7) 36.6	153.4 ± 26.6 (17.3) 153.4	72.2 ± 23.6 (32.7) 72.2			0.47 ± 0.09 (18.8) 0.47		
HMBN	Mar – Apr 2001	q12h x 7.5 days (AM dose)	LC/MS/MS per Lilly	11	5 M 6 F	38.8 ± 11.7 (30.2) 23.0 – 61.0	79.1 ± 15.1 (19.2) [71.2] 66.2 – 113.4	8/3/1/0/0	Mixed			60 mg Cap 20% EC Pellets + TBM	60 mg po q12h 2 hours after a light breakfast	NR	65.2 ± 59.7 (70.0) 64.8	144.0 ± 85.4 (59.3) 113.3	6.0 ± 1.3 (21.1) [6.0]	1375.9 ± 659.2 (53.2) 998.1	114.7 ± 72.4 (63.2) 83.2	57.4 ± 17.3 (30.1) 61.7	62.5 ± 35.9 (57.4) 60.3	0.81 ± 0.49 (60.6) 0.67	1009.4 ± 484.3 (48.0) 1071.6	13.0 ± 6.62 (50.8) 11.74	11.9 ± 1.4 (11.9) 12.2	
				6	M	38.4 ± 5.8 (15.0) [39.0] 29.0 – 44.0	86.2 ± 17.5 (20.3) [83.5] 66.5 – 113.4	3/2/0/0/0	Mixed						40.2 ± 17.0 (42.3) 30.6	78.1 ± 27.0 (35.4) 80.1	6.6 ± 1.7 (29.9) [6.0]	709.2 ± 217.5 (30.7) 580.0	59.1 ± 18.1 (30.7) 46.3	61.7 ± 16.7 (27.0) 62.3	90.7 ± 25.1 (27.7) 103.4	1.12 ± 0.45 (40.0) 1.13	1397.9 ± 287.6 (20.6) 1541.3	17.0 ± 5.89 (34.6) 16.90	10.9 ± 1.1 (10.1) 10.3	
				0	F	39.2 ± 15.8 (40.2) [34.0] 23.0 – 61.0	73.2 ± 11.0 (15.1) [69.9] 66.2 – 95.3	5/0/1/0/0	NS		EM				122.7 ± 56.4 (45.9) 136.8	200.8 ± 74.8 (37.2) 215.1	6.3 ± 0.6 (12.9) [6.0]	1931.2 ± 611.5 (42.0) 2130.6	161.0 ± 67.6 (42.0) 177.6	53.9 ± 18.5 (34.3) 49.4	39.0 ± 24.8 (63.6) 28.3	0.85 ± 0.38 (68.1) 0.41	685.9 ± 355.3 (51.8) 580.6	9.68 ± 5.49 (56.7) 8.20	12.7 ± 1.1 (9.0) 12.8	
				3	M	36.7 ± 6.8 (18.6) [39.0] 29.0 – 42.0	78.0 ± 11.8 (15.1) [74.4] 68.5 – 91.2	2/1/0/0/0	Smokers						28.4 ± 3.2 (11.1) 29.0	57.1 ± 4.9 (8.6) 59.7	4.7 ± 1.2 (24.7) [4.0]	554.1 ± 34.6 (6.3) 567.7	46.2 ± 2.9 (6.2) 47.3	62.1 ± 0.4 (0.6) 62.3	108.6 ± 7.0 (6.5) 105.7	1.41 ± 0.24 (17.2) 1.54	1603.4 ± 81.6 (5.1) 1573.1	20.89 ± 3.45 (16.5) 22.79	10.2 ± 0.1 (1.4) 10.3	
				2	M	41.0 ± 4.2 (10.3) [41.0] 38.0 – 44.0	98.5 ± 21.1 (21.5) [98.5] 83.5 – 113.4	1/1/0/0/0	NS						57.9 ± 10.0 (17.2) 57.9	104.7 ± 12.2 (11.6) 104.7	7.0 ± 1.4 (20.2) 7.0	941.8 ± 79.4 (8.4) 941.9	78.5 ± 6.6 (8.5) 78.5	61.1 ± 33.3 (54.6) 61.1	63.9 ± 5.4 (8.4) 63.9	0.87 ± 0.20 (29.6) 0.87	1089.5 ± 25.0 (2.3) 1089.5	11.30 ± 2.17 (19.2) 11.30	11.9 ± 1.3 (10.7) 11.9	

10.9 APPENDIX 9 SINGLE AND MULTIPLE DOSE DULOXETINE, 4-HYDROXYDULOXETINE GLUCURONIDE, AND 5-HYDROXY, 6-METHOXY DULOXETINE SULFATE PHARMACOKINETIC METRICS (STUDY HMBN)

Table 120 Duloxetine Pharmacokinetic Metrics After a Single 60 mg Dose PO of the To-Be-Marketed Formulation (Study HMBN)

N	Gender	Tobacco Use	2D6 Genotype	Tlag (hours)	Cmax (ng/ml)	Tmax (hours)	AUC∞ (ng/ml x hr^{-1})	$t_{1/2}$ (hours)
12	6 M 6 F	Mixed	11 EM 1 PM		56.1 ± 26.8 48 45.2	5.3 ± 1.3 (24.4) 6.0	845.3 ± 473.6 (56 680.7	10.9 ± 1.8 (16.5) 11.3
6	F	NS	EM		69.5 ± 30.0 43.2 60.0	5.7 ± 0.8 (14.4) 6.0	612.1 ± 385.8 (63.0) 503.9	10.2 ± 2.2 (21.3) 9.0
6	M	Mixed	5 EM 1 PM		42.7 ± 15.5 (36.4) 40.9	5.0 ± 1.7 (33.5) 6.0	1078.5 ± 462.6 42.9 951.4	11.6 ± 1.1 (9.8) 11.6
3	M	Smokers	EM		34.7 ± 11.0 (31.8) 36.3	4.0 ± 2.0 (50.0) 4.0	433.8 ± 168.9 (38.9) 402.2	8.9 ± 0.3 (2.9) 9.0
2	M	NS	EM		41.3 ± 6.0 (14.6) 41.3	6.0	503.9 ± 58.4 (11.6) 503.9	10.6 ± 2.8 (26.4) 10.6
1	M	NS	PM					

Table 121 Duloxetine Pharmacokinetic Metrics After 60 mg PO qAM x 8 Days of the To-Be-Marketed Formulation (Study HMBN)

N	Gender	Tobacco Use	2D6 Genotype	Cmin (ng/ml)	Cmax (ng/ml)	Tmax (hours)	AUCτ (ng/ml x hr^{-1})	Cav (ng/ml)
11	5 M 6 F	Mixed	EM	27.0±17.3 (64.1) 24.4	89.5±35.6 (39.8) 94.1	5.6±1.2 (21.4) 6.0	1175.6±576.7 (49.1) 1080.5	49.0±24.0 (49.0) 45.0
6	F	NS		38.5±14.7 (38.3) 37.8	112.5±28.8 26 112.8	6.0±1.3 (21.1) 6.0	1567.1±471.3 (30.1) 1598.9	65.3±19.6 (30.1) 66.7
5	M	Mixed		13.3±6.7 (50.3) 11.2	61.9±20.0 (32.3) 56.2	5.2±1.1 (21.1) 6.0	705.8±218.6 (31.0) 640.2	29.4±9.1 (30.9) 26.7
3	M	Smokers		9.4±2.3 (23.9) 10.2	53.1±12.0 (22.6) 54.3	5.3±1.2 (21.7) 6.0	591.4±72.6 (12.3) 625.9	24.7±3.0 (12.2) 26.1
2	M	NS		19.0±7.6 (40.2) 19.0	75.3±26.9 (35.8) 75.3	5.0±1.4 (28.3) 5.0	877.5±287.0 (32.7) 877.5	36.6±12.0 (32.7) 36.6

Drop out of poor metabolizer is claimed due to not following instructions of clinical investigator.

Table 122 PM Duloxetine Pharmacokinetic Metrics After 60 mg PO q12h x 7 Days of the To-Be-Marketed Formulation (Study HMBN)

N	Gender	Tobacco Use	2D6 Genotype	Cmin (ng/ml)	Cmax (ng/ml)	Tmax (hours)	AUCτ[z] (ng/ml x hr^{-1})	Cav (ng/ml)	%Fluctuation
11	5 M 6 F	Mixed	EM	79.3 ± 53.4 (67.4) [49.0]	120.0 ± 76.6 (63.8) [77.4]	6.0 ± 1.3 (21.1) [6.0]	1136.5 ± 884.4 (77.8) [748.4]	103.4 ± 68.2 (66.0) [64.5]	41.9 ± 11.9 (28.3) [47.1]
6	F	NS		114.9 ± 47.7 (41.5) [128.1]	170.1 ± 70.2 (41.3) [179.4]	6.3 ± 0.8 (12.9) [6.0]	1591.2 ± 998.9 (62.8) [1939.1]	148.6 ± 61.5 (41.4) [161.6]	36.3 ± 13.1 (36.1) [35.8]
5	M	Mixed		36.5 ± 10.6 (29.1) [33.3]	60.0 ± 15.1 (25.2) [54.3]	5.6 ± 1.7 (29.9) [6.0]	591.0 ± 161.8 (27.4) [535.4]	49.2 ± 13.5 (27.4) [44.6]	48.5 ± 6.0 (12.3) [48.0]
3	M	Smokers		29.1 ± 4.2 (14.3) [29.0]	49.5 ± 6.3 (12.8) [51.9]	4.7 ± 1.2 (24.7) [4.0]	477.4 ± 61.2 (12.8) [483.3]	39.8 ± 5.1 (12.9) [40.3]	51.4 ± 5.0 (9.7) [50.2]
2	M	NS		47.7 ± 1.8 (3.9) [47.7]	75.8 ± 2.3 (3.1) [75.8]	7.0 ± 1.4 (20.2) [7.0]	761.4 ± 18.5 (2.4) [761.4]	63.5 ± 1.5 (2.3) [63.5]	44.1 ± 5.5 (12.5) [44.1]

z AUCtau

Table 123 AM Duloxetine Pharmacokinetic Metrics After 60 mg PO q12h x 7.5 Days of the To-Be-Marketed Formulation (Study HMBN)

N	Gender	Tobacco Use	2D6 Genotype	Cmin (ng/ml)	Cmax (ng/ml)	Tmax (hours)	AUCτ (ng/ml x hr^{-1})	Cav (ng/ml)	% Fluctuation	$t_{1/2}$ (hours)
11	5 M 6 F	Mixed	EM	85.2±59.7 (70.0) 64.9	144.0±85.4 59.3 113.3	6.0±1.3 (21.1) 6.0	1375.8±869.2 (63.2) 998.1	114.7±72.4 (63.2) 83.2	57.4±17.3 (30.1) 61.7	11.9±1.4 (11.9) 12.2
6	F	NS		122.7±56.4 (45.9) 136.8	200.6±74.6 37.2 215.1	6.3±0.8 (12.9) 6.0	1931.2±811.5 (42.0) 2130.6	161.0±67.6 (42.0) 177.6	53.9±18.5 (34.3) 49.4	12.7±1.1 (9.0) 12.8
5	M	Mixed		40.2±17.0 (42.3) 30.6	76.1±27.0 35.4 60.1	5.6±1.7 (29.9) 6.0	709.2±217.5 (30.7) 580.0	59.1±18.1 (30.7) 48.3	61.7±16.7 (27.0) 62.3	10.9±1.1 (10.1) 10.3
3	M	Smokers		28.4±3.2 (11.1) 29.9	57.1±4.9 8.5 59.7	4.7±1.2 (24.7) 4.0	554.1±34.8 (6.3) 567.7	46.2±2.9 (6.2) 47.3	62.1±0.4 (0.6) 62.3	10.2±0.1 (1.4) 10.3
2	M	NS		57.9±10.0 (17.2) 57.9	104.7±12.2 11.6 104.7	7.0±1.4 (20.2) 7.0	941.9±79.4 (8.4) 941.9	78.5±6.6 (8.5) 78.5	61.1±33.3 (54.6) 61.1	11.9±1.3 (10.7) 11.9

z AUCtau

Table 124 4-Hydroxy Duloxetine Glucuronide Pharmacokinetic Metrics After a Single 60 mg PO Dose of the To-Be-Marketed Formulation (Study HMBN)

N	Gender	Tobacco Use	2D6 Genotype	Cmax (ng/ml)	Tmax (hours)	AUC_∞ (ng/ml x hr)	$t_{1/2}$ (hours)
12	6 M 6 F	Mixed	11 EM 1 PM	400.6 ± 143.8 (35.9) [395.6]	6.2 ± 1.4 (22.7) 6]	7254.6 ± 4146.9 (57.2) [5998.63]	12.2 ± 2.2 (18.4) [11.42]
6	F	NS	EM	458.0 ± 140.5 (30.7) [496.2]	6.4 ± 1.7 (26.1) [6]	9716.6 ± 5056.7 (52.0) [9716.64]	13.5 ± 2.7 (20.0) [14.29]
6	M	Mixed	5 EM 1 PM	352.7 ± 139.6 (39.6) [391.75]	6.0 ± 1.3 (21.10 [6]	5203.0 ± 1680.7 (32.3) [5767.765]	11.0 ± 0.9 (8.2) [10.69]
3	M	Smokers	EM	380.8 ± 19.3 (5.1) [387.9]	5.3 ± 1.2 (21.7) [6]	5496.6 ± 760.7 (13.8) [5536.9]	10.7 ± 0.1 (0.9) [10.62]
2	M	NS	EM	324.5 ± 214.4 (66.1) [411.7]	6.7 ± 1.2 (17.3) [6]	4909.4 ± 2494.9 (50.8) [5998.6]3	11.4 ± 1.3 (10.9) [11.42]
1	M	NS	PM				

Table 125 4-Hydroxy Duloxetine Glucuronide Pharmacokinetic Metrics after 60 mg PO qAM x 8 Days of the To-Be-Marketed Formulation (Study HMBN)

N	Gender	Tobacco Use	2D6 Genotype	Cmin (ng/ml)	Cmax (ng/ml)	Tmax (hours)	AUCτ (ng/ml x hr-1)	Cav (ng/ml)	% Fluctuation
11	5 M 6 F	Mixed		169.6 ± 107.7 (63.5) [130.2]	482.5 ± 156.3 (32.4) [452.9]	6.0 ± 0.0 (0.0) [6]	6968.4 ± 2960.4 (42.5) [6120.39]	291.2 ± 122.3 (42.0) [255]	115.7 ± 34.2 (29.6) [109.71]
6	F	NS		207.9 ± 136.8 (65.8) [170.85]	507.8 ± 211.1 (41.6) [485.7]	6.0 ± 0.0 (0.0) [6]	7965.4 ± 3813.2 (47.9) [7473.88]	333.5 ± 156.8 (47.0) [311.4]	97.2 ± 29.1 (29.9) [101.04]5
5	M	Mixed	EM	123.6 ± 27.8 (22.5) [127.6]	452.2 ± 56.8 (12.6) [435.3]	6.0 ± 0.0 (0.0) [6]	5771.9 ± 673.8 (11.7) [6114.65]	240.5 ± 28.1 (11.7) [254.8]	137.8 ± 27.3 (19.8) [134.04]
3	M	Smokers		108.9 ± 20.3 (18.7) [106.8]	463.6 ± 77.3 (16.7) [452.9]	6.0 ± 0.0 (0.0) [6]	5501.4 ± 793.4 (14.4) [6120.4]	229.2 ± 33.0 (14.4) [240.7]	154.6 ± 19.2 (12.4) [157.61]
2	M	NS		145.6 ± 25.5 (17.5) [145.6]	435.3 ± 0.1 (0.0) (435.25]	6.0 ± 0.0 (0.0) [6]	6177.8 ± 89.3 (1.4) [6177.77]	257.4 ± 3.7 (1.4) [257.4]	112.6 ± 11.5 (10.2) [112.61]

Table 126 PM 4-Hydroxy Duloxetine Glucuronide Pharmacokinetic Metrics After 60 mg PO q12h x 7 Days of the To-Be-Marketed Formulation (Study HMBN)

N	Gender	Tobacco Use	2D6 Genotype	Cmin (ng/ml)	Cmax (ng/ml)	Tmax (hours)	AUCτ (ng/ml x hr)	Cav (ng/ml)	%Fluctuation
11	5 M 6 F	Mixed	EM	372.2 ± 210.2 (56.5) [296.8]	570.3 ± 243.4 (42.7) [500.4]	6.7 ± 1.3 (20.0) [6]	5815.8 ± 2738.6 (47.1) [4931.07]	484.7 ± 228.2 (47.1) [410.9]	43.8 ± 15.9 (36.3) [42]
6	F	NS		446.8 ± 270.7 (60.6) [427.85]	640.7 ± 319.7 (49.9) [674.4]	6.7 ± 1.0 (15.5) [6]	6697.3 ± 3573.5 (53.4) [6727.06]	558.1 ± 297.8 (53.4) [560.55]	38.1 ± 17.9 (46.9) [38.535]
5	M	Mixed		282.8 ± 23.8 (8.4) [292.9]	485.8 ± 63.6 (13.1) [493.8]	6.8 ± 1.8 (26.3) [8]	4758.1 ± 473.2 (9.9) [4599.68] 4249.35 -	396.5 ± 39.4 (9.9) [383.3]	50.7 ± 11.2 (22.1) [46.94]
3	M	Smokers		279.8 ± 26.2 (9.4) [292.9]	507.5 ± 64.1 (12.6) [493.8]	6.7 ± 2.3 (34.6) [8]	4870.1 ± 533.5 (11.0) [4599.68]	405.9 ± 44.5 (11.0) [383.3]	55.7 ± 11.9 (21.4) [61.37]
2	M	NS		287.3 ± 28.6 (9.9) [287.3]	453.3 ± 66.6 (14.7) [453.3]	7.0 ± 1.4 (20.2) [7]	4590.2 ± 482.0 (10.5) [4590.21] 4249.35 -	382.5 ± 40.2 (10.5) [382.5]	43.1 ± 5.4 (12.6) [43.11]

Table 127 AM 4-Hydroxy Duloxetine Glucuronide Pharmacokinetic Metrics After 60 mg PO q12h x 7.5 Days of the To-Be-Marketed Formulation (Study HMBN)

N	Gender	Tobacco Use	2D6 Genotype	Cmin (ng/ml)	Cmax (ng/ml)	Tmax (hours)	AUCτ (ng/ml x hr)	Cav (ng/ml)	%Fluctuation	$t_{1/2}$ (hours)
11	5 M 6 F	Mixed	EM	431.8 ± 242.8 (56.2) [373.2]	656.3 ± 241.7 (36.8) [615.9]	5.8 ± 0.6 (10.4) [6]	6465.8 ± 2832.3 (43.8) [5972.5]	538.8 ± 236.0 (43.8) [497.7]	47.8 ± 19.7 (41.3) [45.85]	14.4 ± 2.6 (18.3) [14.79]
6	F	NS		518.8 ± 306.9 (59.2) [519.65]	715.6 ± 322.8 (45.1) [741.25]	6.0 ± 0.0 (0.0) [6]	7268.7 ± 3705.4 (51.0) [7279.91]	605.7 ± 308.8 (51.0) [606.7]	39.8 ± 20.6 (51.7) [36.54]	15.7 ± 2.5 (16.2) [15.505]
5	M	Mixed		327.4 ± 68.0 (20.8) [365.7]	585.1 ± 65.1 (11.1) [586.9]	5.6 ± 0.9 (16.0) [6]	5502.3 ± 875.1 (15.9) [5923.4]	458.5 ± 72.9 (15.9) [493.6]	57.3 ± 15.4 (26.8) [54.84]	12.8 ± 1.9 (14.50 [12.42]
3	M	Smokers		319.2 ± 87.2 (27.3) [365.7]	610.0 ± 68.1 (11.2) [615.9]	5.3 ± 1.2 (21.7) [6]	5674.8 ± 942.5 (16.6) [5923.4]	472.9 ± 78.5 (16.6) [493.6]	63.2 ± 17.3 (27.4) [55.97]	11.5 ± 0.9 (7.6) [11.4]
2	M	NS		339.8 ± 53.0 (15.6) [339.8]	547.9 ± 55.2 (10.1) [547.9]	6.0 ± 0.0 (0.0) [6]	5243.4 ± 1031.1 (19.7) [5243.39]	437.0 ± 85.9 (19.7) [436.95]	48.5 ± 9.0 (18.6) [48.475]	14.7 ± 0.4 (2.5) [14.67]

Table 128 5-Hydroxy, 6-Methoxy Duloxetine Sulfate Pharmacokinetic Metrics After a Single 60 mg PO Dose of the To-Be-Marketed Formulation (Study HMBN)

N	Gender	Tobacco Use	2D6 Genotype	Cmax (ng/ml)	Tmax (hours)	AUC_{∞} (ng/ml x hr)	$t_{1/2}$ (hours)
12	6 M 6 F	Mixed	11 EM 1 PM	284.4 ± 107.8 (37.9) [253.6]	5.6 ± 1.2 (21.4) [6]	3214.4 ± 1502.0 (46.7) [2883.95]	10.4 ± 1.5 (14.2) [10.2]
6	F	NS	EM	282.9 ± 62.7 (22.2) [287.3]	5.2 ± 1.1 (21.1) [6]	3603.0 ± 941.5 (26.1) [3654.46]	11.0 ± 0.9 (8.0) [11.32]
6	M	Mixed	5 EM 1 PM	225.0 ± 198.3 (88.2) [223.85]	6.0 ± 1.3 (21.1) [6]	2890.5 ± 1877.7 (65.0) [2417.085]	9.9 ± 1.7 (17.7) [9.445]
3	M	Smokers	EM	163.6 ± 133.5 (81.6) [194.1]	5.3 ± 1.2 (21.7) [6]	2502.9 ± 680.3 (27.2) [2247.23]	9.2 ± 0.7 (7.7) [8.86]
3	M	NS	EM	286.3 ± 263.1 (91.9) [253.6]	6.7 ± 1.2 (17.3) [6]	3278.0 ± 2810.9 (85.7) [2586.94]	10.5 ± 2.4 (23.0) [10.2]
1	M	NS	PM				

Table 129 5-Hydroxy, 6-Methoxy Duloxetine Sulfate Pharmacokinetic Metrics After 60 mg PO qAM x 8 Days of the To-Be-Marketed Formulation (Study HMBN)

N	Gender	Tobacco Use	2D6 Genotype	Cmin (ng/ml)	Cmax (ng/ml)	Tmax (hours)	AUCτ (ng/ml x hr.)	Cav (ng/ml)	% Fluctuation
11	5 M 6 F	Mixed	EM	57.2 ± 23.9 (41.7) [53.3]	278.0 ± 72.2 (26.0) [278.3]	5.6 ± 0.8 (14.4) [6]	3169.3 ± 870.8 (27.5) [2800.1]	201.8 ± 218.4 (108.2) [130.3]	169.7 ± 28.3 (16.7) [170.64]
6	F	NS		64.8 ± 21.9 (33.7) [61]	277.7 ± 58.4 (21.0) [264.25]	5.7 ± 0.8 (14.4) [6]	3302.0 ± 700.7 (21.2) [2963.32]	137.6 ± 29.2 (21.2) [123.5]	155.8 ± 26.4 (16.9) [163.09]
5	M	Mixed		48.0 ± 25.2 (52.4) [36.5]	278.4 ± 93.6 (33.6) [278.3]	5.6 ± 0.9 (16.0) [6]	3010.1 ± 1106.4 (36.8) [2647.13]	279.0 ± 323.4 (115.9) [132.5]	186.4 ± 22.1 (11.8) [186.25]
3	M	Smokers		37.3 ± 8.7 (23.3) [34.5]	255.4 ± 58.3 (22.8) [278.3]	6.0 ± 0.0 (0.0) [6]	2624.8 ± 567.3 (21.6) [2647.13]	365.3 ± 422.5 (115.7) [132.5]	199.1 ± 19.1 (9.6) [189.96]
2	M	NS		64.1 ± 39.0 (60.9) [64.1]	312.8 ± 156.0 (49.9) [312.8]	5.0 ± 1.4 (28.3) [5]	3588.0 ± 1771.8 (49.4) [3588.04]	149.5 ± 73.8 (49.4) [149.5]	167.5 ± 4.5 (2.7) [167.475]

Table 130 PM 5-Hydroxy, 6-Methoxy Duloxetine Sulfate Pharmacokinetic Metrics After 60 mg PO q12h x 7 Days of the To-Be-Marketed Formulation (Study HMBN)

N	Gender	Tobacco Use	2D6 Genotype	Cmin (ng/ml)	Cmax (ng/ml)	Tmax (hours)	AUCτ (ng/ml x hr^{-1})	Cav (ng/ml)	% Fluctuation
11	5 M 6 F	Mixed	EM	188.4 ± 66.8 (35.4) [181]	312.6 ± 76.0 (24.3) [290.1]	6.2 ± 1.4 (22.7) [6]	3025.2 ± 833.7 (27.6) [2911.49]	252.1 ± 69.5 (27.6) [242.6]	51.6 ± 15.1 (29.3) [52.32]
6	F	NS		203.9 ± 63.8 (31.3) [184.75]	325.2 ± 82.3 (25.3) [326.1]	6.0 ± 1.3 (21.1) [6]	3186.1 ± 808.3 (25.4) [3061.885]	265.5 ± 67.4 (25.4) [255.15]	46.5 ± 9.7 (20.9) [48.59]
5	M	Mixed		169.8 ± 72.5 (42.7) [127.4]	297.4 ± 73.8 (24.8) [289.2]	6.4 ± 1.7 (26.1) [6]	2832.1 ± 914.2 (32.3) [2489.02]	236.0 ± 76.2 (32.3) [207.4]	57.7 ± 19.2 (33.2) [54.42]
3	M	Smokers		144.8 ± 31.4 (21.7) [127.4]	282.7 ± 12.0 (4.3) [289.2]	6.0 ± 2.0 (33.3) [6]	2548.6 ± 344.8 (13.5) [2489.02]	212.4 ± 28.7 (13.5) [207.4]	66.5 ± 18.8 (28.2) [76.64]
2	M	NS		207.5 ± 119.9 (57.8) [207.45]	319.4 ± 140.9 (44.1) [319.35]	7.0 ± 1.4 (20.2) [7]	3257.4 ± 1581.8 (48.6) [3257.365]	271.5 ± 131.9 (48.6) [271.45]	44.6 ± 13.9 (31.2) [44.595]

Table 131 AM 5-Hydroxy, 6-Methoxy Duloxetine Sulfate Pharmacokinetic Metrics After 60 mg PO q12h x 7.5 Days of the To-Be-Marketed Formulation (Study HMBN)

N	Gender	Tobacco Use	2D6 Genotype	Cmin (ng/ml)	Cmax (ng/ml)	Tmax (hours)	AUCτ (ng/ml x hr^{-1})	Cav (ng/ml)	% Fluctuation	$t_{1/2}$ (hours)
11	5 M 6 F	Mixed	EM	199.3 ± 55.7 (28.0) [177.2]	386.2 ± 109.1 (28.3) [375.2]	5.6 ± 0.8 (14.4) [6]	3759.5 ± 1126.6 (30.0) [3741.62]	283.0 ± 71.8 (25.4) [255.8]	65.6 ± 17.8 (27.2) [61.12]	13.2 ± 2.9 (21.8) [14.03]
6	F	NS		208.3 ± 59.8 (28.7) [183.6]	392.3 ± 117.4 (29.9) [424.95]	5.7 ± 0.8 (14.4) [6	3451.1 ± 925.9 (26.8) [3401.46]	287.6 ± 77.2 (26.8) [283.45]	63.1 ± 22.8 (36.1) [53.07]	14.5 ± 2.5 (17.2) [14.41]
5	M	Mixed		188.4 ± 55.0 (29.2) [168.2]	378.9 ± 111.5 (29.4) [348.6]	5.6 ± 0.9 (16.0) [6]	4129.7 ± 1336.9 (32.4) [3971.65]	277.5 ± 73.3 (26.4) [255.8]	68.6 ± 11.3 (16.4) [70.52]	11.7 ± 2.7 (23.1) [9.93]
3	M	Smokers		170.8 ± 50.8 (29.7) [168.2]	351.9 ± 71.6 (20.3) [348.6]	5.3 ± 1.2 (21.7) [6]	4139.4 ± 1852.4 (44.8) [3971.65]	261.6 ± 66.6 (25.5) [255.8]	70.9 ± 10.0 (14.1) [70.52]	9.7 ± 0.2 (2.0) [9.65]
2	M	NS		214.8 ± 67.8 (31.6) [214.75]	419.4 ± 184.4 (44.0) [419.4]	6.0 ± 0.0 (0.0) [6]	4115.1 ± 534.4 (13.0) [4115.105]	301.3 ± 103.4 (34.3) [301.25]	65.1 ± 16.3 (25.1) [65.125]	14.6 ± 0.7 (4.6) [14.59]

10.10 APPENDIX 10 RESULTS OF PHARMACODYNAMIC INTERACTION STUDY OF DULOXETINE AND LORAZEPAM

Table 132 Summary Statistics on Alertness Score by Treatment Group

Day	Treatment	Time (hours)			
		0	3	5.75 or 6	12
4	Duloxetine Alone		40.31 ± 20.23	39 48 ± 20.66	37.53 ± 20.38
	Duloxetine Placebo Alone		26.76 ± 18.66	23.56 ± 19.27	24.01 ± 20.98
	p-value*		0.047	0.009	0.010
5	Duloxetine Alone	38.76 ± 22.03	57.24 ± 17.89	51.63 ± 20.13	38.78 ± 19.89
	Duloxetine Placebo & Lorazepam	26.03 ± 20.66	45.83 ± 17.64	42.15 ± 19.63	32.34 ± 21.41
	p-value*	0.003	0.008	0 066	0.053
8	Duloxetine Alone		45.27 ± 19.6	43.79 ± 16.15	34.33 ± 20.04
	Duloxetine Placebo & Lorazepam		43.55 ± 18.38	44.58 ± 16.6	28.86 ± 23.39
	p-value*		0.711	0 814	0.161

*: p-value from a two-sided t-test to compare means between groups.

Table 133 Summary Statistics on Calmness Score by Treatment Group

Day	Treatment	Time (hours)			
		0	3	5.75 or 6	12
4	Duloxetine Alone		27.69 ± 17.87	33 ± 24.85	30.16 ± 20.07
	Duloxetine Placebo Alone		26.5 ± 19.84	24.69 ± 25.49	26.69 ± 25.38
	p-value*		0.780	0.090	0.370
5	Duloxetine Alone	24.97 ± 14.73	21.44 ± 10.75	22.41 ± 11.41	22.69 ± 14.17
	Duloxetine Placebo & Lorazepam	22.47 ± 16.36	21.59 ± 22.63	25.47 ± 22.3	24.38 ± 20.77
	p-value*	0.269	0.974	0.414	0.630
8	Duloxetine Alone		26.47 ± 18.15	27.78 ± 13.77	28.31 ± 20.98
	Duloxetine Placebo & Lorazepam		26.94 ± 22.94	28.63 ± 22.33	25.16 ± 23.47
	p-value*		0.921	0.887	0.485

*: p-value from a two-sided t-test to compare means between groups.

Table 134 Summary Statistics on Critical Flicker Fusion Threshold Test by Treatment Group

Day	Treatment	Time (hours)			
		0	3	5.75 or 6	12
4	Duloxetine Alone		32.78 ± 2.516	32.83 ± 2.522	32.49 ± 2.603
	Duloxetine Placebo Alone		33.46 ± 3.274	33.03 ± 2.52	32.75 ± 2.655
	p-value		0.351	0.805	0.722
5	Duloxetine Alone	33.59 ± 2.749	31.93 ± 3.005	32.09 ± 2.415	32.31 ± 2.553
	Duloxetine Placebo & Lorazepam	32.8 ± 2.856	31.74 ± 2.858	32.14 ± 2.652	32.54
	p-value	0 132	0.825	0.925	0.693
8	Duloxetine Alone		33.59 ± 2.934	33.32 ± 2.48	33.07 ± 2.497
	Duloxetine Placebo & Lorazepam		32.85	33.39 ± 3.456	33.34 ± 3.134
	p-value		0.324	0.900	0 621

*: p-value from a two-sided t-test to compare means between groups.

Table 135 Summary Statistics on Contentedness Score by Treatment Group

Day	Treatment	Time (hours)			
		0	3	5.75 or 6	12
4	Duloxetine Alone		30.24 ± 13.77	30.34 ± 15.48	30.08 ± 15.29
	Duloxetine Placebo Alone		20.95 ± 15.52	21.13 ± 17.47	19.58 ± 18.21
	p-value		0.031	0.005	0.016
5	Duloxetine Alone	28.85 ± 14.25	31.48 ± 10.78	31.01 ± 12.94	29.24 ± 13.41
	Duloxetine Placebo & Lorazepam	21.21 ± 17.96	24 ± 16.4	22.25 ± 15.85	21.58 ± 16.56
	p-value	0.024	0.011	0.002	0.001
8	Duloxetine Alone		30.65 ± 12.85	30.88 ± 11.96	27.86 ± 16.15
	Duloxetine Placebo & Lorazepam		26.09 ± 16.61	26.96 ± 15.17	21.58 ± 17.83
	p-value		0.170	0.285	0.038

*: p-value from a two-sided t-test to compare means between groups.

Table 136 Summary Statistics on Digit Symbol Substitution Test by Treatment Group

Day	Treatment	Time (hours)			
		0	3	5.75 or 6	12
4	Duloxetine Alone		91 ± 23.52	93.81 ± 24.89	85.88 ± 21.09
	Duloxetine Placebo Alone		100.1 ± 25.56	98.5 ± 29.41	97.56 ± 34.87
	p-value		0.002	0.142	0.001
5	Duloxetine Alone	93.31 ± 24.51	73.81 ± 18.32	83.56 ± 23.67	90.75 ± 22 38
	Duloxetine Placebo & Lorazepam	97.94 ± 30.63	86.63 ± 25.2	94.19 ± 27.58	98.88 ± 31.59
	p-value	0.163	0.000	0.006	0.004
8	Duloxetine Alone		86.63 ± 23.04	91.5 ± 25.45	90.5 ± 24.65
	Duloxetine Placebo & Lorazepam		94.06 ± 29.44	96.06 ± 29.8	98.69 ± 27.63
	p-value*		0.013	0.139	0.025

*: p-value from a two-sided t-test to compare means between groups.

Table 137 Summary Statistics on Delayed Word Recall Test by Treatment Group

	Summary Statistics at 5.75 Hours[a]	
Day	4	8
Duloxetine Alone	13.31 ± 2.496	8.25 ± 4.919
Placebo	13.44 ± 2.279	9.313 ± 4.191
p-value	0.732	0.333

a Mean ± SD, Range
*: p-value from a two-sided t-test to compare means between groups.

Table 138 Summary Statistics on Immediate Word Recall Test by Treatment Group

	Summary Statistics at 5.75 Hours[a]	
Day	4	8
Duloxetine Alone	59.75 ± 8.071	51.5 ± 13.63
Placebo	59.75 ± 8.528	50.75 ± 12.29
p-value	1.000	0.767

a Mean ± SD, Range
*: p-value from a two-sided t-test to compare means between groups.

Table 139 Summary Statistics on Motor Reaction Time by Treatment Group

Day	Treatment	Time (hours)			
		0	3	5.75 or 6	12
4	Duloxetine Alone		266.5 ± 53.84	260.3 ± 48.75	257.4 ± 57.92
	Duloxetine Placebo Alone		257.5 ± 64.53	249.8 ± 80.21	241.2 ± 69.6
	p-value		0.368	0.377	0 241
5	Duloxetine Alone	271.4 ± 71.82	356.1 ± 129.6	336.4 ± 129.8	274.9 ± 88.67
	Duloxetine Placebo & Lorazepam	242.1 ± 75.74	278.4 ± 84.62	265.1 ± 90.21	253.6 ± 73.13
	p-value	0.002	0.006	0 000	0.075
8	Duloxetine Alone		325 9 ± 93.47	318.3 ± 102 1	295.2 ± 82.67
	Duloxetine Placebo & Lorazepam		275.1 ± 81.51	283.4 ± 80.97	263.8 ± 81.6
	p-value		0 003	0.060	0.020

*. p-value from a two-sided t-test to compare means between groups.

Table 140 Summary Statistics on Recognition Reaction Time by Treatment Group

Day	Treatment	Time (hours)			
		0	3	5.75 or 6	12
4	Duloxetine Alone		334.1 ± 30.42	338.4 ± 32.39	344.6 ± 38.44
	Duloxetine Placebo Alone		327.8 ± 28.69	329.6 ± 37.24	337.3 ± 44.13
	p-value		0.244	0.490	0.405
5	Duloxetine Alone	328.6 ± 33.37	379.5 ± 45.26	355.5 ± 40.81	334.8 ± 26.97
	Duloxetine Placebo & Lorazepam	320.6 ± 27.48	358.4 ± 53.7	337 6 ± 39.99	326 ± 34.49
	p-value	0.370	0.232	0.098	0.314
8	Duloxetine Alone		345.4 ± 37.73	345.1 ± 42.4	333.4 ± 40
	Duloxetine Placebo & Lorazepam		334.4 ± 39.22	331.9 ± 34.15	325.7 ± 44.39
	p-value		0.310	0.039	0.486

*: p-value from a two-sided t-test to compare means between groups.

Table 141 Summary Statistics on Total Reaction Time by Treatment Group

Day	Treatment	Time (hours)			
		0	3	5.75 or 6	12
4	Duloxetine Alone		600.4 ± 65.16	598.6 ± 61.44	602 ± 72.34
	Duloxetine Placebo Alone		585.5 ± 79.32	579.4 ± 94.38	578.4 ± 83.13
	p-value		0.156	0.277	0.048
5	Duloxetine Alone	600 ± 76.71	720.4 ± 165.4	686.6 ± 133.9	609.9 ± 100.7
	Duloxetine Placebo & Lorazepam	562.6 ± 84.25	636.9 ± 100.5	602.8 ± 110.7	579.5 ± 76.45
	p-value	0.001	0.027	0.000	0.065
8	Duloxetine Alone		671.3 ± 111.4	663.4 ± 126.7	628.7 ± 98.47
	Duloxetine Placebo & Lorazepam		609.3 ± 93.13	615.4 ± 92.6	589.6 ± 93.4
	p-value		0.004	0.031	0.036

*: p-value from a two-sided t-test to compare means between groups.

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