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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-427

**Clinical Pharmacology and Biopharmaceutics
Review**

New Drug Application - Amendment
Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-427

Type of Submission: NDA

Generic Name: Duloxetine HCl Modified-Release Capsules

Formulation: Encapsulated Enteric Coated Pellets

Strengths: 20 mg, 30 mg, — mg, 60 mg

Route of Administration: PO

Brand Name: Cymbalta™

Sponsor: Lilly
Indianapolis, Indiana

Submission Dates: December 22, 2003
April 29, 2004 – email from sponsor
November 12, 2001*

Related INDs: —
38,838
—
—
—
—

Related NDAs —

Reviewer: Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

* Date of original submission

1 EXECUTIVE SUMMARY

1.1 RECOMMENDATIONS

1.1.1 ACCEPTABILITY OF THE SUBMISSION

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation I (OCPB/DPE-1) has reviewed the supplement to NDA #21-427 submitted December 22, 2003.

OCPB finds this application acceptable provided that currently outstanding issues are adequately addressed.

Comments should be communicated to the sponsor as appropriate, (see § 1.2.2 Comments to the Sponsor on page 2 and § 1.3 Labeling Comments on page 2).

1.1.2 PHASE IV COMMITMENTS

See §5.1 Phase IV Requests

1.2 COMMENTS

1.2.1 COMMENTS TO THE MEDICAL OFFICER

Pharmacokinetic findings were similar to what was found in the original OCPB NDA review.

Pharmacodynamic findings also tend to replicate the findings made in the original review. In most cases there were no significant pharmacodynamic findings at the proposed clinical dosages of 60 mg po qd or 30 mg po BID, under the controlled study conditions. However, in clinical practice higher exposures are likely to be obtained in the presence of drug interactions or in certain subpopulations.

Dose dependent increases in both blood pressure and heart rate were found at doses above 40 mg BID, along with orthostatic systolic hypotension and a reflex orthostatic tachycardia. This is similar to what has previously been reported.

There is a slight dose dependent tyramine effect at duloxetine doses above 40 mg BID. As this occurs with dietary levels of tyramine and is superimposed on a drug induced hypertension the clinical significance of an additive systolic hypertension needs to be evaluated by the medical reviewer.

In study SBBN, two individuals had QTcs of greater than 450 mSec, (456 and 462 mSec), with QTc changes of 45 and 42 mSec respectively at the highest dose of 120 mg BID. These 2 subjects also tended to have among the highest QTcs at baseline seen at any dose. Inspection of the QTc vs. 'Cmax' profiles in the other subjects, indicate that these 2 subjects did not tend to have higher exposures than the other subjects. However, metabolite concentrations which tend to be much higher than the parent compound and might contribute to activity were not examined. Exposures of duloxetine similar to those at which these QTc prolongations occurred are likely to be achieved in the presence of drug interactions or in certain subpopulations, (see § 2.2 Review Findings on page 3 for groups potentially at risk). Consequently, the previously requested phase IV ECG study appears prudent.

It's notable that in the introduction to protocol HMCG, the high dose ECG protocol, the sponsor makes the following statement:

'12 subjects received duloxetine in doses up to 120 mg BID (Study SBBN). Electrocardiogram measurements were obtained under steady-state conditions. All subjects had QTc intervals less than 450 mSec (maximum = 448 mSec). Most subjects showed no change greater than 30 mSec from normal, using both Bazett's and regression-corrected QT. One female subject had an increase of 31 mSec (Regression Correction) and of 34 mSec at 120 mg (Fridericia Correction). The QTc interval of another subject changed by 31 mSec at 80 mg duloxetine BID (Regression correction). There was no statistically significant difference between dosing groups or versus placebo.'

The sponsor's claim of a maximum QTc of 448 mSec in study SBBN is inconsistent with the data which shows a maximum QTc of 462 mSec at 120 mg BID.

1.2.2 COMMENTS TO THE SPONSOR

None.

1.3 LABELING COMMENTS

The sponsor's response to the FDA proposed labeling is quite extensive. OCPB's response to these proposed changes is not addressed in this document, but will be addressed in collaboration with the medical division.

2 SUMMARY OF OCPB FINDINGS

2.1 BACKGROUND

NDA 21-427 for Duloxetine HCl . -Release Capsules was submitted on November 12, 2001 for Major Depressive Disorder (MDD) an approvable letter was issued on September 13, 2002. The recommended dosage for MDD was _____

In a second approvable letter dated September 29, 2003 the following phase IV request was made:

'We also request that you agree to a Phase 4 commitment to conduct a prospectively designed study to evaluate the effect of duloxetine on the QT interval. This study should characterize the duloxetine plasma concentration-response relationship for QTc interval prolongation and evaluate the degree of QTc prolongation at plasma concentrations achieved following maximal potential interaction between duloxetine and the combination of CYP1A2 and CYP2D6 inhibitors. The QT study should be randomized and double-blinded and should include both a placebo control and a positive control. We ask that you include a proposed timeframe for post-approval submission of the proposed study protocol and completed study report as part of your complete response to this letter.'

In the current submission, the sponsor has submitted 3 additional completed clinical pharmacology studies and has also identified 2 additional ongoing studies. The 3 completed studies were all completed near the end or after the original review cycle, (i.e. initial submission date 11-12-2001. OCPB review completed 8-22-2002). [

] Multiple dosing in the 3 studies included doses of 60 mg qd and divided dosing from 20 mg BID to 120 mg BID in Japanese and Caucasian subjects.

2.2 REVIEW FINDINGS

Single Dose Pharmacokinetics

C_{max}s are linear over a single dose range of 20 mg to 60 mg.

When compared to a similar population, mean pharmacokinetic metrics reported in the present submission are similar to mean pharmacokinetic metrics previously reported in the original OCPB review.

Multiple Dose Pharmacokinetics

Upon multiple dosing of 60 mg po qd in Japanese subjects, the ratio of multiple dosing AUC_τ to single dose AUC_∞ was 1.31, indicating a slight degree of nonlinearity. This confirms what was observed in the original NDA submission.

In addition, when compared to a similar population, mean C_{max}s and C_{mins} upon multiple dosing are similar to mean values previously reported in the original OCPB review for men, however values for women are slightly lower.

Intrinsic Factors

Race and Ethnicity

Drug exposures in Japanese subjects are somewhat higher than in Caucasians. A portion of this difference can be explained by lower body weights. However, exposures still tend to be higher in Japanese. Unfortunately, due to differences in CYP2D6 genotype, smoking status, and the small sample sizes it's not possible to tell if the remaining differences are due to ethnicity, other extrinsic factors, or residual variability.

Gender

Similar to what has been described in the original review women tend to have lower clearances and higher exposures than men.

CYP2D6 Genotype

Similar to what has been described in the original review CYP2D6 poor metabolizers tend to have lower clearances and higher exposures.

Extrinsic Factors

Smoking Status

Similar to what has been described in the original review smokers tend to have faster clearances and lower exposures.

Ex Vivo Pharmacodynamics

Extracts of plasma samples obtained at steady-state at 2 hours post-dose from subjects receiving duloxetine exhibit dose responses with respect blockade of serotonin and norepinephrine reuptake channels, and that the extract is relative more selective for serotonin blockade as compared with norepinephrine channel blockade.

As these are 2 hours samples inhibition is unlikely to be maximal, if we assume that 80% blockade is needed to contribute to efficacy, then even doses higher than previously recommended are unlikely to contribute additional efficacy by either increased serotonin or norepinephrine channel blockade.

In Vivo Pharmacodynamics

Effect on Catecholamines

There is a clear dose response relationship over a dose range of 40 mg BID to 120 mg BID on the plasma catecholamines epinephrine, norepinephrine, and DHPG, and that there is a greater effect at each dose level when subjects are upright as compared with laying down. In addition, urinary excretion of norepinephrine increased significantly from the predose urinary excretion for all duloxetine doses and the observed increase appears to be related to the dose of duloxetine.

Effects on Blood Pressure

At single doses of less than or equal to 60 mg and at BID dosing of 40 mg BID or less there does not appear to be any significant effect on diastolic blood pressure.

There is a clear dose response relationship over a dose range of 40 mg BID to 120 mg BID on supine and standing systolic blood pressure. In addition, orthostatic systolic hypotension appears to be occurring at around T_{max} for in a dose dependent manner at doses 80 mg BID and above. Orthostatic hypotension for diastolic pressure does not appear to be occurring as it does for systolic pressure, although orthostasis with systolic pressure is more important clinically.

Effects on Heart Rate

At doses of 40 mg BID or less there is no clinically significant effect on heart rate. However at higher doses there is a clear dose response relationship over a dose range of 40 mg BID to 120 mg BID on both the supine and standing heart rate and pulse, and that there is a greater effect at each dose level when subjects are upright as compared with lying down. The greater effect when standing is likely compensatory in order to prevent excessive orthostatic hypotension.

Effects on ECG

At the lower doses in studies HMCU and SBAZ, (60 mg qd, and up to 40 mg BID respectively), there were no obvious changes in QTc. However, in both studies ECGs were obtained when C_{min} is expected, i.e. for study HMCU the ECG was obtained 2 hours before breakfast, and for study SBAZ ECGs were obtained immediately prior to dosing and 24 hours after dosing.

In contrast, in study SBBN where higher doses of up to 120 mg BID were used, ECGs were obtained 4 hours post dose and the duloxetine concentration was determined at around 6 - 7 hours post dose which is around the expected T_{max}.

In this study, 2 subjects had QTcs of greater than 450 mSec at the highest dose of 120 mg BID. These 2 subjects also tended to have among the high QTcs at baseline and at any dose. Unfortunately, these 2 subjects did not have duloxetine 'C_{max}' concentrations determined in conjunction with these ECGs. However, inspection of the QTc vs. 'C_{max}' profiles in the other subjects, indicate that these 2 subjects did not tend to have higher exposures than the other subjects.

The fact that there were QTcs > 450 mSec at doses of 120 mg BID may suggest that exposures associated with this dose may be of concern. Such exposures will be achieved in clinical practice in some subjects especially those with receiving multiple interacting drugs or are CYP2D6 PMs and also receive a CYP1A inhibitor such as ciprofloxacin, and or have other factors that result in higher exposures such as age, gender or renal dysfunction. Based on this data it seems prudent to examine the effect on ECG more rigorously as per the previous phase IV request.

Tyramine Effect

The mean dose of tyramine required to raise systolic blood pressure by 30 mmHg increased with increasing doses of duloxetine above 40 mg BID. However, this is on top of change in BP due to drug therefore total SBP may be quite high, i.e. there might be a potential for severe systolic hypertension. In addition, these are very small tyramine doses, (i.e. 4.5 – 13 mg of tyramine and a tyramine rich meal may contain up to 40 mg tyramine).

Other Peripheral and Central Nervous System Effects

A variety of tests to evaluate the effect on the peripheral and central nervous systems were conducted at a daily duloxetine dose of 60 mg qd. These included the following tests:

- Pupil dilation test
- Sway path length and sway area
- Stabilometry
- EEG
- Audiometry
- Tapping test
- Reaction Time
- Critical flicker fusion frequency

No major changes in of the aforementioned tests were observed. However, this does not preclude clinically significant changes at higher exposures such as might occur with drug interactions or other situations.

3 SIGNATURES



Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

Date

Senior Reviewer
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Ray Baweja, Ph.D.

Date

Team Leader
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CC: NDA 21-427 (orig., 1 copy)
HFD-120 (Katz R, Laughren T, Andreason P, Rosloff B, Oliver T, Fossom L, John C)
HFD-860 (Kavanagh, Baweja, Mehta, Rahman)
Central Document Room (Barbara Murphy)

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5 REVIEW

5.1 PHASE IV REQUESTS – STATUS UPDATES

In the note to the reviewer in this submission Lilly made the following statement:

Lilly acknowledges FDA's request to agree to a Phase 4 commitment to conduct a prospectively designed study to evaluate the effect of duloxetine on the QT interval. A proposed protocol has been submitted electronically for review. Lilly requests that FDA confirm that the protocol design as submitted, addresses this request. The proposed timeframe for post-approval submission of this report is within three months of approval of duloxetine for MDD.

The original request follows and is from the Sept 29, 2003 2nd round approvable letter:

We also request that you agree to a Phase 4 commitment to conduct a prospectively designed study to evaluate the effect of duloxetine on the QT interval. This study should characterize the duloxetine plasma concentration-response relationship for QTc interval prolongation and evaluate the degree of QTc prolongation at plasma concentrations achieved following maximal potential interaction between duloxetine and the combination of CYP1A2 and CYP2D6 inhibitors. The QT study should be randomized and double-blinded and should include both a placebo control and a positive control. We ask that you include a proposed timeframe for post-approval submission of the proposed study protocol and completed study report as part of your complete response to this letter.

Typically a study of this type necessitates population PK/PD analysis. Consequently OCPB searched for the protocol in order to evaluate the analysis.

No protocol could be found in the electronic document room in this submission or in any other submission to this NDA. On April 29th, 2004 the project manager was informed that this protocol could not be found and a request was made to determine the status of the submission of this protocol.

An e-mail from the sponsor dated April 29th, 2004 indicated the protocol was a 'High Dose ECG Study', (HMCg), that had been requested by DRUDP in its action letter of August 2003. According to the sponsor this protocol was submitted via e-mail sometime around 8 October 2003. The sponsor also indicates that input has been received from DRUDP, the Cardio-renal Division and [] IRB, and the protocol was subsequently amended. Both the original and amended versions of the protocol were attached to the e-mail.

The study data lock occurred during the week of April 18th 2004 and data analysis is now underway. The study report will not be ready until some time after the action date.

APPEARS THIS WAY
ON ORIGINAL

5.2 STUDIES SUBMITTED

The sponsor has submitted 3 additional completed clinical pharmacology studies in this submission and has also identified 2 additional ongoing studies, (see Table 1). The 3 completed studies were all completed near the end or after the original review cycle, (i.e. initial submission date 11-12-2001, review completed 8-22-2002).

Table 1 List of Completed and Ongoing Studies Reported in this Submission.

Protocol #	Study Title	Status
HMCU (0210A201E)	LY248686 (Duloxetine) Phase I Clinical Study: Repeated-Dose Study (60 mg, 7 days)	Completed 11-7-2002
F1J-FW-SBAZ	Pharmacokinetic Study of Duloxetine in Japanese and Caucasian Subjects	Completed 11-17-2002
F1J-LC-SBBN	Assessment of Pharmacodynamic Effects and Safety During Treatment with Increasing Doses of Duloxetine	Completed 6-2002
	Tolerability and safety of 40 mg and 100 mg duloxetine BID given over 7 days in healthy female subjects. A randomized, placebo-controlled double-blind trial.	Ongoing
	Safety and Tolerance of Duloxetine in Healthy Females at Supratherapeutic Doses Achieved by a Progressive 1- to 3-Day Titration	Ongoing

5.3 STUDY DESIGNS

Study HMCU was a randomized, single-blind, placebo-controlled, parallel design study in healthy adult Japanese males presumably. Subjects were administered duloxetine 60 mg capsules once daily after breakfast for 7 consecutive days. Single dose and multiple dose pharmacokinetics as well as the pharmacodynamic effects on ECG, EEG, pupil dilation, equilibrium function, and psychological performance test were assessed.

Study SBBN was a single-blind, randomized, placebo controlled, parallel design study in healthy male and female adults conducted in the US of duloxetine doses from 80 mg BID to 120 mg BID. Pharmacokinetic sampling was limited to sparse sampling. The primary purpose was to evaluate the effect of increasing dose levels of duloxetine on the ECG, HR, BP, and the hormonal effects of the blockade of NE transport by assessing the degree of changes in plasma and urinary norepinephrine and its metabolite DHPG, tyramine pressor effects, melatonin stimulation, and ex-vivo NE and 5-HT transporter.

Study SBAZ compared single-dose and multiple pharmacokinetics between Japanese and Caucasian subjects.

Details of the study designs may be found in **Appendix 1 § 6.1.1 Completed Studies**.

5.4 DEMOGRAPHICS

Table 2 Summary of Demographic Variables by Study and Treatment Group

Study	Treatment Group	N	Age (yr)	Gender	Race / Ethnicity	Height (cm)	Weight (kg)	BMI (kg/m ²)	BSA	EtOH	Smoking Status	CYP2D6 Genotype
HMCU	Duloxetine 60 mg qd x 7	6	22.83 ± 2.71 (11.9) 20 - 26 [22.5]	M	Not Mentioned (Conducted in Japan)	171.55 ± 4.32 (2.5) 163.6 - 176.6 [172.55]	60.83 ± 3.74 (6.1) 55.8 - 66.4 [60.3]					
SBBN	Duloxetine Rising MD Study 40 mg – 120 mg BID x 1 Week ^a	12	26.3 ± 5.0 (19.1) 20 - 39 [25.5]	4M 8F	11 Caucasian 1 Hispanic	170.8 ± 9.7 (5.7) 156 - 188 [168.5]	70.3 ± 14.9 (21.2) 48 - 96.3 [67.4]	24.0 ± 3.6 (15.1) 17.6 - 31.7 [24.05]	1.8 ± 0.2 (13.2) 1.4 - 2.2 [1.8]	8 Y 4 N	2Y:10N	
SBAZ Part A	Single Rising Doses of Duloxetine 20 mg 40 mg 60 mg	24	25 ± 3 (12) 20 - 31 [25]	10M 14F	Japanese	163 ± 9 (5.5) 149 - 178 [163]	58.7 ± 9 (15.3) 44.5 - 79.1 [58.95]	21.9 ± 2.1 (9.6) 19.3 - 25.9 [21.4]			4Y:20N	UM 0 EM 17 IM 6 PM 1
		24	22.7 ± 3.5 (15.2) 20 - 30 [21]	11M 13F	Caucasian	169.0 ± 10.9 (6.4) 157 - 187 [167.5]	69.2 ± 12.9 (18.6) 52.8 - 83 [70.85]	24.2 ± 3.7 (15.2) 20.6 - 29.9 [23.5]			4Y:20N	UM 0 EM 21 IM 0 PM 3
SBAZ Part B	Placebo	4	26.3 ± 4.6 (17.7) 20 - 31 [27]	2M 2F	Japanese	161.8 ± 5.4 (3.4) 156 - 169 [161]	55.5 ± 6.5 (11.8) 49.8 - 64.6 [53.75]	21.1 ± 1.3 (6.2) 19.4 - 22.6 [21.15]			1Y:3N	UM 0 EM 2 IM 2 PM 0
	Duloxetine 20mg BID	8	25.0 ± 3.5 (14.2) 21 - 30 [25]	6M 2F	Japanese	169.3 ± 6.0 (3.6) 156 - 176 [171]	61.3 ± 5.8 (9.4) 52.8 - 68.7 [61.75]	21.4 ± 1.3 (6.1) 19.1 - 23.5 [21.6]			4Y:4N	UM 0 EM 4 IM 4 PM 0
	Duloxetine 40mg BID	8	24.3 ± 5.3 (21.8) 20 - 34 [22.5]	6M 2F	Japanese	168.3 ± 5.3 (3.2) 157 - 174 [170]	64.9 ± 5.6 (8.7) 58 - 73 [65.3]	23.0 ± 2.4 (10.5) 19.6 - 26.5 [23.8]			3Y:5N	UM 0 EM 6 IM 2 PM 0
	Placebo	4	26.0 ± 4.2 (16.3) 22 - 31 [25.5]	4M 0F	Caucasian	180.3 ± 5.6 (3.1) 173 - 186 [181]	83.8 ± 14.8 (17.7) 66.5 - 98.9 [84.8]	25.8 ± 3.7 (14.2) 20.9 - 29.7 [26.25]			0Y:4N	UM 0 EM 4 IM 0 PM 0
	Duloxetine 20mg BID	8	29.8 ± 10.7 (35.9) 20 - 48 [24.5]	6M 2F	Caucasian	172.8 ± 8.6 (5.0) 158 - 182 [174.5]	71.0 ± 8.8 (12.4) 59.4 - 82.1 [70.35]	23.8 ± 2.1 (8.8) 20.5 - 26.8 [24.2]			1Y:7N	UM 0 EM 8 IM 0 PM 0
	Duloxetine 40mg BID	8	27.9 ± 7.9 (28.5) 19 - 40 [24.5]	5M 3F	Caucasian	172.0 ± 4.4 (2.6) 165 - 180 [173]	74.0 ± 10.0 (13.5) 61.8 - 88.3 [71.9]	25.0 ± 2.4 (9.7) 21.4 - 28.9 [24.65]			2Y:6N	UM 1 EM 7 IM 0 PM 0
250a	40mg		45	F	Caucasian	169	81.3	28.6			N	EM

NA= not applicable; N = No; Y=Yes;

UM = ultra-rapid metabolizer; EM = extensive metabolizer; IM = intermediate metabolizer; PM = poor metabolizer

5.5 PHARMACOKINETICS

5.5.1 SINGLE DOSE PHARMACOKINETICS

C_{max}s in study SBAZ are linear over a single dose range of 20 mg to 60 mg, (see Table 3 to Table 8)

When compared to a similar population, mean pharmacokinetic metrics reported in study SBAZ are similar to mean pharmacokinetic metrics previously reported in the original OCPB review, (see Table 8 in the present review and Table 118 in File C:\Kavanagh Data\Reviews\DNPD\NDA\21-427 Duloxetine – Lilly\Review Final\21-427 Review Final.doc in DFS folder [N 021427 N 000 12-Nov-2001])

5.5.2 MULTIPLE DOSE PHARMACOKINETICS

Upon multiple dosing of 60 mg po qd in Japanese subjects, the ratio of AUC_τ upon multiple dose to AUC_∞ with a single dose was 1.31, indicating a slight degree of nonlinearity. This finding confirms what has been previously been observed in the original NDA submission, (see Table 9).

In addition, when compared to a similar population, mean C_{max}s and C_{min}s reported in study SBBN are similar to mean values previously reported in the original OCPB review for men, however values for women are slightly lower, (see Table 10 Table 12) in the present review and Table 119 in File C:\Kavanagh Data\Reviews\DNPD\NDA\21-427 Duloxetine – Lilly\Review Final\21-427 Review Final.doc in DFS folder [N 021427 N 000 12-Nov-2001]). Values reported in study SBAZ are also slightly lower than previously reported in the original submission. However, CYP2D6 genotype was not reporting in the original NDA for the relevant study, therefore this slight difference might be due to either normal variability and the small sample size, or to differences in CYP2D6 phenotype.

5.5.3 INTRINSIC FACTORS

5.5.3.1 Race and Ethnicity

As noted above single dose kinetic metrics in Japanese males in study SBAZ are similar to those previously reported in the original NDA. In contrast, when multiple dose metrics in Japanese subjects are compared directly to metrics in Caucasians in study SBAZ, the Japanese have higher exposures. A portion of this difference can be explained by lower body weights. However, exposures still tend to be higher in Japanese. Unfortunately, due to differences in CYP2D6 genotype, smoking status, and the small sample sizes it's not possible to tell if the remaining differences are real or not.

5.5.3.2 Gender

Similar to what has been described in the original review women tend to have lower clearances than men, (see Table 3 to Table 8 and Table 13 to Table 16).

5.5.3.3 CYP2D6 Genotype

Similar to what has been described in the original review CYP2D6 poor metabolizers tend to have lower clearances, (see Table 3 to Table 8 and Table 13 to Table 16).

5.5.4 EXTRINSIC FACTORS

5.5.4.1 Smoking Status

Similar to what has been described in the original review smokers tend to have faster clearances, (see Table 3 to Table 8 and Table 13 to Table 16).

Table 3 Duloxetine 20 mg Single Dose Pharmacokinetic Summary Statistics in Healthy Japanese Adults – Study SBAZ

Dosage (mg)	Race / Ethnicity	Sex	Smoking Status	CYP2D6 Genotype	N	Age (yr)	Weight (kg)	C _{max} (ng/mL)	C _{max,norm} [(ng/mL) / (mg/kg)]	T _{max} (hr)	AUC(0-∞), (ng·h/mL)	AUC(0-∞)norm [(ng·h/mL) / (mg/kg)]	t _{1/2} (hr)	CL/F (L/hr)	CL/F,norm [(L/hr)/kg]	V _d /F (L)	V _d /F,norm (L/kg)	MRT (hr)
20 mg	Japanese	M / F	Smkr / NS	EM, IM, PM	23	25.2 ± 3.5 (13.9) 20 - 31 [24]	59.3 ± 8.8 (14.8) 44.5 - 79.1 [59.6]	16.6 ± 6.5 (39.2) 5.7 - 30.1 [14.7]	47.8 ± 16.6 (34.7) 19.8 - 85.9 [45.2]	5.6 ± 1.3 (24.1) 2 - 8 [6]	239.1 ± 134.3 (56.2) 68.7 - 667 [185]	681.8 ± 342.2 (50.2) 238.0 - 1764.2 [589.5]	10.2 ± 2.1 (20.3) 7.14 - 16.5 [9.92]	109.3 ± 60.8 (55.6) 30 - 291 [108]	1.8 ± 0.9 (47.6) 0.57 - 4.2 [1.7]	1504.9 ± 654.1 (43.5) 582 - 3660 [1500]	25.1 ± 9.2 (36.4) 11 - 52.8 [24.6]	14.2 ± 2.8 (19.6) 9.97 - 21.5 [14]
		F	Smkr / NS	EM, IM, PM	13	25.3 ± 3.4 (13.4) 21 - 31 [26]	53.3 ± 5.2 (9.7) 44.5 - 60.7 [52.9]	19.4 ± 6.5 (33.5) 11.5 - 30.1 [19.2]	51.5 ± 17.5 (34.0) 29.8 - 85.9 [47.1]	5.9 ± 1.0 (16.9) 4 - 8 [6]	297.2 ± 144.1 (48.5) 135 - 667 [274]	787.3 ± 382.0 (48.5) 350.3 - 1764.2 [664.5]	10.8 ± 2.3 (20.9) 8.64 - 16.5 [10.1]	80.7 ± 33.6 (41.7) 30 - 148 [73.1]	1.5 ± 0.6 (40.5) 0.57 - 2.88 [1.5]	1200.2 ± 409.2 (34.1) 582 - 1860 [1130]	22.5 ± 7.3 (32.4) 11 - 35.9 [22.6]	15.6 ± 2.5 (16.3) 13.1 - 21.5 [14.9]
		M	Smkr / NS	EM / IM	10	25.0 ± 3.8 (15.2) 20 - 31 [23.5]	67.0 ± 5.9 (8.8) 59.6 - 79.1 [66.65]	13.0 ± 4.6 (35.4) 5.7 - 21.3 [12.7]	43.1 ± 14.9 (34.5) 19.8 - 67.9 [41.05]	5.2 ± 1.7 (32.4) 2 - 6 [6]	163.6 ± 72.0 (44.0) 68.7 - 319 [180.5]	544.7 ± 233.7 (42.9) 238.0 - 1017.6 [570.4]	9.5 ± 1.6 (17.2) 7.14 - 12.2 [9.685]	146.5 ± 69.2 (47.3) 62.7 - 291 [125]	2.2 ± 1.0 (46.1) 0.98 - 4.2 [1.76]	1901.0 ± 717.1 (37.7) 1110 - 3660 [1720]	28.5 ± 10.5 (37.0) 17.3 - 52.8 [25.5]	12.2 ± 1.7 (14.1) 9.97 - 15.3 [12.1]
		F	NS	EM	7	26.0 ± 4.0 (15.5) 21 - 31 [27]	54.3 ± 6.6 (12.1) 44.5 - 60.7 [57.7]	20.2 ± 6.8 (33.8) 11.8 - 28.3 [19.7]	54.0 ± 18.2 (33.7) 33.5 - 85.9 [57.4]	5.7 ± 0.8 (13.3) 4 - 6.03 [6]	269.1 ± 90.7 (33.7) 171 - 401 [246]	725.4 ± 260.7 (35.9) 498.5 - 1217.0 [664.4]	9.7 ± 0.8 (7.8) 8.64 - 10.8 [9.59]	81.9 ± 26.8 (32.7) 49.9 - 117 [81.4]	1.5 ± 0.4 (29.0) 0.82 - 2.01 [1.5]	1147.3 ± 410.9 (35.8) 712 - 1700 [1070]	21.0 ± 8.4 (30.2) 12.2 - 29.2 [22.5]	15.0 ± 1.1 (7.1) 13.1 - 16.4 [14.7]
			Smkr	EM	2	26.0 ± 0.0 (0.0) 26 - 26 [26]	50.2 ± 2.4 (4.8) 48.5 - 51.9 [50.2]	15.1 ± 5.1 (33.7) 11.5 - 18.7 [15.1]	37.6 ± 11.0 (29.2) 29.8 - 45.3 [37.55]	5.0 ± 1.4 (28.3) 4 - 6 [5]	204.5 ± 98.3 (48.1) 135 - 274 [204.5]	507.4 ± 222.1 (43.8) 350.3 - 664.5 [507.4]	10.7 ± 2.8 (25.8) 8.71 - 12.6 [10.655]	110.6 ± 53.0 (47.9) 73.1 - 148 [110.55]	2.2 ± 1.0 (43.7) 1.51 - 2.86 [2.185]	1595.0 ± 374.8 (23.5) 1330 - 1860 [1595]	31.7 ± 5.9 (18.7) 27.5 - 35.9 [31.7]	14.0 ± 1.3 (9.1) 13.1 - 14.9 [14]
			NS	IM	3	24.0 ± 3.6 (15.0) 21 - 28 [23]	53.4 ± 4.0 (7.5) 49 - 56.9 [54.3]	17.1 ± 4.0 (23.3) 12.5 - 19.6 [19.2]	45.6 ± 11.0 (24.2) 33.9 - 55.8 [47]	6.0 ± 0.0 (0.0) 6 - 6 [6]	301.3 ± 124.0 (41.1) 184 - 431 [289]	792.6 ± 279.4 (35.2) 499.8 - 1056.0 [822.2]	12.6 ± 3.5 (27.6) 9.92 - 16.5 [11.3]	74.9 ± 31.7 (42.3) 46.4 - 109 [69.3]	1.4 ± 0.6 (39.5) 0.95 - 2.01 [1.22]	1266.7 ± 254.2 (20.1) 1110 - 1560 [1130]	23.7 ± 4.5 (19.0) 19.9 - 28.7 [22.6]	16.7 ± 4.2 (24.9) 13.8 - 21.5 [14.9]
			NS	PM	1	23	52.9	30.1	79.6	8	667	1764.2	13.5	30	0.57	582	11	20.4
		M	NS	EM	7	25.6 ± 4.4 (17.0) 20 - 31 [24]	66.0 ± 4.9 (7.4) 59.6 - 70.9 [66.6]	12.2 ± 4.2 (34.5) 5.7 - 18.8 [12.6]	40.1 ± 14.7 (36.5) 19.8 - 68.6 [37.5]	5.4 ± 1.5 (27.9) 2 - 6 [6]	141.2 ± 55.2 (39.1) 68.7 - 220 [154]	465.7 ± 192.0 (41.2) 238.0 - 779.9 [458.9]	9.1 ± 1.4 (16.9) 7.14 - 11 [9.59]	165.1 ± 73.3 (44.4) 90.9 - 291 [130]	2.5 ± 1.0 (42.0) 1.28 - 4.2 [2.17]	2085.7 ± 778.8 (37.3) 1280 - 3660 [2010]	31.6 ± 11.1 (35.1) 18.1 - 52.8 [32.3]	11.7 ± 1.8 (15.5) 9.97 - 15.3 [11.7]
			NS	IM	2	22.5 ± 4.2 (18.6) 22 - 23 [22.5]	71.9 ± 7.3 (10.1) 64.7 - 79.1 [71.9]	11.8 ± 4.8 (41.6) 9.8 - 13.4 [11.6]	41.1 ± 16.8 (40.9) 38.8 - 43.3 [41.05]	6.0 ± 1.8 (29.8) 6 - 6 [6]	164.5 ± 56.0 (34.0) 146 - 183 [164.5]	584.7 ± 199.3 (34.1) 577.4 - 592.0 [584.7]	9.4 ± 1.6 (17.2) 8.21 - 10.6 [9.405]	123.0 ± 80.0 (65.1) 109 - 137 [123]	1.7 ± 1.2 (67.2) 1.69 - 1.74 [1.715]	1650.0 ± 936.4 (56.8) 1630 - 1670 [1650]	23.3 ± 13.9 (59.7) 20.6 - 25.9 [23.25]	13.8 ± 2.1 (15.1) 13.5 - 14 [13.75]
		Y		IM	1	26	63.8	21.3	67.9	2	319	1017.6	12.2	62.7	0.98	1110	17.3	12.9

Table 4 Duloxetine 20 mg Single Dose Pharmacokinetic Summary Statistics in Healthy Caucasian Adults – Study SBAZ

Dosage (mg)	Race / Ethnicity	Sex	Smoking Status	CYP2D6 Genotype	N	Age (yr)	Weight (kg)	C _{max} (ng/mL)	C _{max,norm} [(ng/mL) / (mg/kg)]	T _{max} (hr)	AUC(0-∞), (ng·m x hr ⁻¹)	AUC(0-∞)norm [(ng·m x hr ⁻¹) / (mg/kg)]	t _{1/2} (hr)	CL/F (L/hr)	CL/F,norm [(L/hr)/kg]	V _d /F (L)	V _d /F,norm (L/kg)	MRT (hr)
20 mg	Caucasian	M / F	Smokers / NS	EM, PM	23	29.2 ± 9.3 (31.9) 20 - 47 [25]	70.7 ± 11.2 (15.8) 48.7 - 90.5 [70.1]	13.7 ± 5.9 (43.0) 5.9 - 28.2 [12]	47.2 ± 18.2 (38.5) 21.2 - 90 [45.5]	5.3 ± 1.3 (24.4) 2 - 8 [6]	201.8 ± 139.7 (69.2) 75 - 757 [175]	689.8 ± 434.2 (62.9) 260 - 2410 [591]	10.1 ± 2.9 (28.7) 6.69 - 19.9 [9.63]	129.2 ± 62.5 (48.3) 26.4 - 267 [114]	1.8 ± 0.8 (45.5) 0.41 - 3.85 [1.69]	1779.3 ± 782.9 (44.0) 619 - 3760 [1760]	25.3 ± 10.8 (42.7) 9.71 - 52.5 [24.4]	13.2 ± 2.9 (21.8) 8.24 - 21 [13.5]
		F	Smokers / NS	EM, PM	13	26.8 ± 8.9 (33.1) 20 - 45 [22]	66.3 ± 11.3 (17.0) 48.7 - 83 [67.3]	15.2 ± 6.2 (41.0) 6.3 - 28.2 [12.2]	49.8 ± 20.2 (40.6) 21.2 - 90 [45.9]	5.2 ± 1.3 (24.9) 2 - 6 [5]	239.7 ± 170.0 (70.9) 77.2 - 757 [188]	781.2 ± 540.2 (69.2) 260 - 2410 [644]	10.4 ± 3.6 (35.0) 6.69 - 19.9 [9.5]	110.8 ± 57.4 (51.9) 26.4 - 259 [106]	1.7 ± 0.9 (50.8) 0.41 - 3.85 [1.55]	1537.5 ± 740.8 (48.2) 619 - 3530 [1430]	23.7 ± 11.4 (48.1) 9.71 - 52.5 [22.5]	13.8 ± 3.0 (21.7) 9.57 - 21 [13.9]
		M	Smokers / NS	EM, PM	10	32.2 ± 9.4 (29.3) 20 - 47 [31]	76.6 ± 8.4 (11.0) 64.5 - 90.5 [76.3]	11.7 ± 5.0 (42.9) 5.9 - 23.5 [10.7]	43.8 ± 15.6 (35.5) 21.2 - 77.7 [44.6]	5.4 ± 1.3 (25.0) 4 - 8 [6]	152.5 ± 68.3 (43.5) 75 - 302 [147.5]	571.1 ± 210.0 (36.8) 270 - 998 [574.5]	9.8 ± 1.7 (17.1) 7.27 - 12.5 [9.94]	153.3 ± 63.2 (41.2) 66.2 - 267 [135.5]	2.0 ± 0.8 (40.1) 1 - 3.71 [1.74]	2093.8 ± 756.5 (36.1) 968 - 3760 [1935]	27.3 ± 10.2 (37.2) 14.6 - 52.3 [24.4]	12.4 ± 2.6 (21.3) 8.24 - 15.9 [12.85]
		F	NS	EM	9	29.3 ± 9.8 (33.3) 21 - 45 [24]	70.0 ± 11.4 (16.3) 48.7 - 83 [69.8]	13.9 ± 5.3 (38.2) 6.3 - 24.9 [12.1]	48.5 ± 18.4 (37.9) 21.2 - 75 [45.9]	5.3 ± 1.4 (26.5) 2 - 6 [6]	194.6 ± 79.6 (40.9) 77.2 - 324 [188]	674.0 ± 266.5 (39.5) 260 - 1060 [644]	10.0 ± 3.9 (39.1) 6.69 - 19.9 [9.28]	122.4 ± 61.1 (49.9) 61.7 - 259 [106]	1.8 ± 0.9 (51.8) 0.85 - 3.85 [1.55]	1666.4 ± 812.6 (48.8) 874 - 3530 [1430]	24.5 ± 12.7 (51.6) 11.8 - 52.5 [22.5]	13.0 ± 2.5 (19.0) 9.57 - 17.4 [13.9]
			Smokers	EM	2	22.0 ± 1.4 (6.4) 21 - 23 [22]	57.3 ± 2.6 (4.6) 55.4 - 59.1 [57.25]	11.7 ± 0.8 (6.7) 11.1 - 12.2 [11.65]	33.3 ± 0.7 (2.1) 32.8 - 33.8 [33.3]	5.0 ± 1.4 (28.3) 4 - 6 [5]	171.0 ± 7.1 (4.1) 166 - 176 [171]	488.5 ± 2.1 (0.4) 487 - 490 [488.5]	9.9 ± 0.3 (3.4) 9.63 - 10.1 [9.865]	117.5 ± 4.9 (4.2) 114 - 121 [117.5]	2.0 ± 0.0 (0.3) 2.04 - 2.05 [2.045]	1670.0 ± 127.3 (7.6) 1580 - 1760 [1670]	29.2 ± 0.9 (3.2) 28.5 - 29.8 [29.15]	14.1 ± 0.8 (6.0) 13.5 - 14.7 [14.1]
			N	PM	1	20	63.8	28.2	90	4	757	2410	16.2	26.4	0.41	619	9.71	21
			Y	PM	1	21	52.8	20.6	54.4	6	266	702	9.5	75.3	1.43	1030	19.5	13.2
		M	N	EM	8	34.0 ± 9.7 (28.4) 20 - 47 [36.5]	76.4 ± 9.5 (12.4) 64.5 - 90.5 [75.7]	11.4 ± 5.6 (49.1) 5.9 - 23.5 [9.5]	42.2 ± 17.0 (40.2) 21.2 - 77.7 [41.35]	5.3 ± 1.5 (28.3) 4 - 8 [5]	157.7 ± 71.4 (45.3) 75 - 302 [147.5]	588.5 ± 222.7 (38.0) 270 - 998 [574.5]	9.9 ± 1.6 (15.8) 7.67 - 12.5 [9.94]	150.5 ± 68.7 (44.3) 66.2 - 267 [135.5]	2.0 ± 0.8 (43.1) 1 - 3.71 [1.74]	2104.8 ± 852.0 (40.5) 968 - 3760 [1930]	27.6 ± 11.5 (41.7) 14.6 - 52.3 [24.2]	12.3 ± 2.5 (20.0) 8.24 - 15.5 [12.85]
			Y	EM	1	22	78.2	11.5	45	6	94.2	368	7.27	212	2.72	2230	28.5	9.57
			N	PM	1	28	76.5	14.6	55.8	6	170	651	11	117	1.53	1870	24.4	15.9

Table 5 Duloxetine 40 mg Single Dose Pharmacokinetic Summary Statistics in Healthy Japanese Adults – Study SBAZ

Dosage (mg)	Race / Ethnicity	Sex	Smoking Status	CYP2D6 Genotype	N	Age (yr)	Weight (kg)	C _{max} (ng/mL)	C _{max,norm} [(ng/mL) / (mg/kg)]	T _{max} (hr)	AUC(0-∞), (ng·m x hr ⁻¹)	AUC(0-∞)norm [(ng·m x hr ⁻¹) / (mg/kg)]	t _{1/2} (hr)	CL/F (L/hr)	CL/F,norm [(L/hr)/kg]	V _z /F (L)	V _z /F,norm [(L/kg)]	MRT (hr)
40 mg	Japanese	M / F	Smkr / NS	EM, IM, PM	23	25.2 ± 3.5 (13.9) 20 - 31 [24]	59.3 ± 8.8 (14.8) 44.5 - 79.1 [59.6]	32.2 ± 15.0 (46.5) 12.3 - 67.3 [30.9]	46.5 ± 19.5 (41.9) 18.6 - 65.7 [45.7]	5.9 ± 1.0 (16.1) 4 - 8.03 [6]	509.4 ± 341.0 (66.9) 183 - 1610 [401]	721.3 ± 430.2 (59.6) 279 - 2130 [585]	10.8 ± 2.2 (20.6) 8.03 - 17.4 [10.2]	108.2 ± 56.9 (52.6) 24.6 - 219 [99.8]	1.8 ± 0.9 (47.5) 0.47 - 3.59 [1.71]	1587.6 ± 751.1 (47.3) 624 - 3320 [1370]	26.4 ± 10.6 (40.4) 11.8 - 48.8 [24.4]	15.7 ± 2.8 (18.1) 12.3 - 22.4 [14.9]
		F	Smkr / NS	EM, IM, PM	13	25.3 ± 3.4 (13.4) 21 - 31 [26]	53.3 ± 5.2 (9.7) 44.5 - 60.7 [52.9]	35.3 ± 17.0 (48.2) 12.3 - 67.3 [31.2]	46.2 ± 21.3 (46.1) 16.6 - 83.4 [40.1]	6.0 ± 1.2 (19.3) 4 - 8.03 [6]	632.2 ± 398.2 (63.0) 191 - 1610 [490]	829.8 ± 517.4 (62.4) 279 - 2130 [585]	11.6 ± 2.6 (22.3) 9.05 - 12.4 [10.9]	88.8 ± 53.1 (59.7) 24.6 - 209 [81.7]	1.6 ± 0.9 (54.2) 0.47 - 3.59 [1.71]	1372.8 ± 686.0 (50.0) 624 - 2840 [1190]	25.3 ± 11.0 (43.3) 11.8 - 48.8 [24.3]	17.1 ± 2.9 (17.1) 13.5 - 22.4 [16.6]
		M	Smkr / NS	EM, IM	10	25.0 ± 3.8 (15.2) 20 - 31 [23.5]	67.0 ± 5.9 (8.8) 59.6 - 79.1 [66.65]	28.3 ± 11.5 (40.7) 14.8 - 53.7 [27.65]	46.9 ± 18.0 (38.4) 25.6 - 65.7 [48.1]	5.8 ± 0.6 (10.9) 4 - 6.02 [6]	349.9 ± 150.7 (43.1) 183 - 695 [346.5]	580.2 ± 237.2 (40.9) 285 - 1110 [574.5]	9.7 ± 1.0 (9.8) 8.03 - 10.9 [9.835]	133.3 ± 54.0 (40.5) 57.6 - 219 [116]	2.0 ± 0.8 (40.1) 0.9 - 3.51 [1.745]	1866.7 ± 773.6 (41.4) 847 - 3320 [1630]	27.7 ± 10.6 (38.3) 13.3 - 47.9 [24.5]	13.9 ± 1.4 (10.2) 12.3 - 16.8 [13.7]
		F	NS	EM	7	26.0 ± 4.0 (15.5) 21 - 31 [27]	54.3 ± 6.6 (12.1) 44.5 - 60.7 [57.7]	29.1 ± 14.2 (48.6) 12.3 - 60.9 [30.8]	38.7 ± 18.6 (48.1) 18.6 - 64.5 [34.7]	6.0 ± 1.2 (19.2) 4 - 8 [6]	482.1 ± 270.7 (56.2) 191 - 877 [439]	646.4 ± 375.0 (58.0) 279 - 1240 [488]	10.8 ± 1.2 (11.2) 9.05 - 12.2 [10.8]	109.3 ± 60.1 (54.9) 45.6 - 209 [91.2]	2.0 ± 1.0 (49.1) 0.8 - 3.59 [2.05]	1623.3 ± 828.5 (51.0) 801 - 2840 [1190]	29.5 ± 13.0 (44.2) 13.7 - 48.8 [26.7]	15.7 ± 1.4 (9.2) 13.5 - 17.4 [16.3]
			Smkr	EM	2	26.0 ± 0.0 (0.0) 26 - 26 [26]	50.2 ± 2.4 (4.8) 48.5 - 51.9 [50.2]	49.1 ± 25.7 (52.4) 30.9 - 67.3 [49.1]	60.9 ± 29.3 (48.2) 40.1 - 81.6 [60.85]	5.0 ± 1.4 (28.3) 4 - 6 [5]	680.5 ± 382.5 (56.2) 410 - 951 [680.5]	840.5 ± 437.7 (52.1) 531 - 1150 [840.5]	11.4 ± 2.5 (22.2) 9.62 - 13.2 [11.41]	69.9 ± 39.4 (56.4) 42 - 97.7 [69.85]	1.4 ± 0.7 (51.9) 0.87 - 1.88 [1.375]	1080.5 ± 395.3 (36.6) 801 - 1360 [1080.5]	21.3 ± 6.8 (31.9) 16.5 - 26.1 [21.3]	17.0 ± 4.4 (25.8) 13.9 - 20.1 [17]
			NS	IM	3	24.0 ± 3.6 (15.0) 21 - 28 [23]	53.4 ± 4.0 (7.5) 49 - 56.9 [54.3]	31.1 ± 8.2 (26.4) 21.8 - 37.3 [34.2]	41.3 ± 10.2 (24.8) 29.6 - 48.6 [45.7]	6.7 ± 1.2 (17.6) 6 - 8.03 [6]	624.0 ± 314.9 (50.5) 369 - 976 [527]	817.0 ± 354.3 (43.4) 501 - 1200 [750]	12.4 ± 3.4 (27.5) 9.43 - 16.1 [11.6]	75.0 ± 33.5 (44.7) 41 - 108 [75.9]	1.4 ± 0.6 (41.9) 0.84 - 2 [1.33]	1233.0 ± 267.4 (21.7) 949 - 1480 [1270]	23.0 ± 3.9 (17.2) 19.4 - 27.2 [22.3]	18.6 ± 3.4 (18.0) 15.2 - 21.9 [16.7]
			NS	PM	1	23	52.9	63.1	83.4	6.02	1610	2130	17.4	24.8	0.47	624	11.8	22.4
		M	NS	EM	7	25.6 ± 4.4 (17.0) 20 - 31 [24]	66.0 ± 4.9 (7.4) 59.6 - 70.9 [68.6]	25.6 ± 7.0 (29.1) 14.8 - 33.6 [27.1]	42.3 ± 12.3 (34.4) 25.6 - 58.7 [47.8]	5.7 ± 0.8 (13.2) 4 - 6 [6]	309.0 ± 90.0 (29.1) 183 - 401 [325]	511.3 ± 160.4 (31.4) 285 - 710 [557]	9.6 ± 1.1 (11.6) 8.03 - 10.9 [9.48]	142.0 ± 50.7 (35.7) 99.8 - 219 [123]	2.2 ± 0.8 (37.2) 1.41 - 3.51 [1.8]	1957.1 ± 710.5 (36.3) 1370 - 3320 [1670]	29.7 ± 10.4 (35.2) 19.3 - 47.9 [24.6]	13.2 ± 0.9 (6.9) 12.3 - 14.8 [13]
			NS	IM	2	22.5 ± 4.2 (18.6) 22 - 23 [22.5]	71.9 ± 7.3 (10.1) 64.7 - 79.1 [71.9]	25.1 ± 9.6 (38.1) 15.5 - 34.7 [25.1]	43.4 ± 14.9 (34.4) 30.7 - 56.1 [43.4]	6.0 ± 0.9 (14.8) 6 - 6.02 [6.01]	320.5 ± 109.5 (34.2) 213 - 428 [320.5]	556.5 ± 181.1 (32.5) 421 - 692 [556.5]	10.0 ± 1.1 (10.9) 9.57 - 10.4 [9.985]	140.8 ± 55.9 (39.7) 93.5 - 188 [140.75]	1.9 ± 0.9 (45.6) 1.45 - 2.38 [1.915]	2060.0 ± 921.3 (44.7) 1290 - 2830 [2060]	27.9 ± 12.2 (43.8) 20 - 35.8 [27.9]	14.8 ± 1.2 (6.3) 14.3 - 15.2 [14.75]
		Y		IM	1	26	63.8	53.7	85.7	6	695	1110	10.2	57.6	0.9	847	13.3	16.8

Table 6 Duloxetine 40 mg Single Dose Pharmacokinetic Summary Statistics in Healthy Caucasian Adults – Study SBAZ

Dosage (mg)	Race / Ethnicity	Sex	Smoking Status	CYP2D6 Genotype	N	Age (yr)	Weight (kg)	C _{max} (ng/mL)	C _{max,norm} [(ng/mL) / (mg/kg)]	T _{max} (hr)	AUC(0-∞), (ng·m x hr ⁻¹)	AUC(0-∞)norm [(ng·m x hr ⁻¹) / (mg/kg)]	t _{1/2} (hr)	CL/F (L/hr)	CL/F,norm [(L/hr)/kg]	V _d /F (L)	V _d /F,norm (L/kg)	MRT (hr)
40 mg	Caucasian	M / F	Smokers / NS	EM, PM	23	29.2 ± 9.3 (31.9) 20 - 47 [25]	70.7 ± 11.2 (15.8) 48.7 - 90.5 [70.1]	26.6 ± 10.6 (39.8) 10.6 - 55.8 [23.9]	46.6 ± 18.6 (39.8) 19.1 - 89 [39.1]	4.9 ± 1.6 (32.4) 2 - 6.02 [6]	426.4 ± 275.5 (64.6) 121 - 1440 [372]	738.2 ± 445.8 (60.4) 217 - 2290 [553]	10.3 ± 2.3 (22.4) 7.15 - 17.6 [9.66]	123.5 ± 65.6 (53.1) 27.9 - 331 [107]	1.8 ± 0.9 (51.0) 0.44 - 4.61 [1.81]	1697.7 ± 666.4 (39.3) 708 - 3630 [1690]	24.3 ± 9.5 (39.0) 11.1 - 50.5 [23.6]	14.2 ± 2.8 (19.9) 10.1 - 20.3 [13.6]
		F	Smokers / NS	EM, PM	13	26.8 ± 8.9 (33.1) 20 - 45 [22]	66.3 ± 11.3 (17.0) 48.7 - 83 [67.3]	29.9 ± 11.4 (38.1) 15.1 - 55.8 [29.4]	49.9 ± 21.2 (42.5) 25.4 - 89 [41.7]	5.1 ± 1.6 (30.6) 2 - 6 [6]	509.4 ± 328.0 (64.4) 201 - 1440 [421]	843.9 ± 542.0 (64.2) 337 - 2290 [555]	10.6 ± 2.4 (22.9) 8.63 - 17.6 [9.61]	101.3 ± 47.0 (46.3) 27.9 - 199 [95.1]	1.6 ± 0.8 (48.0) 0.44 - 2.96 [1.8]	1448.2 ± 567.1 (39.2) 708 - 2720 [1300]	22.5 ± 9.3 (41.3) 11.1 - 40.5 [22.6]	14.6 ± 2.6 (18.0) 11.4 - 20.3 [13.8]
		M	Smokers / NS	EM, PM	10	32.2 ± 9.4 (29.3) 20 - 47 [31]	76.6 ± 8.4 (11.0) 64.5 - 90.5 [76.3]	22.3 ± 8.1 (36.1) 10.6 - 36.3 [19.85]	42.4 ± 14.4 (34.0) 19.1 - 66.7 [37.25]	4.6 ± 1.6 (35.8) 2 - 6.02 [5]	318.5 ± 138.5 (43.5) 121 - 575 [300.5]	600.8 ± 238.6 (39.7) 217 - 949 [530]	10.0 ± 2.2 (22.3) 7.15 - 13.2 [10.6]	152.3 ± 77.2 (50.7) 69.6 - 331 [134]	2.0 ± 1.0 (52.5) 1.05 - 4.61 [1.885]	2022.0 ± 670.7 (33.2) 1300 - 3630 [1895]	26.7 ± 9.7 (36.4) 17 - 50.5 [24.15]	13.8 ± 3.2 (23.0) 10.1 - 20 [12.9]
		F	NS	EM	9	29.3 ± 9.6 (33.3) 21 - 45 [24]	70.0 ± 11.4 (16.3) 48.7 - 83 [69.6]	28.5 ± 9.7 (34.0) 15.1 - 43.1 [29.4]	50.4 ± 19.9 (39.4) 25.4 - 75.2 [58.7]	5.3 ± 1.4 (26.5) 2 - 6 [6]	447.7 ± 206.0 (46.0) 201 - 783 [429]	786.9 ± 372.9 (47.4) 337 - 1370 [891]	10.1 ± 1.4 (13.5) 8.63 - 12.7 [9.61]	108.3 ± 50.3 (46.5) 51.1 - 199 [93.2]	1.6 ± 0.8 (50.6) 0.73 - 2.96 [1.12]	1522.1 ± 615.8 (40.5) 824 - 2720 [1300]	22.5 ± 10.1 (45.0) 11.8 - 40.5 [16.7]	14.3 ± 2.3 (16.0) 11.4 - 17.1 [13.6]
			Smokers	EM	2	22.0 ± 1.4 (6.4) 21 - 23 [22]	57.3 ± 2.8 (4.6) 55.4 - 59.1 [57.25]	22.5 ± 2.1 (9.1) 21 - 23.9 [22.45]	32.1 ± 1.5 (4.6) 31 - 33.1 [32.05]	5.0 ± 1.4 (28.3) 4 - 6 [5]	366.0 ± 48.1 (13.1) 332 - 400 [366]	522.0 ± 43.8 (8.4) 491 - 553 [522]	10.1 ± 0.8 (7.7) 9.51 - 10.6 [10.055]	110.0 ± 14.1 (12.9) 100 - 120 [110]	1.9 ± 0.2 (8.4) 1.81 - 2.04 [1.925]	1610.0 ± 339.4 (21.1) 1370 - 1850 [1610]	26.1 ± 4.6 (16.4) 24.8 - 31.3 [28.05]	14.1 ± 0.4 (2.5) 13.8 - 14.3 [14.05]
			N	PM	1	20	63.8	55.8	89	6	1440	2290	17.6	27.9	0.44	708	11.1	20.3
			Y	PM	1	21	52.8	31.6	41.7	2	421	555	8.79	95.1	1.8	1200	22.8	12.1
		M	N	EM	8	34.0 ± 9.7 (28.4) 20 - 47 [36.5]	78.4 ± 9.5 (12.4) 64.5 - 90.5 [75.7]	21.3 ± 7.5 (35.3) 10.6 - 36.3 [19.85]	40.4 ± 13.1 (32.4) 19.1 - 60 [37.25]	4.5 ± 1.8 (39.4) 2 - 6.02 [5]	311.9 ± 141.2 (45.3) 121 - 575 [300.5]	584.9 ± 236.7 (40.5) 217 - 949 [530]	10.2 ± 2.3 (22.8) 7.15 - 13.2 [10.6]	157.0 ± 82.8 (52.8) 69.6 - 331 [134]	2.1 ± 1.1 (54.7) 1.05 - 4.61 [1.885]	2116.3 ± 702.6 (33.2) 1300 - 3630 [1925]	28.1 ± 10.3 (36.6) 19.6 - 50.5 [24.15]	13.9 ± 3.3 (24.1) 10.1 - 20 [12.9]
			Y	EM	1	22	78.2	17.7	34.6	4	220	430	7.56	182	2.33	1990	25.4	10.9
			N	PM	1	28	76.5	34.9	66.7	6	470	899	10.6	85.1	1.11	1300	17	15.7

Table 7 Duloxetine 60 mg Single Dose Pharmacokinetic Summary Statistics in Healthy Japanese Adults – Study SBZ

Dosage (mg)	Race / Ethnicity	Sex	Smoking Status	CYP2D6 Genotype	N	Age (yr)	Weight (kg)	C _{max} (ng/mL)	C _{max,norm} [(ng/mL) / (mg/kg)]	T _{max} (hr)	AUC(0-∞) (ng·m x hr ⁻¹)	AUC(0-∞)norm [(ng·m x hr ⁻¹) / (mg/kg)]	t _{1/2} (hr)	CL/F (L/hr)	CL/F,norm [(L/hr/kg)]	V _d /F (L)	V _d /F,norm (L/kg)	MRT (hr)
60 mg	Japanese	M / F	Smkr / NS	EM, IM, / PM	23	25.2 ± 3.5 (13.9) 20 - 31 [24]	59.3 ± 8.8 (14.8) 44.5 - 79.1 [59.6]	51.3 ± 25.4 (49.5) 20 - 121.4 [43.4]	48.5 ± 21.3 (43.9) 20.8 - 107 [40.65]	6.2 ± 0.8 (13.2) 4 - 8 [6]	887.5 ± 638.0 (71.9) 250 - 3250 [647]	828.9 ± 537.7 (64.9) 260 - 2860 [689.5]	11.4 ± 2.9 (25.2) 7.38 - 18.9 [10.6]	93.8 ± 52.0 (55.5) 18.5 - 240 [92.9]	1.6 ± 0.8 (48.8) 0.35 - 3.85 [1.445]	1422.3 ± 615.4 (43.3) 440 - 2750 [1335]	24.0 ± 9.7 (40.4) 8.31 - 49.8 [22.1]	18.5 ± 3.5 (21.1) 12.6 - 24 [15.35]
		F	Smkr / NS	EM, IM, / PM	13	25.3 ± 3.4 (13.4) 21 - 31 [26]	53.3 ± 5.2 (9.7) 44.5 - 60.7 [52.9]	59.2 ± 27.8 (46.9) 29.6 - 121.4 [48.1]	51.4 ± 23.5 (45.7) 23.1 - 107 [40.65]	6.3 ± 1.1 (17.0) 4 - 8 [6]	1109.9 ± 727.0 (65.5) 445 - 3250 [969.5]	965.2 ± 626.4 (64.9) 428 - 2860 [801.5]	12.4 ± 3.3 (26.6) 8.57 - 18.9 [11.85]	69.5 ± 31.0 (44.5) 18.5 - 135 [61.85]	1.3 ± 0.5 (41.2) 0.35 - 2.34 [1.25]	1178.3 ± 514.1 (43.6) 440 - 2320 [1140]	22.3 ± 10.1 (45.1) 8.31 - 49.8 [21.1]	17.8 ± 3.9 (22.0) 12.6 - 24 [17.1]
		M	Smkr / NS	EM / IM	10	25.0 ± 3.8 (15.2) 20 - 31 [23.5]	67.0 ± 5.9 (8.8) 59.6 - 79.1 [66.65]	40.4 ± 17.6 (43.7) 20 - 73.6 [38]	44.5 ± 18.2 (40.8) 20.8 - 78.3 [42.35]	6.0 ± 0.0 (0.1) 6 - 6.02 [6]	576.3 ± 303.9 (52.7) 250 - 1290 [531]	638.1 ± 320.7 (50.3) 260 - 1380 [573]	10.1 ± 1.4 (14.1) 7.38 - 13 [10.035]	127.7 ± 57.7 (45.2) 46.4 - 240 [114]	1.9 ± 0.9 (47.0) 0.73 - 3.85 [1.745]	1763.9 ± 603.1 (34.2) 869 - 2750 [1680]	26.4 ± 9.1 (34.5) 13.6 - 41 [25.15]	14.8 ± 1.8 (17.4) 12.6 - 17.8 [14.5]
		F	NS	EM	7	26.0 ± 4.0 (15.5) 21 - 31 [27]	54.3 ± 6.6 (12.1) 44.5 - 60.7 [57.7]	52.2 ± 23.7 (45.5) 29.6 - 86.1 [42.3]	45.4 ± 16.0 (35.3) 29.8 - 71.6 [39.7]	6.3 ± 1.4 (22.0) 4 - 8 [6]	862.1 ± 309.4 (36.9) 445 - 1330 [929]	761.1 ± 229.5 (30.2) 428 - 1120 [794]	10.7 ± 1.9 (17.6) 8.57 - 13.3 [9.61]	78.8 ± 31.6 (40.1) 45.1 - 135 [64.6]	1.4 ± 0.5 (33.6) 0.89 - 2.34 [1.26]	1202.6 ± 464.3 (36.6) 693 - 1870 [1240]	21.7 ± 8.5 (30.1) 15.6 - 32.4 [20.4]	17.3 ± 3.6 (20.6) 12.7 - 21.3 [16.8]
			Smkr	EM	2	26.0 ± 0.0 (0.0) 26 - 26 [26]	50.2 ± 2.4 (4.8) 46.5 - 51.9 [50.2]	45.4 ± 15.0 (33.1) 29.8 - 59.8 [46.5]	37.2 ± 12.9 (34.6) 23.1 - 48.3 [40.2]	6.0 ± 0.0 (0.0) 6 - 6 [6]	779.3 ± 235.6 (30.2) 620 - 1050 [668]	634.3 ± 186.2 (29.3) 517 - 849 [537]	13.5 ± 4.1 (30.1) 9.85 - 17.9 [12.8]	81.2 ± 21.2 (26.1) 57.1 - 96.7 [69.9]	1.7 ± 0.4 (25.0) 1.18 - 1.93 [1.86]	1583.3 ± 656.5 (41.5) 1060 - 2320 [1370]	32.7 ± 15.0 (45.9) 21.8 - 49.8 [26.5]	15.7 ± 3.6 (22.8) 12.6 - 19.6 [14.8]
			NS	IM	3	24.0 ± 3.6 (15.0) 21 - 28 [23]	53.4 ± 4.0 (7.5) 49 - 56.9 [54.3]	68.6 ± 23.7 (34.5) 42.8 - 89.4 [73.6]	61.2 ± 23.1 (37.7) 38.7 - 84.8 [60.1]	6.7 ± 1.2 (17.3) 6 - 8 [6]	1305.0 ± 605.7 (48.4) 765 - 1960 [1190]	1140.7 ± 454.1 (39.8) 692 - 1600 [1130]	13.7 ± 4.5 (32.9) 10.8 - 18.9 [11.4]	53.2 ± 24.0 (45.1) 30.7 - 78.4 [50.4]	1.0 ± 0.4 (41.9) 0.63 - 1.44 [0.89]	962.7 ± 222.9 (23.2) 829 - 1220 [839]	18.0 ± 4.0 (22.1) 14.6 - 22.4 [17.1]	18.8 ± 4.4 (23.5) 15.3 - 23.8 [17.4]
			NS	PM	1	23	52.9	121.4	107	6	3250	2860	16.5	18.5	0.35	440	8.31	24
		M	NS	EM	7	25.6 ± 4.4 (17.0) 20 - 31 [24]	66.0 ± 4.9 (7.4) 59.6 - 70.9 [68.6]	34.9 ± 12.2 (35.0) 20 - 53.1 [33]	38.4 ± 13.3 (34.6) 20.8 - 52.7 [33.8]	6.0 ± 0.0 (0.0) 6 - 6 [6]	458.6 ± 146.3 (31.9) 250 - 607 [480]	505.6 ± 168.8 (33.4) 260 - 714 [487]	9.6 ± 1.1 (11.5) 7.38 - 10.7 [9.87]	145.3 ± 54.4 (37.5) 98.9 - 240 [125]	2.2 ± 0.9 (39.4) 1.4 - 3.85 [2.05]	1961.4 ± 534.0 (27.2) 1410 - 2750 [1630]	29.8 ± 8.2 (27.6) 19.8 - 41 [30.1]	13.9 ± 1.0 (7.4) 12.6 - 15.4 [13.7]
			NS	IM	2	22.5 ± 4.2 (18.8) 22 - 23 [22.5]	71.9 ± 7.3 (10.1) 64.7 - 79.1 [71.9]	42.8 ± 17.3 (40.6) 25.7 - 59.8 [42.75]	49.2 ± 17.3 (35.2) 33.9 - 64.5 [49.2]	6.0 ± 0.0 (0.1) 6 - 6.02 [6.01]	631.5 ± 222.1 (33.4) 419 - 844 [631.5]	731.0 ± 244.2 (60.1) 552 - 910 [731]	10.1 ± 1.4 (13.5) 9.44 - 10.7 [10.07]	107.1 ± 64.4 (36.1) 71.1 - 143 [107.05]	1.5 ± 1.1 (73.9) 1.1 - 1.81 [1.455]	1520.0 ± 628.9 (41.4) 1090 - 1950 [1520]	20.8 ± 9.5 (45.8) 16.9 - 24.7 [20.8]	16.4 ± 1.8 (11.0) 15.5 - 17.3 [16.4]
		Y		IM	1	26	63.8	73.6	78.3	6	1290	1380	13	46.4	0.73	869	13.6	17.8

Table 8 Duloxetine 60 mg Single Dose Pharmacokinetic Summary Statistics in Healthy Caucasian Adults – Study SB4Z

Dosage (mg)	Race / Ethnicity	Sex	Smoking Status	CYP2D6 Genotype	N	Age (yr)	Weight (kg)	C _{max} (ng/mL)	C _{max,norm} [(ng/mL) / (mg/kg)]	T _{max} (hr)	AUC(0-∞), (ng·m x hr ⁻¹)	AUC(0-∞)norm [(ng·m x hr ⁻¹) / (mg/kg)]	t _{1/2} (hr)	CL/F (L/hr)	CL/F,norm [(L/hr)/kg]	V _d /F (L)	V _d /F,norm [(L/kg)]	MRT (hr)
60 mg	Caucasian	M / F	Smokers / NS	EM, PM	24	29.2 ± 9.3 (31.9) 20 - 47 [25]	70.7 ± 11.2 (15.8) 48.7 - 90.5 [70.1]	43.3 ± 18.7 (43.2) 16.3 - 93.8 [38.3]	50.3 ± 20.5 (40.8) 19.5 - 93.3 [44.65]	5.2 ± 1.3 (25.3) 2 - 6.03 [8]	647.3 ± 327.4 (50.6) 211 - 1510 [586]	743.0 ± 341.5 (46.0) 253 - 1810 [680.5]	10.0 ± 2.1 (21.2) 6.96 - 14.9 [9.45]	116.0 ± 58.0 (50.0) 39.6 - 284 [102.3]	1.6 ± 0.8 (47.0) 0.62 - 3.95 [1.48]	1583.6 ± 608.3 (38.4) 666 - 2850 [1620]	22.5 ± 8.6 (38.0) 9.87 - 39.7 [21.65]	14.2 ± 2.5 (17.8) 10.9 - 19.1 [13.8]
		F	Smokers / NS	EM, PM	13	26.8 ± 8.9 (33.1) 20 - 45 [22]	66.3 ± 11.3 (17.0) 48.7 - 83 [67.3]	51.9 ± 20.1 (38.8) 27.3 - 93.8 [50.9]	57.3 ± 23.3 (40.6) 26.9 - 93.3 [50.8]	5.2 ± 1.3 (24.9) 2 - 6.03 [6]	788.2 ± 355.1 (45.1) 397 - 1510 [714]	862.2 ± 382.6 (44.4) 461 - 1810 [734]	10.2 ± 1.9 (18.5) 7.01 - 13.2 [9.83]	89.6 ± 35.3 (39.3) 39.6 - 151 [84]	1.4 ± 0.6 (40.9) 0.62 - 2.17 [1.36]	1312.8 ± 567.8 (43.3) 666 - 2290 [1240]	20.2 ± 9.0 (44.5) 9.87 - 38.8 [19.3]	14.8 ± 2.1 (14.5) 12.1 - 18.8 [14.6]
		M	Smokers / NS	EM, PM	11	32.2 ± 9.4 (29.3) 20 - 47 [31]	76.6 ± 8.4 (11.0) 64.5 - 90.5 [76.3]	33.2 ± 10.5 (31.6) 16.3 - 49.2 [31.5]	41.9 ± 13.2 (31.6) 19.5 - 61.2 [40.6]	5.1 ± 1.4 (27.0) 2 - 6 [6]	480.6 ± 198.8 (41.0) 211 - 878 [482]	602.1 ± 226.4 (37.9) 253 - 967 [570]	9.7 ± 2.4 (24.9) 6.96 - 14.9 [8.96]	147.1 ± 65.4 (44.4) 66.4 - 284 [124]	1.9 ± 0.9 (45.8) 1.03 - 3.95 [1.75]	1903.6 ± 506.1 (26.6) 1280 - 2850 [1720]	25.3 ± 7.5 (29.5) 16.4 - 39.7 [23.3]	13.6 ± 2.9 (21.2) 10.9 - 19.1 [13.1]
		F	NS	EM	9	29.3 ± 9.6 (33.3) 21 - 45 [24]	70.0 ± 11.4 (16.3) 48.7 - 83 [69.8]	52.4 ± 20.9 (39.8) 28.8 - 93.8 [54.4]	60.8 ± 23.4 (38.5) 31.6 - 93.3 [63.3]	5.1 ± 1.5 (28.5) 2 - 8.03 [8]	753.7 ± 327.6 (43.5) 397 - 1440 [714]	866.9 ± 345.1 (39.8) 464 - 1430 [988]	10.0 ± 1.9 (19.4) 7.01 - 13.2 [9.83]	92.6 ± 36.3 (39.2) 41.8 - 151 [84]	1.3 ± 0.6 (41.7) 0.7 - 2.15 [1.01]	1327.7 ± 541.9 (40.8) 666 - 2140 [1300]	19.2 ± 8.0 (41.6) 9.87 - 30.5 [19.3]	14.8 ± 2.0 (13.9) 12.1 - 17.9 [14.6]
			Smokers	EM	2	22.0 ± 1.4 (6.4) 21 - 23 [22]	57.3 ± 2.6 (4.6) 55.4 - 59.1 [57.25]	36.6 ± 13.2 (35.9) 27.3 - 45.9 [36.6]	34.7 ± 11.0 (31.6) 26.9 - 42.4 [34.65]	5.0 ± 1.4 (28.3) 4 - 6 [5]	560.0 ± 130.1 (23.2) 468 - 652 [560]	531.5 ± 99.7 (18.8) 461 - 602 [531.5]	10.9 ± 2.2 (20.0) 9.33 - 12.4 [10.865]	110.1 ± 25.4 (23.1) 92.1 - 128 [110.05]	1.9 ± 0.4 (18.8) 1.66 - 2.17 [1.915]	1765.0 ± 742.5 (42.1) 1240 - 2290 [1765]	30.8 ± 11.8 (37.9) 22.4 - 38.8 [30.6]	14.8 ± 0.8 (5.3) 14.2 - 15.3 [14.75]
			N	PM	1	20	63.8	79	84	6	1510	1610	12.2	39.6	0.62	699	11	16.8
			Y	PM	1	21	52.8	50.9	44.8	6	834	734	8.55	72	1.36	888	16.8	12.5
		M	N	EM	9	34.0 ± 9.7 (28.4) 20 - 47 [36.5]	76.4 ± 9.5 (12.4) 64.5 - 90.5 [75.7]	33.2 ± 10.9 (32.9) 16.3 - 49.2 [31.5]	41.8 ± 13.8 (33.1) 19.5 - 61.2 [40.8]	5.3 ± 1.0 (18.8) 4 - 6 [8]	487.8 ± 210.9 (43.2) 211 - 878 [482]	607.7 ± 243.8 (40.1) 253 - 967 [570]	9.7 ± 2.6 (27.0) 6.96 - 14.9 [8.96]	147.8 ± 70.5 (47.7) 66.4 - 284 [124]	2.0 ± 1.0 (49.1) 1.03 - 3.95 [1.75]	1900.0 ± 548.2 (28.9) 1280 - 2850 [1720]	25.5 ± 8.2 (32.2) 16.4 - 39.7 [23.3]	13.7 ± 3.0 (21.9) 11 - 19.1 [13.1]
			Y	EM	1	22	78.2	24.5	31.9	2	328	428	8.35	183	2.34	2200	28.2	10.9
			N	PM	1	28	76.5	41.6	53	6	569	728	10.8	105	1.38	1640	21.4	15.6

5.5.5 SINGLE AND MULTIPLE DOSE PHARMACOKINETICS

Table 9 Duloxetine 60 mg Single and Multiple Dose Pharmacokinetics— Study HMCU

Metric	Day 1	Day 7	p-Value
N	6	6	
C_{max}¹ (ng/ml)	46.2 ± 25.7 (55.6) [42.3]	68.1 ± 20.8 (30.6) [66.2]	0.014
T_{max}¹ (hr)	5.8 ± 1.2 (20.0) 5 - 8 [5.5]	5.7 ± 0.5 (9.1) 5 - 6 [6]	0.74
AUC(0-∞)² (ng/ml x hr-1)	708.7 ± 312.8 (44.1) 409.6 - 1138.5 [619.6]	871.1 ± 341.6 (39.2) 470.8 - 1430.5 [784.95]	—
AUC₀₋₂₄⁴ AUC(0-∞), (ng/ml x hr-1)	519.1 ± 267.4 (51.5) 256.3 - 889.7 [476.6]	895.8 ± 344.3 (38.4) 495.9 - 1452.2 [838.1]	—
Ratio AUC₀₋₂₄ : AUC_∞	1.31 ± 0.22 (16.7) 0.97 - 1.57 [1.32]		0.037
t_{1/2}(α)² (hr)	1.5 ± 0.3 (18.2) 1.32 - 2.04 [1.405]	1.7 ± 1.5 (87.9) 0.62 - 4.75 [1.235]	0.76
t_{1/2}(β)² (hr)	13.5 ± 5.0 (37.4) 8.86 - 19.8 [11.205]	13.2 ± 2.3 (17.1) 11.11 - 17.29 [12.59]	0.92
t_{1/2}(z)³ (hr)	10.5 ± 2.3 (21.7) 8.21 - 14.44 [9.985]	12.2 ± 2.3 (18.5) 8.92 - 15.54 [11.825]	0.20

1) Measured value

2) Calculated using parameter value obtained by model-fitting

3) Obtained by linear regression using elimination-phase data converted to logarithmic values

4) Obtained using trapezoidal rule

5) For mean plasma concentration

5.5.6 MULTIPLE DOSE PHARMACOKINETICS

Table 10 Duloxetine Multiple-Dose Normalized Pharmacokinetic Metrics by Gender, and Social Habits - Study SBBN

N	Sex	Race / Ethnicity	EtOH	Smoking Status	Age	Wt	BID dose (mg)	N			Dose Normalized Concentration [(ng/ml) / mg]			Dose and Weight Normalized Concentration [(ng/ml) / (mg/kg)]		
								7 hours	12 hours	22 hours	7 hours	12 hours	22 hours	7 hours	12 hours	22 hours
8	F	34 Caucasian 5 Hispanic	Y / N	N	24.4 ± 2.7 (10.9) 20 - 29 [25]	63.4 ± 10.5 (16.5) 48 - 84.8 [62.9]	40, 60, 80, 100, 120	36	38	39	1.64 ± 0.82 (49.9) 0.23 - 3.22 [1.51]	1.36 ± 0.82 (60.2) 0.41 - 3.78 [1.11]	1.32 ± 0.71 (54.1) 0.39 - 3.49 [1.19]	0.026 ± 0.012 (45.9) 0.0035 - 0.0530 [0.0250]	0.021 ± 0.010 (49.0) 0.0066 - 0.0446 [0.0189]	0.021 ± 0.009 (45.9) 0.0061 - 0.0412 [0.0200] +
4	M	20 Caucasian	Y / N	Y / N	30.3 ± 5.7 (18.8) 25 - 39 [28.5]	85.0 ± 8.5 (10.0) 75.7 - 96.3 [84]	40, 60, 80, 100, 120	20	20	20	1.51 ± 0.81 (53.3) 0.20 - 3.50 [1.50]	1.05 ± 0.50 (47.5) 0.12 - 2.31 [1.08]	1.16 ± 0.54 (46.5) 0.39 - 2.67 [1.12]	0.018 ± 0.010 (55.2) 0.003 - 0.046 [0.017]	0.012 ± 0.006 (49.6) 0.002 - 0.030 [0.012]	0.014 ± 0.007 (48.3) 0.005 - 0.035 [0.012]

Table 11 Duloxetine Multiple-Dose Pharmacokinetic Metrics by Race, Social Habits and Dose in Women - Study SBBN

N	Sex	Race / Ethnicity	EtOH	Smk	Age	Wt	BID dose (mg)	Post-Dose Concentration (ng/ml)			Dose Normalized Concentration [(ng/ml) / mg]			Dose and Weight Normalized Concentration [(ng/ml) / (mg/kg)]		
								7 hours	12 hours	22 hours	7 hours	12 hours	22 hours	7 hours	12 hours	22 hours
6	F	Caucasian	Y	N	24.7 ± 2.7 (10.8) 22 - 29 [24.5]	64.6 ± 11.1 (17.1) 51.5 - 84.8 [62.1]	40	39.7 ± 25.4 (64.0) 9.3 - 81.8 [34.3]	38.9 ± 15.1 (39.0) 16.5 - 55.7 [44.15]	41.4 ± 14.6 (35.3) 15.4 - 55.7 [46.65]	0.99 ± 0.64 (64.0) 0.23 - 2.05 [0.86]	0.97 ± 0.38 (39.0) 0.41 - 1.39 [1.10]	1.04 ± 0.37 (35.3) 0.39 - 1.39 [1.17]	0.016 ± 0.012 (70.8) 0.004 - 0.034 [0.012]	0.015 ± 0.006 (37.8) 0.007 - 0.021 [0.017]	0.016 ± 0.006 (39.0) 0.006 - 0.023 [0.016]
							60	84.1 ± 30.8 (36.6) 40 - 115.1 [91.45]	72.1 ± 34.5 (47.8) 30.6 - 133.3 [70.5]	67.9 ± 30.4 (44.8) 25.7 - 112.2 [72.1]	1.40 ± 0.51 (36.6) 0.67 - 1.92 [1.52]	1.20 ± 0.57 (47.8) 0.51 - 2.22 [1.20]	1.13 ± 0.51 (44.8) 0.43 - 1.87 [1.20]	0.022 ± 0.008 (37.6) 0.011 - 0.032 [0.022]	0.018 ± 0.007 (35.6) 0.008 - 0.026 [0.019]	0.018 ± 0.007 (41.2) 0.007 - 0.027 [0.019]
							80	151.6 ± 60.0 (39.6) 71.1 - 218 [155.7]	108.4 ± 67.7 (62.5) 44.8 - 220 [86.75]	107.2 ± 54.4 (50.8) 52.3 - 188.6 [104.1]	1.89 ± 0.75 (39.6) 0.89 - 2.73 [1.95]	1.35 ± 0.85 (62.5) 0.56 - 2.75 [1.08]	1.34 ± 0.68 (50.8) 0.65 - 2.36 [1.30]	0.030 ± 0.011 (36.7) 0.014 - 0.041 [0.032]	0.021 ± 0.011 (51.5) 0.009 - 0.032 [0.020]	0.021 ± 0.010 (47.9) 0.010 - 0.034 [0.021]
							100	191.5 ± 113.9 (59.5) 75.2 - 322.1 [163.2]	150.3 ± 105.4 (70.1) 51.5 - 294.7 [107.8]	118.3 ± 68.0 (57.5) 46.6 - 224.5 [106.45]	1.92 ± 1.14 (59.5) 0.75 - 3.22 [1.63]	1.50 ± 1.05 (70.1) 0.52 - 2.95 [1.08]	1.18 ± 0.68 (57.5) 0.47 - 2.25 [1.08]	0.030 ± 0.016 (55.6) 0.012 - 0.053 [0.032]	0.023 ± 0.013 (58.3) 0.008 - 0.037 [0.021]	0.018 ± 0.009 (50.4) 0.007 - 0.027 [0.018]
							120	237.1 ± 120.0 (50.6) 110.6 - 389.9 [219.6]	192.6 ± 148.7 (77.2) 64.2 - 453.5 [126.75]	195.6 ± 120.6 (61.6) 74 - 418.7 [174.2]	1.98 ± 1.00 (50.6) 0.92 - 3.08 [1.83]	1.61 ± 1.24 (77.2) 0.54 - 3.78 [1.06]	1.63 ± 1.00 (61.6) 0.62 - 3.49 [1.45]	0.031 ± 0.015 (47.5) 0.015 - 0.051 [0.035]	0.024 ± 0.015 (62.0) 0.009 - 0.045 [0.019]	0.024 ± 0.011 (46.6) 0.010 - 0.041 [0.025]
1 / 1	F	Caucasian HISPANIC	N N	N N	20 26	48 68.5	40	33.2	24	26.4	0.83	0.60	0.66	0.017	0.013	0.014
							40	47.6	35.9	43.5	1.19	0.90	1.09	0.017	0.013	0.016
							60	68	48	40.9	1.13	0.80	0.68	0.024	0.017	0.014
							60	147.2	108.8	137.3	2.45	1.81	2.29	0.036	0.026	0.033
							80	90.4	60.4	50.4	1.13	0.76	0.63	0.024	0.016	0.013
							80	228.2	213.7	225.6	2.85	2.67	2.82	0.042	0.039	0.041
							100	151.9	125.7	97.6	1.52	1.26	0.98	0.032	0.026	0.020
							100	254.7	249.3	245.7	2.55	2.49	2.46	0.037	0.036	0.036
							120	251.6	238.3	230.1	2.10	1.99	1.92	0.031	0.029	0.028

Table 12 Duloxetine Multiple-Dose Pharmacokinetic Metrics by Race, Social Habits and Dose in Men – Study SBBN

Age (years)	Sex	Race / Ethnicity	Weight (kg)	EtOH	Smoking Status	N	BID Dose (mg)	Post-Dose Concentration (ng/ml)			Dose Normalized Concentration [(ng/ml) / mg]			Dose and Weight Normalized Concentration [(ng/ml) / (mg/kg)]		
								7 hours	12 hours	22 hours	7 hours	12 hours	22 hours	7 hours	12 hours	22 hours
32.0 ± 9.9 (30.9) 25 - 39 [32]	M	Caucasian	92.8 ± 4.9 (5.3) 89.3 - 96.3 [92.8]	N	N	2	40	59.4 ± 12.4 (21.0) 50.6 - 68.2 [59.4]	34.3 ± 9.1 (26.6) 27.8 - 40.7 [34.25]	51.9 ± 13.8 (26.6) 42.1 - 61.6 [51.85]	1.49 ± 0.31 (21.0) 1.27 - 1.71 [1.49]	0.86 ± 0.23 (26.6) 0.70 - 1.02 [0.86]	1.30 ± 0.34 (26.6) 1.05 - 1.54 [1.30]	0.016 ± 0.004 (26.1) 0.013 - 0.019 [0.016]	0.009 ± 0.003 (31.7) 0.007 - 0.011 [0.009]	0.014 ± 0.004 (31.7) 0.011 - 0.017 [0.014]
								117.7 ± 56.6 (48.1) 77.7 - 157.7 [117.7]	76.3 ± 20.1 (26.3) 62.1 - 90.5 [76.3]	80.5 ± 16.5 (20.5) 68.8 - 92.1 [80.45]	1.96 ± 0.94 (48.1) 1.30 - 2.63 [1.96]	1.27 ± 0.33 (26.3) 1.04 - 1.51 [1.27]	1.34 ± 0.27 (20.5) 1.15 - 1.54 [1.34]	0.021 ± 0.011 (52.7) 0.013 - 0.029 [0.021]	0.014 ± 0.004 (31.4) 0.011 - 0.017 [0.014]	0.015 ± 0.004 (25.7) 0.012 - 0.017 [0.015]
								146.8 ± 14.3 (9.7) 136.7 - 156.9 [146.8]	83.1 ± 9.9 (11.9) 76.1 - 90.1 [83.1]	105.0 ± 13.8 (13.1) 95.2 - 114.7 [104.95]	1.84 ± 0.18 (9.7) 1.71 - 1.96 [1.84]	1.04 ± 0.12 (11.9) 0.95 - 1.13 [1.04]	1.31 ± 0.17 (13.1) 1.19 - 1.43 [1.31]	0.020 ± 0.003 (15.0) 0.018 - 0.022 [0.020]	0.011 ± 0.002 (17.2) 0.010 - 0.013 [0.011]	0.014 ± 0.003 (18.4) 0.012 - 0.016 [0.014]
								199.5 ± 46.4 (23.3) 166.7 - 232.3 [199.5]	129.8 ± 12.7 (9.8) 120.8 - 138.8 [129.8]	140.2 ± 40.5 (28.9) 111.5 - 168.8 [140.15]	2.00 ± 0.46 (23.3) 1.67 - 2.32 [2.00]	1.30 ± 0.13 (9.8) 1.21 - 1.39 [1.30]	1.40 ± 0.41 (28.9) 1.12 - 1.69 [1.40]	0.022 ± 0.006 (28.4) 0.017 - 0.026 [0.022]	0.014 ± 0.002 (15.1) 0.013 - 0.016 [0.014]	0.015 ± 0.005 (34.0) 0.012 - 0.019 [0.015]
								244.7 ± 50.5 (20.6) 209 - 280.4 [244.7]	180.4 ± 36.9 (20.5) 154.3 - 206.5 [180.4]	192.8 ± 11.7 (6.1) 184.5 - 201.1 [192.8]	2.04 ± 0.42 (20.6) 1.74 - 2.34 [2.04]	1.50 ± 0.31 (20.5) 1.29 - 1.72 [1.50]	1.61 ± 0.10 (6.1) 1.54 - 1.68 [1.61]	0.022 ± 0.006 (25.8) 0.018 - 0.026 [0.022]	0.016 ± 0.002 (15.2) 0.014 - 0.018 [0.016]	0.017 ± 0.000 (0.8) 0.017 - 0.017 [0.017]
28.5 ± 3.5 (12.4) 26 - 31 [28.5]	M	Caucasian	77.2 ± 2.1 (2.7) 75.7 - 78.7 [77.2]	Y	Y	2	40	21.2 ± 9.7 (45.8) 14.3 - 28 [21.15]	26.7 ± 8.6 (32.3) 20.6 - 32.8 [26.7]	21.3 ± 4.5 (21.0) 18.1 - 24.4 [21.25]	0.53 ± 0.24 (45.8) 0.36 - 0.70 [0.53]	0.67 ± 0.22 (32.3) 0.52 - 0.82 [0.67]	0.53 ± 0.11 (21.0) 0.45 - 0.61 [0.53]	0.007 ± 0.003 (48.2) 0.005 - 0.009 [0.007]	0.009 ± 0.003 (29.7) 0.007 - 0.010 [0.009]	0.007 ± 0.001 (18.3) 0.006 - 0.008 [0.007]
								39.9 ± 2.7 (6.7) 38 - 41.8 [39.9]	25.0 ± 2.1 (8.5) 23.5 - 26.5 [25]	26.5 ± 4.5 (16.8) 23.3 - 29.6 [26.45]	0.67 ± 0.04 (6.7) 0.63 - 0.70 [0.67]	0.42 ± 0.04 (8.5) 0.39 - 0.44 [0.42]	0.44 ± 0.07 (16.8) 0.39 - 0.49 [0.44]	0.009 ± 0.000 (4.0) 0.008 - 0.009 [0.009]	0.005 ± 0.000 (5.7) 0.005 - 0.006 [0.005]	0.006 ± 0.001 (14.1) 0.005 - 0.006 [0.006]
								102.4 ± 5.3 (5.2) 98.6 - 106.1 [102.4]	80.5 ± 19.9 (24.8) 66.4 - 94.6 [80.5]	73.2 ± 8.1 (11.0) 67.5 - 78.9 [73.2]	1.28 ± 0.07 (5.2) 1.23 - 1.33 [1.28]	1.01 ± 0.25 (24.8) 0.83 - 1.18 [1.01]	0.92 ± 0.10 (11.0) 0.84 - 0.99 [0.92]	0.017 ± 0.000 (2.4) 0.016 - 0.017 [0.017]	0.013 ± 0.003 (22.1) 0.011 - 0.015 [0.013]	0.012 ± 0.001 (8.3) 0.011 - 0.013 [0.012]
								237.3 ± 158.7 (66.9) 125.1 - 349.5 [237.3]	174.5 ± 79.3 (45.5) 118.4 - 230.6 [174.5]	171.9 ± 135.1 (78.6) 76.3 - 267.4 [171.85]	2.37 ± 1.59 (66.9) 1.25 - 3.50 [2.37]	1.75 ± 0.79 (45.5) 1.18 - 2.31 [1.75]	1.72 ± 1.35 (78.6) 0.76 - 2.67 [1.72]	0.031 ± 0.021 (69.0) 0.016 - 0.046 [0.031]	0.023 ± 0.011 (47.9) 0.015 - 0.030 [0.023]	0.023 ± 0.018 (80.5) 0.010 - 0.035 [0.023]
								115.0 ± 128.2 (111.5) 24.3 - 205.6 [114.95]	85.6 ± 101.3 (118.3) 14 - 157.2 [85.6]	125.0 ± 12.7 (10.2) 116 - 134 [125]	0.96 ± 1.07 (111.5) 0.20 - 1.71 [0.96]	0.71 ± 0.84 (118.3) 0.12 - 1.31 [0.71]	1.04 ± 0.11 (10.2) 0.97 - 1.12 [1.04]	0.012 ± 0.014 (110.5) 0.003 - 0.022 [0.012]	0.009 ± 0.011 (117.5) 0.002 - 0.017 [0.009]	0.014 ± 0.002 (12.9) 0.012 - 0.015 [0.014]

Table 13 Steady State Pharmacokinetic Summary Statistics After Duloxetine 20 mg BID in Healthy Japanese Adults – Study SBAZ

Dose	Race / Ethnicity	Sex	Smoking Status	CYP2D6 Genotype	N	Age (yr)	Weight (kg)	C _{max,ss} (ng/mL)	C _{max,ss,norm} [(ng/mL)/(mg/kg)]	C _{min,ss} (ng/mL)	T _{max} (hr)	AUC(0-4) (ng/ml x hr-1)	t _{1/2} (hr)	CL _{ss/F} (L/hr)	CL _{ss/F, norm} [(L/hr)/kg]	V _{z,ss/F} (L)	V _{z,ss/F, norm} (L/kg)	MRT _{ss} (hr)
20 BID	Japanese	M/F	Y / N	EM, IM	8	25.0 ± 3.5 (14.2) 21 - 30 [25]	61.3 ± 5.8 (9.4) 52.8 - 68.7 [61.75]	28.6 ± 11.9 (41.5) 13.8 - 53.4 [25.7]	85.9 ± 29.5 (34.4) 42.1 - 141 [82.5]	13.3 ± 6.5 (48.8) 5.5 - 27.6 [12.1]	5.8 ± 0.7 (12.3) 4 - 6.02 [6]	237.1 ± 104.9 (44.2) 103 - 458 [210.5]	11.8 ± 1.6 (13.5) 9.6 - 13.7 [12.2]	99.2 ± 44.5 (44.8) 43.7 - 195 [95.5]	1.6 ± 0.7 (44.3) 0.827 - 3.19 [1.455]	1634.0 ± 562.8 (34.4) 852 - 2700 [1600]	26.5 ± 8.9 (33.5) 16.1 - 44.2 [24.55]	19.1 ± 2.7 (14.3) 15 - 23.7 [19.25]
		F	Y	EM, IM	2	21.0 ± 0.0 (0.0) 21 - 21 [21]	54.3 ± 2.1 (3.8) 52.8 - 55.7 [54.25]	38.4 ± 21.2 (55.2) 23.4 - 53.4 [38.4]	103.1 ± 53.6 (52.0) 65.2 - 141 [103.1]	19.3 ± 11.8 (61.3) 10.9 - 27.6 [19.25]	6.0 ± 0.0 (0.2) 6 - 6.02 [6.01]	322.0 ± 192.3 (59.7) 186 - 458 [322]	12.6 ± 1.3 (10.1) 11.7 - 13.5 [12.6]	75.9 ± 45.5 (59.9) 43.7 - 108 [75.85]	1.4 ± 0.8 (56.6) 0.827 - 1.93 [1.3785]	1336.0 ± 684.5 (51.2) 852 - 1820 [1336]	24.4 ± 11.7 (48.1) 16.1 - 32.7 [24.4]	21.9 ± 2.6 (12.0) 20 - 23.7 [21.85]
		M	Y / N	EM / IM	6	26.3 ± 3.0 (11.4) 22 - 30 [26.5]	63.6 ± 4.4 (6.9) 57.4 - 68.7 [63]	25.3 ± 7.4 (29.4) 13.8 - 33.9 [25.3]	80.2 ± 22.1 (27.6) 42.1 - 108 [82.5]	11.3 ± 3.4 (30.3) 5.5 - 14.9 [12.1]	5.7 ± 0.8 (14.4) 4 - 6 [6]	208.8 ± 64.5 (30.9) 103 - 289 [210.5]	11.6 ± 1.7 (14.8) 9.6 - 13.7 [11.9]	107.0 ± 45.4 (42.4) 69.3 - 195 [95.5]	1.7 ± 0.7 (44.4) 1.21 - 3.19 [1.455]	1733.3 ± 549.9 (31.7) 1110 - 2700 [1600]	27.2 ± 9.0 (32.9) 19.3 - 44.2 [24.55]	18.2 ± 2.2 (12.3) 15 - 21.2 [18.55]
		F	Y	EM	1	21	52.8	53.4	141	27.6	6	458	13.5	43.7	0.827	852	16.1	23.7
			Y	IM	1	21	55.7	23.4	65.2	10.9	6.02	186	11.7	108	1.93	1820	32.7	20
		M	N	EM	3	25.0 ± 3.6 (14.4) 22 - 29 [24]	62.3 ± 5.7 (9.2) 57.4 - 68.6 [61]	22.7 ± 9.0 (39.6) 13.8 - 31.8 [22.6]	70.3 ± 25.4 (36.1) 42.1 - 91.3 [77.5]	9.9 ± 4.7 (47.8) 5.5 - 14.9 [9.3]	5.3 ± 1.2 (21.7) 4 - 6 [6]	191.7 ± 93.3 (48.7) 103 - 289 [183]	10.1 ± 0.8 (8.3) 9.6 - 11.1 [9.7]	124.4 ± 64.3 (51.6) 69.3 - 195 [109]	2.0 ± 1.1 (52.6) 1.21 - 3.19 [1.59]	1780.0 ± 824.0 (46.3) 1110 - 2700 [1530]	28.6 ± 13.6 (47.7) 19.3 - 44.2 [22.2]	16.5 ± 1.6 (9.5) 15 - 18.1 [16.3]
			N	IM	1	30	68.7	21.7	74.5	11.5	6	201	13.7	100	1.45	1960	28.6	21.2
			Y	IM	2	26.5 ± 0.7 (2.7) 26 - 27 [26.5]	63.0 ± 0.7 (1.1) 62.5 - 63.5 [63]	31.0 ± 4.2 (13.5) 28 - 33.9 [30.95]	97.8 ± 14.5 (14.8) 87.5 - 108 [97.75]	13.2 ± 0.7 (5.4) 12.7 - 13.7 [13.2]	6.0 ± 0.0 (0.0) 6 - 6 [6]	238.5 ± 26.2 (11.0) 220 - 257 [238.5]	12.7 ± 0.0 (0.0) 12.7 - 12.7 [12.7]	84.5 ± 9.3 (11.0) 77.9 - 91 [84.45]	1.3 ± 0.2 (12.1) 1.23 - 1.46 [1.345]	1550.0 ± 169.7 (10.9) 1430 - 1670 [1550]	24.6 ± 3.0 (12.4) 22.4 - 26.7 [24.55]	19.3 ± 0.4 (1.8) 19 - 19.5 [19.25]

Table 14 Steady State Pharmacokinetic Summary Statistics After Duloxetine 40 mg BID in Healthy Japanese Adults – Study SBAZ

Dose	Origin	Sex	Smoker Status	CYP2D6 Status	N	Age (yr)	Weight (kg)	C _{max,ss} (ng/mL)	C _{max,ss,norm} [(ng/mL)/ (mg/kg)]	C _{min,ss} (ng/mL)	T _{max} (hr)	AUC(0-t) (ng/ml x hr-1)	t _{1/2} (hr)	CL _{ss/F} (L/hr)	CL _{ss/F, norm} [(L/hr)/kg]	V _{zss/F} (L)	V _{zss/F,norm} (L/kg)	MRT _{ss} (hr)
40 BID	Japanese	M/F	Y / N	EM, IM	8	24.3 ± 5.3 (21.8) 20 - 34 [22.5]	64.9 ± 5.6 (8.7) 58 - 73 [65.3]	83.2 ± 81.0 (97.3) 40.3 - 282.7 [56.95]	140.8 ± 152.2 (108.1) 68 - 516 [95]	45.8 ± 52.9 (115.6) 20.5 - 176.1 [27.45]	5.8 ± 1.3 (22.4) 4 - 8.02 [6]	767.0 ± 797.0 (103.9) 380 - 2730 [489]	12.3 ± 1.8 (14.7) 9.88 - 14.9 [12.5]	75.5 ± 27.4 (36.4) 14.7 - 105 [81.9]	1.2 ± 0.4 (37.6) 0.201 - 1.56 [1.225]	1300.6 ± 478.0 (36.7) 315 - 1880 [1375]	20.3 ± 7.2 (35.6) 4.31 - 27.8 [22.5]	20.4 ± 2.4 (11.8) 17.2 - 24.7 [20.25]
		F	Y	EM	2	28.5 ± 7.8 (27.3) 23 - 34 [28.5]	63.9 ± 5.2 (8.1) 60.2 - 67.5 [63.85]	54.3 ± 19.8 (36.5) 40.3 - 68.3 [54.3]	85.5 ± 24.7 (28.9) 68 - 103 [85.5]	29.5 ± 12.2 (41.5) 20.8 - 38.1 [29.45]	5.0 ± 1.4 (28.3) 4 - 6 [5]	516.5 ± 193.0 (37.4) 380 - 653 [516.5]	12.6 ± 0.2 (1.7) 12.4 - 12.7 [12.55]	83.2 ± 30.9 (37.2) 61.3 - 105 [83.15]	1.3 ± 0.4 (29.6) 1.02 - 1.56 [1.29]	1500.0 ± 537.4 (35.8) 1120 - 1880 [1500]	23.2 ± 6.5 (28.0) 18.6 - 27.8 [23.2]	21.9 ± 0.4 (1.6) 21.6 - 22.1 [21.85]
		M	Y / N	EM, IM	6	22.8 ± 4.2 (18.3) 20 - 31 [21.5]	65.3 ± 6.2 (9.5) 58 - 73 [65.3]	92.9 ± 93.1 (100.2) 49.3 - 282.7 [56.95]	159.2 ± 175.2 (110.1) 71.5 - 516 [95]	51.2 ± 61.3 (119.6) 20.5 - 176.1 [27.45]	6.0 ± 1.3 (21.2) 4 - 8.02 [6]	850.5 ± 921.1 (108.3) 440 - 2730 [489]	12.2 ± 2.1 (17.4) 9.88 - 14.9 [11.7]	72.9 ± 28.8 (39.5) 14.7 - 90.9 [81.9]	1.1 ± 0.5 (42.8) 0.201 - 1.55 [1.225]	1234.2 ± 490.8 (39.8) 315 - 1740 [1375]	19.3 ± 7.7 (40.1) 4.31 - 24.4 [22.5]	19.9 ± 2.6 (13.3) 17.2 - 24.7 [19.5]
		F	Y	EM	2	28.5 ± 7.8 (27.3) 23 - 34 [28.5]	63.9 ± 5.2 (8.1) 60.2 - 67.5 [63.85]	54.3 ± 19.8 (36.5) 40.3 - 68.3 [54.3]	85.5 ± 24.7 (28.9) 68 - 103 [85.5]	29.5 ± 12.2 (41.5) 20.8 - 38.1 [29.45]	5.0 ± 1.4 (28.3) 4 - 6 [5]	516.5 ± 193.0 (37.4) 380 - 653 [516.5]	12.6 ± 0.2 (1.7) 12.4 - 12.7 [12.55]	83.2 ± 30.9 (37.2) 61.3 - 105 [83.15]	1.3 ± 0.4 (29.6) 1.02 - 1.56 [1.29]	1500.0 ± 537.4 (35.8) 1120 - 1880 [1500]	23.2 ± 6.5 (28.0) 18.6 - 27.8 [23.2]	21.9 ± 0.4 (1.6) 21.6 - 22.1 [21.85]
		M	N	IM	2	22.5 ± 0.7 (3.1) 22 - 23 [22.5]	65.3 ± 1.1 (1.7) 64.5 - 66.1 [65.3]	58.2 ± 2.1 (3.6) 56.7 - 59.7 [58.2]	95.0 ± 1.8 (1.9) 93.7 - 96.3 [95]	27.5 ± 0.8 (2.8) 26.9 - 28 [27.45]	6.0 ± 0.0 (0.0) 6 - 6 [6]	499.5 ± 0.7 (0.1) 499 - 500 [499.5]	11.2 ± 1.9 (17.1) 9.88 - 12.6 [11.24]	80.1 ± 0.1 (0.2) 80 - 80.2 [80.1]	1.2 ± 0.0 (1.7) 1.21 - 1.24 [1.225]	1300.0 ± 226.3 (17.4) 1140 - 1460 [1300]	19.9 ± 3.1 (15.6) 17.7 - 22.1 [19.9]	18.8 ± 2.3 (12.0) 17.2 - 20.4 [18.8]
			N	EM	3	24.0 ± 6.1 (25.3) 20 - 31 [21]	67.6 ± 7.8 (11.5) 58.7 - 73 [71.2]	130.5 ± 131.8 (101.0) 51.6 - 282.7 [57.2]	231.2 ± 247.0 (106.8) 75.7 - 516 [102]	77.3 ± 85.6 (110.6) 25.7 - 176.1 [30.2]	5.3 ± 1.2 (21.7) 4 - 6 [6]	1216.3 ± 1311.0 (107.8) 440 - 2730 [479]	13.4 ± 2.2 (16.7) 10.8 - 14.9 [14.4]	63.1 ± 42.0 (66.7) 14.7 - 90.9 [83.6]	1.0 ± 0.7 (71.4) 0.201 - 1.55 [1.17]	1158.3 ± 747.7 (64.5) 315 - 1740 [1420]	17.6 ± 11.5 (65.4) 4.31 - 24.4 [24.2]	21.2 ± 3.1 (14.4) 18.9 - 24.7 [20.1]
			Y	EM	1	20	58	49.3	71.5	20.5	8.02	455	10.5	87.9	1.52	1330	22.9	18.1

Table 15 Steady State Pharmacokinetic Summary Statistics After Duloxetine 20 mg BID in Healthy Caucasian Adults – Study SBZ

Dose	Origin	Sex	Smoker Status	CYP2D6 Status	N	Age (yr)	Weight (kg)	C _{max,ss} (ng/mL)	C _{max,ss,norm} [(ng/mL)/(mg/kg)]	C _{min,ss} (ng/mL)	T _{max} (hr)	AUC(0-1) (ng/ml x hr-1)	t _{1/2} (hr)	CL _{ss/F} (L/hr)	CL _{ss/F, norm} [(L/hr)/kg]	V _{zss/F} (L)	V _{zss/F, norm} (L/kg)	MRT _{ss} (hr)
20 BID	Caucasian	M/F	Y / N	EM	8	29.8 ± 10.7 (35.9) 20 - 48 [24.5]	71.0 ± 8.8 (12.4) 59.4 - 82.1 [70.35]	23.1 ± 13.0 (56.3) 11.7 - 48.7 [19.2]	79.0 ± 38.5 (48.7) 46.3 - 158 [67.55]	11.7 ± 8.4 (71.6) 3.3 - 28.4 [9.65]	5.8 ± 1.7 (29.0) 2 - 8 [6]	201.0 ± 126.4 (62.9) 81.6 - 447 [170.5]	10.7 ± 1.8 (14.8) 8.02 - 12.6 [11.05]	134.1 ± 71.6 (53.4) 44.7 - 245 [119]	1.8 ± 0.9 (48.3) 0.688 - 3.37 [1.81]	1958.3 ± 818.9 (41.8) 766 - 3120 [2080]	27.2 ± 10.2 (37.5) 11.8 - 42.9 [27.6]	17.5 ± 3.4 (19.3) 10.3 - 22 [18.1]
		F	N	EM	2	32.5 ± 12.0 (37.0) 24 - 41 [32.5]	60.5 ± 1.5 (2.5) 59.4 - 61.5 [60.45]	29.1 ± 10.3 (35.5) 21.8 - 36.4 [29.1]	87.5 ± 29.0 (33.1) 67 - 108 [87.5]	15.7 ± 4.4 (27.9) 12.6 - 18.8 [15.7]	6.0 ± 0.0 (0.0) 6 - 6 [6]	262.0 ± 93.3 (35.6) 196 - 328 [262]	11.2 ± 0.9 (8.2) 10.5 - 11.8 [11.15]	81.5 ± 29.0 (35.6) 61 - 102 [81.5]	1.3 ± 0.4 (33.1) 1.03 - 1.66 [1.345]	1295.0 ± 360.6 (27.8) 1040 - 1550 [1295]	21.3 ± 5.4 (25.2) 17.5 - 25.1 [21.3]	18.8 ± 0.2 (1.1) 18.6 - 18.9 [18.75]
		M	Y / N	EM	6	28.8 ± 11.3 (39.1) 20 - 48 [23.5]	74.5 ± 7.0 (9.4) 65 - 82.1 [75.9]	21.1 ± 14.0 (66.4) 11.7 - 48.7 [15.65]	76.1 ± 43.2 (56.7) 46.3 - 158 [59.05]	10.4 ± 9.3 (89.5) 3.3 - 28.4 [7.9]	5.7 ± 2.0 (34.7) 2 - 8 [6]	180.7 ± 136.6 (75.6) 81.6 - 447 [136.5]	10.6 ± 1.8 (17.0) 8.02 - 12.6 [11.05]	151.6 ± 74.3 (49.0) 44.7 - 245 [147.5]	2.0 ± 1.0 (48.1) 0.688 - 3.37 [1.97]	2179.3 ± 823.5 (37.8) 766 - 3120 [2455]	29.1 ± 11.0 (37.8) 11.8 - 42.9 [31.25]	17.0 ± 3.9 (22.8) 10.3 - 22 [17.45]
		M	N	EM	5	30.2 ± 12.0 (39.8) 20 - 48 [25]	72.9 ± 6.6 (9.0) 65 - 79.8 [72.7]	22.0 ± 15.5 (70.3) 11.7 - 48.7 [14.7]	77.7 ± 48.1 (61.9) 46.3 - 158 [50]	11.0 ± 10.2 (93.2) 3.3 - 28.4 [8.5]	5.6 ± 2.2 (39.1) 2 - 8 [6]	192.0 ± 149.5 (77.9) 81.6 - 447 [149]	10.5 ± 2.0 (19.0) 8.02 - 12.6 [11.4]	149.7 ± 83.0 (55.4) 44.7 - 245 [134]	2.0 ± 1.1 (53.5) 0.688 - 3.37 [1.98]	2121.2 ± 906.8 (42.8) 766 - 3120 [2440]	28.9 ± 12.3 (42.5) 11.8 - 42.9 [32.4]	16.9 ± 4.3 (25.5) 10.3 - 22 [17.3]
		Y		EM	1	22	82.1	16.6	68.1	7.3	6	124	10.7	161	1.96	2470	30.1	17.6

Table 16 Steady State Pharmacokinetic Summary Statistics After Duloxetine 40 mg BID in Healthy Caucasian Adults – Study SBAZ

Dose	Origin	Sex	Smker Status	CYP2D6 Status	N	Age (yr)	Weight (kg)	Cmax,ss (ng/mL)	Cmax,ss,norm [(ng/mL)/(mg/kg)]	Cmin,ss (ng/mL)	Tmax (hr)	AUC(0-t) (ng/ml x hr-1)	t½ (hr)	CLss/F (L/hr)	CLss/F, norm [(L/hr)/kg]	Vzss/F (L)	Vz,ss/F,norm (L/kg)	MRTss (hr)
40 BID	Caucasian	M/F	Y / N	UM, EM	8	27.9 ± 7.9 (28.5) 19 - 40 [24.5]	74.0 ± 10.0 (13.5) 61.8 - 88.3 [71.9]	52.2 ± 35.1 (67.4) 16.2 - 129.5 [41.8]	94.6 ± 60.0 (63.5) 30 - 226 [81.55]	25.7 ± 17.9 (69.7) 7 - 65.5 [20.76]	5.3 ± 1.5 (28.3) 2 - 6 [6]	440.9 ± 293.5 (66.6) 151 - 1110 [360.5]	11.1 ± 1.7 (15.6) 9.15 - 13.9 [11.25]	121.6 ± 68.3 (56.2) 36 - 266 [112.5]	1.6 ± 0.9 (55.7) 0.516 - 3.59 [1.455]	1861.4 ± 842.4 (45.3) 601 - 3510 [1825]	25.3 ± 11.6 (45.7) 8.61 - 47.4 [22.95]	18.1 ± 3.1 (17.4) 12.9 - 22 [17.95]
		F	Y / N	UM / EM	3	21.3 ± 2.1 (9.8) 19 - 23 [22]	65.1 ± 4.2 (6.4) 61.8 - 69.8 [63.8]	79.6 ± 45.1 (56.6) 41.9 - 129.5 [67.4]	132.9 ± 83.5 (62.8) 64.7 - 226 [108]	39.5 ± 22.7 (57.5) 23.9 - 65.5 [29]	4.7 ± 2.3 (49.5) 2 - 6 [6]	678.0 ± 378.7 (55.9) 403 - 1110 [521]	12.2 ± 1.5 (12.6) 11 - 13.9 [11.6]	70.6 ± 32.0 (45.3) 36 - 99 [76.8]	1.1 ± 0.6 (49.9) 0.516 - 1.61 [1.2]	1270.3 ± 895.9 (54.8) 601 - 1990 [1220]	20.0 ± 11.8 (59.2) 8.61 - 32.2 [19.1]	20.5 ± 1.9 (9.1) 18.4 - 22 [21]
		M	N	EM	5	31.8 ± 7.5 (23.7) 24 - 40 [31]	79.3 ± 8.5 (10.7) 69 - 88.3 [77.6]	35.7 ± 15.5 (43.5) 16.2 - 58.2 [32.5]	71.5 ± 32.5 (45.5) 30 - 113 [71.7]	17.4 ± 8.7 (49.7) 7 - 31 [16.7]	5.6 ± 0.9 (16.0) 4 - 6 [6]	298.6 ± 107.7 (36.1) 151 - 451 [305]	10.5 ± 1.7 (15.8) 9.15 - 12.9 [9.7]	152.1 ± 67.3 (44.2) 88.7 - 266 [131]	2.0 ± 1.0 (50.3) 1.14 - 3.59 [1.48]	2216.0 ± 761.9 (34.4) 1650 - 3510 [2090]	28.5 ± 11.4 (40.0) 18.9 - 47.4 [24.6]	16.7 ± 3.0 (17.7) 12.9 - 20.9 [16.8]
		F	Y	EM	2	21.0 ± 2.8 (13.5) 19 - 23 [21]	65.8 ± 5.7 (8.6) 61.8 - 69.8 [65.8]	85.7 ± 61.9 (72.3) 41.9 - 129.5 [65.7]	145.4 ± 114.1 (78.5) 64.7 - 226 [145.35]	44.7 ± 29.4 (65.8) 23.9 - 65.5 [44.7]	4.0 ± 2.8 (70.7) 2 - 6 [4]	756.5 ± 499.9 (66.1) 403 - 1110 [756.5]	12.8 ± 1.6 (12.8) 11.6 - 13.9 [12.75]	67.5 ± 44.5 (66.0) 36 - 99 [67.5]	1.1 ± 0.8 (72.8) 0.516 - 1.61 [1.063]	1295.5 ± 982.2 (75.8) 601 - 1990 [1295.5]	20.4 ± 16.7 (81.7) 8.61 - 32.2 [20.405]	21.5 ± 0.7 (3.3) 21 - 22 [21.5]
			N	UM	1	22	63.8	67.4	108	29	6	521	11	76.8	1.2	1220	19.1	18.4
		M	N	EM	5	31.8 ± 7.5 (23.7) 24 - 40 [31]	79.3 ± 8.5 (10.7) 69 - 88.3 [77.6]	35.7 ± 15.5 (43.5) 16.2 - 58.2 [32.5]	71.5 ± 32.5 (45.5) 30 - 113 [71.7]	17.4 ± 8.7 (49.7) 7 - 31 [16.7]	5.6 ± 0.9 (16.0) 4 - 6 [6]	298.6 ± 107.7 (36.1) 151 - 451 [305]	10.5 ± 1.7 (15.8) 9.15 - 12.9 [9.7]	152.1 ± 67.3 (44.2) 88.7 - 266 [131]	2.0 ± 1.0 (50.3) 1.14 - 3.59 [1.48]	2216.0 ± 761.9 (34.4) 1650 - 3510 [2090]	28.5 ± 11.4 (40.0) 18.9 - 47.4 [24.6]	16.7 ± 3.0 (17.7) 12.9 - 20.9 [16.8]

5.6 PHARMACODYNAMICS

5.6.1 EX VIVO PHARMACODYNAMICS

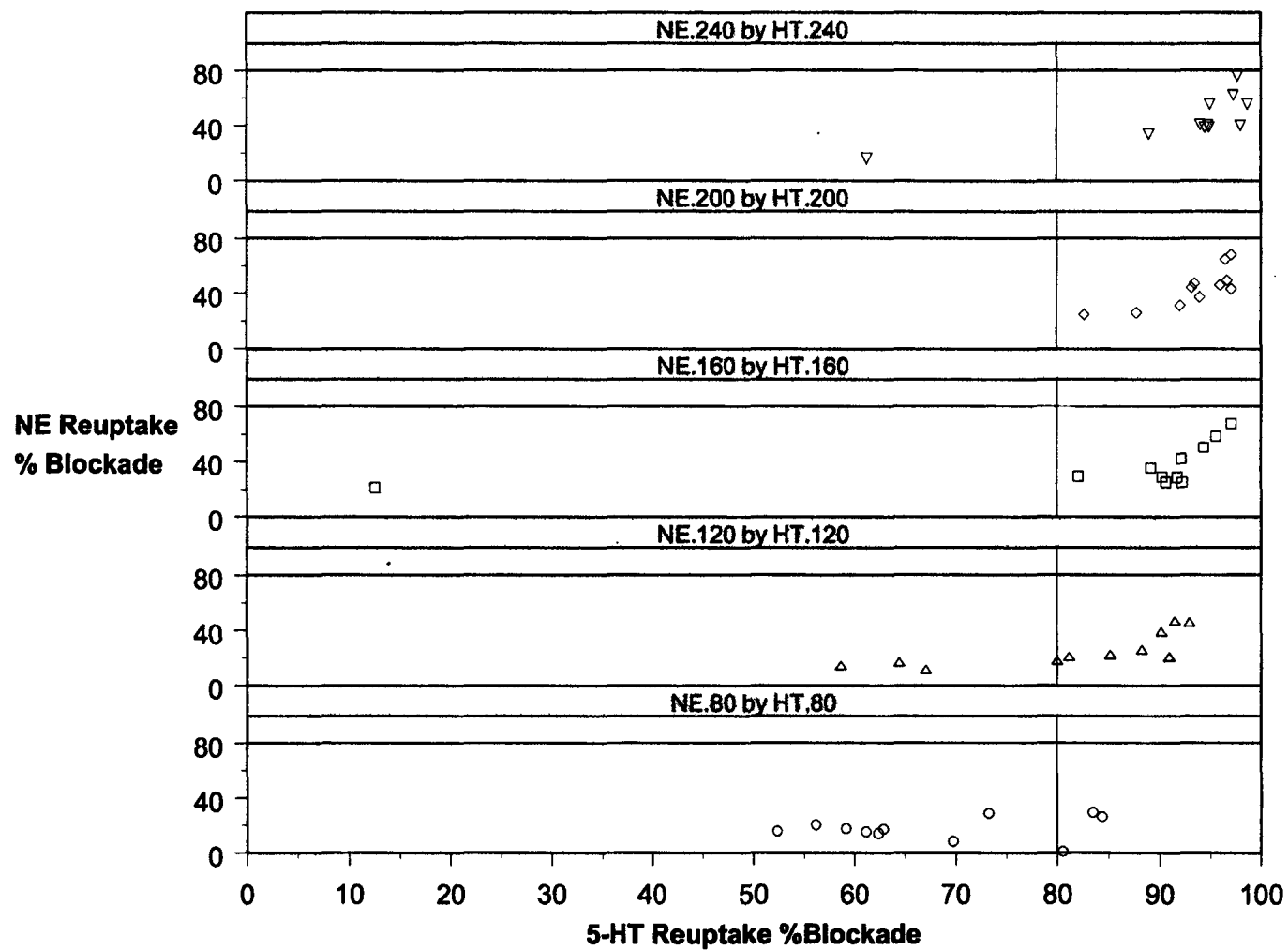
Extracts of plasma samples obtained at steady-state at 2 hours post-dose from subjects receiving duloxetine exhibit dose responses with respect blockade of serotonin and norepinephrine reuptake channels, and that the extract is relative more selective for serotonin blockade as compared with norepinephrine channel blockade, (see Table 17 and Figure 1).

Although these are 2 hours samples and therefore inhibition is unlikely to be maximal, if we assume that 80% blockade is needed to contribute to efficacy, then even doses higher than previously recommended are unlikely to contribute additional efficacy by either increased serotonin or norepinephrine channel blockade.

Table 17 Ex Vivo Serotonin and Norepinephrine Reuptake Channel Blockade by Dose - Study SBBN

Dose Level		0 mg (Baseline)	40 mg BID	60 mg BID	80 mg BID	100 mg BID	120 mg BID
N		12	12	12	12	12	11
Serotonin	Percent of Baseline Activity	104.3 ± 2.8 (2.6) 101.0 - 109.1 [103.1]	35.2 ± 10.7 (30.3) [38.8]	22.5 ± 11.1 (49.3) [19.4]	19.7 ± 22.4 (113.6) [13.6]	18.1 ± 26.2 (144.9) [10.4]	12.2 ± 10.2 (83.9) [8.2]
	Percent of Channels Blocked	—	69.1 ± 11.7 (17.0) [66.3]	81.7 ± 11.9 (14.6) [86.7]	84.6 ± 23.0 (27.2) [91.2]	86.2 ± 24.9 (28.9) [93.7]	92.2 ± 10.6 (11.5) [94.8]
Norepinephrine	Percent of Baseline Activity	102.8 ± 2.3 (2.2) 99.5 - 106.1 [103.1]	87.0 ± 8.3 (9.5) [86.8]	78.6 ± 11.4 (14.5) [80.3]	66.6 ± 14.2 (21.3) [74.4]	63.0 ± 18.5 (29.4) [59.1]	57.6 ± 15.9 (27.5) [61.0]
	Percent of Channels Blocked	—	15.7 ± 10.0 (63.4) [16.2]	24.2 ± 12.0 (49.4) [19.9]	36.2 ± 15.2 (42.0) [29.0]	39.8 ± 19.5 (48.9) [43.7]	45.1 ± 16.1 (35.6) [40.0]

Figure 1 *Ex Vivo* Serotonin and Norepinephrine Reuptake Channel Blockage by Dose - Study SBBN



5.6.2 IN VIVO PHARMACODYNAMICS

5.6.2.1 Plasma Catecholamines

Table 18 to Table 34 demonstrate a clear dose response relationship over a dose range of 40 mg BID to 120 mg BID on the plasma catecholamines epinephrine, norepinephrine, and DHPG, and that there is a greater effect at each dose level when subjects are upright as compared with laying down.

Table 18 Table SBBN.11.5. Summary Statistics for Plasma Catecholamine Epinephrine pg/ml Concentrations at Each Study Period for Duloxetine Treated Subjects (Posture Test)^a

Treatment Dose	N	Supine		Upright	
Pre-dose	15	17	(16.69)	48	(32.00)
80 mg	12	19	(7.31)	39	(21.08)
120 mg	12	23	(15.10)	43	(17.48)
160 mg	12	20	(17.91)	45	(34.06)
200 mg	12	41	(69.96)	43	(20.64)
240 mg	11	14	(5.12)	26	(10.69)

^a Values in parentheses not defined by sponsor

**APPEARS THIS WAY
ON ORIGINAL**

Table 19 Table SBBN.11.5. Summary Statistics for Plasma Norepinephrine Concentrations (pg/ml) at Each Study Period for Duloxetine Treated Subjects (Posture Test)^a

Treatment Dose	N	Supine		Upright	
Pre-dose	15	101	(51.47)	487	(211.94)
80 mg	12	125	(56.95)	568	(210.75)
120 mg	12	137	(46.10)	577	(192.65)
160 mg	12	164	(58.81)	589	(169.82)
200 mg	12	237	(146.08)	645	(183.31)
240 mg	11	203	(64.17)	744	(285.99)

^a Values in parentheses not defined by sponsor

Table 20 Table SBBN.11.6. Summary of Statistical Analysis of Norepinephrine Concentration Change from Predose for Placebo and Duloxetine Treated Subjects (Posture Test)

Supine					
Norepinephrine Baseline (pg/ml): 106.35					
Placebo			Duloxetine		
Treatment Period	% Change from Baseline	P-Value	Dose (mg)	% Change from Baseline	P-Value
I	-14.0	.680	80	20.4	.206
II	-21.2	.478	120	46.9	.001
III	-28.4	.338	160	73.3	<.001
IV	-35.5	.257	200	99.8	<.001
V	-42.7	0.227	240	126.2	<.001
Upright					
Norepinephrine Baseline (pg/ml): 451.55					
Placebo			Duloxetine		
Treatment Period	% Change from Baseline	P-Value	Dose (mg)	% Change from Baseline	P-Value
I	40.6	.325	80	78.7	.102
II	10.1	.751	120	119.6	.009
III	-20.4	.477	160	160.5	.001
IV	-50.9	.123	200	201.5	<.001
V	-81.4	.056	240	242.4	<.001

Table 21 Table SBBN.11.5. Summary Statistics for Plasma DHPG pg/ml Catecholamine Concentrations at Each Study Period for Duloxetine Treated Subjects (Posture Test)^a

Treatment Dose	N	Supine		Upright	
Pre-dose	15	805	(204.79)	1018	(273.47)
80 mg	12	690	(242.73)	828	(233.17)
120 mg	12	700	(217.86)	755	(214.15)
160 mg	12	700	(140.09)	671	(265.15)
200 mg	12	684	(224.11)	737	(246.84)
240 mg	11	630	(223.68)	677	(209.41)

a Values in parentheses not defined by sponsor

Table 22 Table SBBN.11.7. Summary of Statistical Analysis of DHPG Concentration Change from Predose for Placebo and Duloxetine Treated Subjects (Posture Test)

Supine					
DHPG Baseline (pg/ml): 850.36					
Placebo			Duloxetine		
Treatment Period	% Change from Baseline	P-Value	Dose (mg)	% Change from Baseline	P-Value
I	4.6	.961	80	-126.9	.006
II	-6.4	.944	120	-137.7	.002
III	-17.4	.845	160	-148.4	.001
IV	-28.4	.755	200	-159.2	<.001
V	-39.4	.680	240	-170.0	<.001
Upright					
DHPG Baseline (pg/ml): 1070.5					
Placebo			Duloxetine		
Treatment Period	% Change from Baseline	P-Value	Dose (mg)	% Change from Baseline	P-Value
I	59.9	.525	80	-262.8	<.001
II	20.1	.819	120	-291.9	<.001
III	-19.7	.820	160	-321.0	<.001
IV	-59.4	.512	200	-350.1	<.001
V	-99.2	.312	240	-379.2	<.001

Table 23 Table SBBN.11.5. Summary Statistics for Plasma Catecholamine Concentrations Ratio of DHPG to Norepinephrine at Each Study Period for Duloxetine Treated Subjects (Posture Test)

Treatment Dose	N	Supine	Upright
Pre-dose	15	10.7	2.34
80 mg	12	6.26	1.63
120 mg	12	5.50	1.46
160 mg	12	4.69	1.14
200 mg	12	3.45	1.19
240 mg	11	3.40	1.02

Table 24 Table SBBN.11.8. Summary of Statistical Analysis of Change from Predose for the Ratio of DHPG Concentration to Norepinephrine for Placebo and Duloxetine Treated Subjects (Posture Test)

Supine					
Baseline DHPG:Norepinephrine Ratio: 10.54					
Placebo			Duloxetine		
Treatment Period	% Change from Baseline	P-Value	Dose (mg)	% Change from Baseline	P-Value
I	0.8	.841	80	-4.4	<.001
II	1.7	.607	120	-5.2	<.001
III	2.5	.412	160	-5.9	<.001
IV	3.3	.321	200	-6.7	<.001
V	4.1	.322	240	-7.5	<.001
Upright					
Baseline DHPG:Norepinephrine Ratio: 2.67					
Placebo			Duloxetine		
Treatment Period	% Change from Baseline	P-Value	Dose (mg)	% Change from Baseline	P-Value
I	0.2	.584	80	-1.1	<.001
II	0.3	.088	120	-1.2	<.001
III	0.4	.020	160	-1.4	<.001
IV	0.5	.004	200	-1.5	<.001
V	0.6	.046	240	-1.7	<.001

5.6.2.2 Urine Catecholamines

According to the sponsor: 'Urinary excretion of norepinephrine increased significantly from the predose urinary excretion for all duloxetine doses. Additionally, the observed increase appears to be related to the dose of duloxetine.'

Table SBBN.11.12 summarizes the statistical analysis of the mean change in norepinephrine, epinephrine, DHPG and the ratio of DHPG to norepinephrine relative to the mean predose urinary excretion. The statistical analysis clearly showed a significant increase in mean norepinephrine concentrations and a decrease in the mean ratio between DHPG to norepinephrine with increasing duloxetine doses.'

(See Table 25)

Table 25 Table SBBN.11.12. Summary of Statistical Analysis of Change from Predose for Urine Catecholamines for Duloxetine Treated Subjects

Baseline Mean	N	Dose Level	Change from Baseline	P-Value
Norepinephrine(μg/g creatinine over 24-hour collection)				
23.59	12	80mg	8.97	0.03
	12	120mg	11.89	0.005
	12	160mg	14.80	0.0009
	12	200mg	17.71	0.0002
	11	240mg	20.62	<0.0001
Epinephrine(μg/g creatinine over 24-hour collection)				
1.55	12	80mg	0.94	0.06
	12	120mg	0.80	0.06
	12	160mg	0.66	0.10
	12	200mg	0.51	0.22
	11	240mg	0.37	0.45
DHPG (μg/g creatinine over 24-hour collection period)				
50.70	12	80mg	-10.02	0.06
	12	120mg	-9.69	0.05
	12	160mg	-9.35	0.05
	12	200mg	-9.01	0.07
	11	240mg	-8.67	0.10
Ratio DHPG to Norepinephrine over 24 hour collection period				
2.24	12	80mg	-1.04	<0.0001
	12	120mg	-1.08	<0.0001
	12	160mg	-1.13	<0.0001
	12	200mg	-1.17	<0.0001
	11	240mg	-1.22	<0.0001

5.6.2.3 Posture Test – Effect on Systolic Blood Pressure

Table 26 and Table 27 demonstrate a clear dose response relationship over a dose range of 40 mg BID to 120 mg BID on supine and standing systolic blood pressure. In addition, orthostatic hypotension appears to be occurring at around Tmax in a dose dependent manner at doses of 80 mg BID and above.

Table 26 Table SBBN.11.10. Summary of Statistical Analysis of Change from Predose for Systolic BP for Placebo and Duloxetine Treated Subjects (Posture Test)

Systolic BP Supine					
Baseline Supine Systolic BP (mm Hg): 109.78					
Placebo Group			Duloxetine Group		
Study Phase or Study Period	% Change from Baseline change	P-Value	Dosage	% Change from Baseline change	P-Value
I	-5.9	.002	80	5.3	.011
II	-5.2	<.001	120	6.4	.001
III	-4.4	<.001	160	7.6	<.001
IV	-3.7	<.001	200	8.7	<.001
V	-3.0	.067	240	9.8	<.001
Systolic BP Upright					
Baseline Upright Systolic BP (mm Hg): 105.99					
Placebo Group			Duloxetine Group		
Study Phase or Study Period	% Change from Baseline change	P-Value	Dosage	% Change from Baseline change	P-Value
I	3.0	.236	80	7.3	.005
II	3.4	.133	120	8.0	<.001
III	3.9	.105	160	8.7	<.001
IV	4.3	.075	200	9.4	<.001
V	4.7	.075	240	10.1	<.001

Table 27 Table SBBN.12.3. Mean (min, max) Supine Systolic Blood Pressure at Baseline and at 6 hrs Post First Dose for Study Periods of Duloxetine or Duloxetine Placebo Doses of 60 mg BID through 120 mg BID

Study Periods	Duloxetine Group									Placebo Group								
	n=12									n=3								
	Supine SBP			Standing SBP			Orthostatic SBP (Standing-Supine)			Supine SBP			Standing SBP			Orthostatic SBP (Standing-Supine)		
	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max
SCREENING	113.7			114.1			0.4			113.7			116.7			3.0		
ADMISSION	113.8			117.0			3.2			112.0			119.7			7.7		
	6-hrs Post First Dose																	
60 mg BID	121.0			119.8			-1.3			115.3			128.3			13.0		
80 mg BID	123.6			115.0			-8.6			108.3			119.7			11.3		
100 mg BID	120.1			110.4			-9.7			117.3			135.0			17.7		
120 mg BID	126.9			114.0			-13.2			114.3			126.7			12.3		

At single doses of less than or equal to 60 mg and at BID dosing of 40 mg BID or less, there does not appear to be any significant effect on systolic blood pressure, (see Table 28 and Table 29).

Table 28 Table SBAZ.14.36. Mean SBP for Part A Subjects (Single Doses)

Dose	Time Point	Caucasian			Japanese		
		N	Mean (SD) SBP (mmHg)	Mean Change from Predose (95% C.I.)	N	Mean (SD) SBP (mmHg)	Mean Change from Predose (95% C.I.)
20 mg	Predose	23	117 (13.9)	—	23	111 (9.22)	—
	Day2	20	115 (12.0)	-2.50 -8.49,3.49)	23	111 (10.0)	0.70 -3.92,5.31)
40 mg	Predose	23	116 (10.7)	—	23	113 (11.0)	—
	Day 2	23	112 (12.2)	-4.22 -9.80,1.36)	23	114 (9.22)	1.48 -2.36,5.32)
60 mg	Predose	24	112 (12.6)	—	24	111 (11.4)	—
	Day 2	22	116 (10.8)	5.18 -0.70,11.1)	24	111 (12.1)	-0.92 -6.77,4.93)

Day 2 values were taken 24 hr post-dose

Table 29 Table SBAZ.14.38. Mean SBP for Part B Subjects (Multiple Dosing)

Dose	Time Point	Caucasian			Japanese		
		N	Mean (SD) SBP (mmHg)	Mean Change from Predose (95% C.I.)	N	Mean (SD) SBP (mmHg)	Mean Change from Predose (95% C.I.)
Placebo	Predose	4	121 (8.5)	—	4	112 (15.3)	—
	Day 1	4	116 (4.8)	-5.0 (-25.5, 15.5)	4	110 (12.2)	-2.0 (-10.6, 6.6)
	Day 4	4	126 (9.5)	5.0 (-18.4, 28.4)	4	113 (9.6)	0.5 (-10.9, 11.9)
	Day 5	4	120 (14.1)	-1.3 (-35.9, 33.4)	4	111 (8.5)	-0.8 (-12.3, 10.8)
	Day 6	4	119 (11.8)	-2.5 (-34.7, 29.7)	4	111 (10.3)	-0.8 (-14.6, 13.1)
20 mg BID	Predose	8	116 (10.5)	—	8	115 (11.7)	—
	Day 1	8	124 (6.9)	8.0 (-2.5, 18.5)	8	116 (9.5)	1.3 (-9.7, 12.2)
	Day 4	8	127 (7.0)	11.1 (2.5, 19.8)	8	124 (9.8)	9.4 (4.1, 14.7)
	Day 5	8	129 (13.6)	13.0 (-1.9, 27.9)	8	124 (15.1)	8.8 (-1.8, 19.3)
	Day 6	8	117 (10.3)	1.1 (-12.8, 15.1)	8	120 (13.5)	4.8 (-5.9, 15.4)
40 mg BID	Predose	8	114 (9.7)	—	8	110 (8.1)	—
	Day 1	8	118 (11.0)	3.9 (-0.6, 8.3)	8	118 (11.9)	8.0 (-0.1, 16.1)
	Day 4	8	128 (12.0)	13.9 (4.3, 23.4)	8	121 (10.8)	10.4 (4.9, 15.9)
	Day 5	8	126 (10.6)	12.6 (7.9, 17.4)	8	123 (9.7)	12.6 (7.0, 18.3)
	Day 6	8	121 (8.3)	7.3 (0.0, 14.5)	8	117 (9.4)	6.3 (0.6, 11.9)

Day 1 values were taken 6 hr post-dose.

Day 4 values were taken at admission in the evening.

Day 5 values were taken 6 hr post-dose.

Day 6 values were taken before discharge, 24 hr post-dose.