CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-323

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

Escitalopram Tablets (5, 10 and 20 mg)

Forest Laboratories, Jersey City, NJ 07311

NDA 21-323

Reviewer: Iftekhar Mahmood, Ph. D.

Submission Date: March 23, 2001

Received by OCPB: March 28, 2001

Indication: Antidepressant

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45 Day File-Refuse to File Meeting

This is 505(b)(1) submission. This NDA consists of 72 volumes. There are 8 pharmacokinetic study reports. Citalopram is a racemic mixture and is indicated for the management of depression. Citalopram was approved by the FDA on July 17, 1998. Most of the pharmacological activity lies in the S-enantiomer of citalopram. Therefore, the Sponsor, Forest Laboratories, are now planning to market escitalopram as an antidepressant and have submitted the following studies:

1. Two comparative bioavailability and bioequivalence studies.

a. A single-dose 20 mg escitalopram (clinical vs commercial) BE study.

b. A single-dose (20 mg), randomised, four way crossover study.

Treatment A – Lundbeck (HLu) marketing formulation, 4x5 mg tablets

Treatment B – HLu marketing formulation, 1x20 mg tablets

Treatment C – HLu clinical formulation, 2x10 mg tablets

Treatment D – Forest (FRX) clinical formulation, 2x10 mg tablets.

2. A Single dose pharmacokinetic study comparing 40-mg racemic citalopram with 20-mg escitalopram.

3. A multiple dose pharmacokinetic study comparing 20 mg and 60-mg racemic citalopram with 10 mg and 30-mg escitalopram.

4. A multiple dose study comparimg pharmacokinetics of escitalopram in healthy elderly and young subjects.

5. Three drug interaction studies:

a. Interaction of escitalopram or fluoxetine with desipramine in young healthy subjects.

b. Interaction of metoprolol with escitalopram or paroxetine in young healthy subjects.

c. Interaction of escitalopram with ritonavir in young healthy subjects.

6. In-vitro drug metabolism study (published papers).

7. Concentration-response relationship. Attempts were made to relate the primary efficacy parameter, Montgomery Asberg Depression Rating Scale (MADRS) with one plasma concentration on week 8 using Pearson correlation coefficient.

8. In-vitro dissolution study on 5, 10 and 20 mg tablets.

9. Formulations used in the studies.

10. Analytical methods.

In addition, the Sponsor, requests in-vivo bioequivalence waiver for 10 mg escitalopram commercial tablets. These commercial tablets were manufactured by Forest Laboratories (Ireland), whereas10 mg escitalopram tablets used in clinical studies were manufactured at

Recommendation:

This NDA is fileable.

Iftekhar Mahmood, Ph.D.

RD/FT initiated by Raman Baweja, Ph.D. ______________________________

cc: HFD-120, HFD-860 (Mahmood, Baweja, Sahajwalla, Mehta).

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Table 6-1. Summary of Escitalopram Studies

Protocol/Report No.	*Protocol Title*	*Investigator Location Date*	*Objectives*	*Design*	*No. of Subjects*	*Results*
I. BIOEQUIVALENCE/BIOAVAILABILITY STUDIES						
SCT-PK-04	A Single-Dose, Open Label, Randomized, Three-Way Crossover, Bioequivalence Study Comparing Lu 26-054 Tablets (20 mg) Used in Clinical Studies Administered in the Fasted State with Lu 26-054 Tablets (20 mg) Intended for Commercial Use Administered in the Fasted and Fed State in Human Volunteers	James Carlson Fargo, ND USA 2000	To compare the rate and extent of absorption of 20 mg escitalopram tablets intended for commercial use to 20 mg escitalopram tablets used in clinical studies and to document the bioequivalence of these products	Open-label, single dose, randomized, three-way crossover, bioequivalence study	18 healthy young male and female subjects	Based on the 90% confidence intervals for the pharmacokinetic parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} for escitalopram, bioequivalence was demonstrated between the 20 mg escitalopram tablets intended for commercial use and the 20 mg escitalopram tablets presently being used in clinical studies. No food effect was observed for the commercial formulation.
98113	An Open, Single-Dose (20 mg), Randomized, Four-Way Crossover Study in Healthy Volunteers, Investigating Bioequivalence of Four Different Formulations of Lu 26-054: 5 and 20 mg Tablets, Lundbeck Marketing Formulation; 10 mg Tablets, Lundbeck Clinical Formulation; and 10 mg Tablets, Forest Clinical Formulation.	D. Wilbraham GDRU Limited United Kingdom 2000	To compare the serum pharmacokinetics of escitalopram and the demethylcitalopram metabolite (S-DCT) after a single dose (20 mg) administration of 4 different formulation of escitalopram: 5 and 20 mg Tablets, Lundbeck Marketing Formulation; 10 mg Tablets, Lundbeck Clinical Formulation; and 10 mg Tablets, Forest Clinical Formulation.	single center, single dose, open, randomized, four-way crossover study	16 healthy male subjects	H. Lundbeck marketing formulations (5 and 20 mg tablets), were found to be bioequivalent to the H. Lundbeck escitalopram clinical formulation (10 mg tablet) with respect to escitalopram and S-DCT in healthy male subjects. The H. Lundbeck clinical formulation (10 mg tablet) was bioequivalent to the Forest escitalopram clinical formulation (10 mg tablet). The other pharmacokinetic parameters, T_{max}, t½, metabolic ratio, CL/F, and Vz/F were also not significantly different between formulations.

Table 6-1. Summary of Escitalopram Studies

Protocol/Report No.	Protocol Title	Investigator Location Date	Objectives	Design	No. of Subjects	Results
II. PHARMACOKINETIC STUDIES: ADME (ABSORPTION, DISTRIBUTION, METABOLISM AND ELIMINATION) STUDIES						
98106	A Single-dose, Crossover, Open Label Pharmacokinetic Study Comparing Racemic Citalopram (40 mg Tablet) with S-Citalopram (20 mg Tablet) in Human Volunteers	Erik van der Worp Zuidlaren, The Netherlands 1998	To compare the pharmacokinetics of escitalopram in plasma and urine after a single dose of 40 mg racemic citalopram (CT) hydrobromide and after a single dose of 20 mg escitalopram tablets; to examine whether interconversion occurs from escitalopram to R-citalopram.	Open label, single center, single dose, crossover study	24 healthy male subjects; 9 female subjects were also dosed in the first period (5, racemic citalopram; 4, escitalopram)	Following administration of a single dose of 20 mg escitalopam tablet, peak plasma escitalopran concentrations (ca. 19 ng/mL) were achieved at 3 hours. The half-life of escitalopram was ca. 27 hours. These parameters were similar to those obtained with the 40-mg racemic citalopram dose. The 20-mg escitalopram tablet was bioequivalent to the 40-mg racemic CT tablet. No interconversion from escitalopam to the R enantiomer occurred after single dose.
98107	A Multiple Dose Two-way Crossover Double-blind Study Comparing the Pharmacokinetics and Tolerability of S-citalopram (Lu 26-054) (oral capsules, 10 mg/day and 30 mg/day) and Racemic Citalopram (Lu 10-171) (oral capsules, 20 mg/day and 60 mg/day) in Two Panels of Human Healthy Volunteers	Jolanda van de Logt Utrecht, The Netherlands 1999	To compare the pharmacokinetics of escitalopram and its metabolites, following multiple dose administration of escitalopram and multiple dose administration of racemic CT (two dose levels: 10 and 30 mg/day escitalopram vs. 20 and 60 mg/day racemic CT); to examine whether interconversion occurs from escitalopram to R-citalopram.	single center, double blind, randomized, multiple dose two-way crossover study	36 healthy young male and female subjects	Following administration of multiple doses of 10 or 30 mg escitalopram tablets, peak plasma escitalopram concentrations were achieved at ca. 4 hours. The half-life of escitalopram was ca. 31 hours. The 10-mg escitalopram tablet was bioequivalent to the 20-mg racemic tablet. The escitalopram levels from the 30-mg escitalopram tablets were slightly lower than those of the 60-mg racemic CT tablets (90% CI: C_{max} 79.5-88.2, AUC 78.9-90.6). No interconversion from escitalopram to the R enantiomer occurred after multiple dose.

Table 6-1. Summary of Escitalopram Studies

Protocol/Report No.	*Protocol Title*	*Investigator Location Date*	*Objectives*	*Design*	*No. of Subjects*	*Results*
II. PHARMACOKINETIC STUDIES: EFFECTS OF AGE						
SCT-PK-05	A Multiple Dose Pharmacokinetic Study of Lu 26-054 in Healthy Elderly and Young Subjects	Albert Cohen Miami, FL USA 2000	To measure the pharmacokinetics of escitalopram and its metabolites S-DCT and S-DDCT following administration of escitalopram in young and elderly healthy male and female volunteers.	Open label, multiple dose	36 (9 young males, 9 young females, 9 elderly males and 9 elderly females)	**Escitalopram C_{max} was approximately 34% higher and the $AUC_{0-\infty}$ was approximately 50% larger in the elderly compared to the young subjects. The t½ values in the elderly were longer compared to the young subjects (41.0 vs. 27.3 h). No gender effects were observed.**
II. PHARMACOKINETIC STUDIES: INTERACTION WITH OTHER DRUGS						
SCT-PK-01	A Comparison of the Pharmacokinetic Interaction of Lu 26-054 or fluoxetine with Desipramine in Healthy Young Subjects	Larita Frazier-O'Bannon Cincinnati, OH USA 2000	To compare the effects of escitalopram and fluoxetine on desipramine pharmacokinetics in humans.	Double blind, single-center, parallel, multiple dose, randomized study	40 young healthy male and female subjects (20 in each group)	**Escitalopram increased the C_{max}, AUC, T_{max}, and t½ of desipramine by 41%, 107%, 10% and 41%, respectively. The corresponding effects of fluoxetine on these parameters were 83%, 311%, 14% and 170%. Despite the increases in concentrations of desipramine after escitalopram or fluoxetine treatment, there were no clinically significant changes observed in psychomotor function, visual analog scales and Pittsburgh Sleep Quality Index.**

Table 6-1. Summary of Escitalopram Studies

Protocol/Report No.	Protocol Title	Investigator Location Date	Objectives	Design	No. of Subjects	Results
SCT-PK-02	A Pharmacokinetic Study of the Combined Administration of Lu 26-054 and Ritonavir in Healthy Young Subjects	Maria Gutierrez Ft. Lauderdale, FL USA 2000	To evaluate the pharmacokinetic interaction of a single dose of ritonavir (600 mg) and a single dose of escitalopram (20 mg) in healthy young subjects.	Single center, open label, randomized, three-way crossover study	18 young healthy male and female subjects	Coadministration of a single dose of ritonavir and escitalopram did not affect the pharmacokinetics of escitalopram or ritonavir compared to when ritonavir or escitalopram were administered alone.
SCT-PK-03	A Comparison of the Pharmacokinetic Interaction of Metoprolol with Lu 26-054 or Paroxetine in Healthy Young Subjects	Krishna Talluri Morrisville, NC USA 2000	To compare the effects of paroxetine (40 mg) with those of escitalopram (20 mg) on the pharmacokinetics of metoprolol (100 mg) in healthy young subjects	Double blind, parallel, randomized, multiple dose study	28 young healthy male and female subjects (14 in each group).	Coadministration of escitalopram caused an increase in metoprolol C_{max} (75%), T_{max} (40%), AUC (127%) and t½ (46%) and a decrease in CL/F (48%). The effects of paroxetine were significantly larger than those of escitalopram. There were no resultant effects on cardiovascular dynamics from the coadministration of multiple doses of either SSRI with a single dose of metoprolol.
III. OTHER STUDIES						
SCT-MD-01	Fixed Dose Comparison of the Safety and Efficacy of Lu 26-054, Citalopram, and Placebo in the Treatment of Major Depressive Disorder	Multiple sites, 2000	To evaluate the safety and efficacy of escitalopram 10 and 20 mg/day compared to placebo in the treatment of depression.	Double-blind, parallel, randomized, 8-week, fixed dose study	155 evaluable patients	There was no significant relationship between escitalopram concentration and the decrease in MADRS score.

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Iftekhar Mahmood
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BIOPHARMACEUTICS

Raman Baweja
5/17/01 10:08:25 AM
BIOPHARMACEUTICS

Escitalopram Oxalate Tablets (5, 10 and 20 mg)
Forest Laboratories, Jersey City, NJ 07311
NDA 21-323
Reviewer: Iftekhar Mahmood, Ph. D.
Submission Date: March 23, 2001
Received by OCPB: March 28, 2001
Indication: [redacted]

SUMMARY

Escitalopram is s-enantiomer of racemic citalopram which was approved in 1998 under NDA 20-822. This NDA consists of four 8-week placebo controlled multicenter, double-blind, parallel group, fixed or flexible dose clinical trials in adults with depression. There are 9 clinical pharmacology studies containing bioequivalence studies which link clinical to 'to be marketed' tablets, pharmacokinetic studies which show no interconversion between enantiomers, effect of food, age and gender, and interaction studies with metoprolol, desipramine and ritonavir.

Escitalopram oxalate is an orally administered selective serotonin reuptake inhibitor. The pharmacological effect of citalopram resides in the S-enantiomer. Escitalopram is twice as potent as racemic citalopram and more than 100 fold more potent than R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. Molecular formula of escitalopram is $C_{20}H_{21}FN_2O.C_2H_2O_4$ and its molecular weight is 414. Escitalopram is a white to slightly yellow powder and is sparingly soluble in water.

Following a single 20 mg oral dose of escitalopram, the mean C_{max} and T_{max} were 21 ng/mL and 5 hours, respectively. Absorption of escitalopram is not affected by food. The oral clearance of escitalopram is 600 mL/min and the renal clearance is less than 10% of the oral clearance (approximately 42 mL/min). The elimination half-life of escitalopram is about 25 hours. Following multiple once daily dosing, steady state is reached within one week. The accumulation ratio was 3.3 in young healthy subjects. There was no evidence of interconversion from the S- to the R- enantiomer following single and multiple dosing.

After a single dose, the pharmacokinetics of escitalopram was similar between young and the elderly (>65 years). At steady state, however, the AUC and half-life of

escitalopram were increased by 50% in the elderly as compared to the young. There was no effect of gender on the pharmacokinetics of escitalopram.

The major metabolites of escitalopram are s-desmethylcitalopram (DCT) and s-didesmethylcitalopram (DDCT). CYP3A4 and CYP2C19 are major isozymes involved in the N-demethylation of escitalopram. Escitalopram and S-DCT produced negligible inhibitory effect on 1A, 2C9, 2C19, 3A4, and 2E1 in vitro. However, in-vivo studies with CYP2D6 substrates (metoprolol and desipramine) indicated that escitalopram has inhibitory effect on CYP2D6. Co-administration of escitalopram (20 mg/day for 21 days) with metoprolol (single dose of 100 mg) or desipramine (single dose of 50 mg) increased the AUC of metoprolol by 82% and desipramine by 100%.

Co-administration of escitalopram (20 mg) with ritonavir (600 mg), produced no effect on the pharmacokinetics of ritonavir or escitalopram.

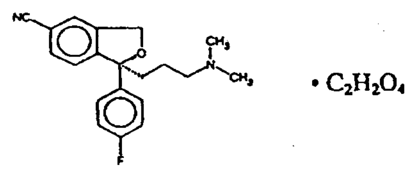
No relationship between plasma concentration and efficacy (change in MADRS score from baseline) was found (Pearson correlation coefficient = -0.43) over the dose range of 10 to 20 mg of escitalopram.

FDA's proposed dissolution method and specification for escitalopram oxalate tablets for all three strengths is as follows:
Apparatus 2 at 50 rpm, 900 mL, 0.1 N HCl at 37^{0}C
Q = [redacted] at 30 minutes.

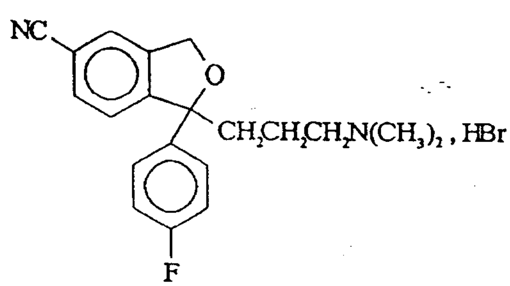
Pharmacokinetics of racemic citalopram:
Absolute bioavailability = 80%
Cmax = 42 ng/mL (single oral dose of 30 mg tablet)
Tmax : 1 to 6 hours
Vss = 12.3 L/kg.
Systemic clearance = 330 mL/min
Renal clearance = 60 mL/min
Plasma protein binding = 82%
Elimination half-life = 35 hours
Dose linearity = 10-60 mg

Food has no effect on the pharmacokinetics of citalopram tablets.

The major metabolites of citalopram are desmethylcitalopram (DCT) and didesmethyl citalopram (DDCT). Minor metabolites of citalopram are N-Oxide and propionic acid. CYP3A4 and CYP2C19 are major isozymes involved in the N-demethylation of citalopram.



Escitalopram Oxalate



Citalopram Hydrobromide

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Study #1

Title:A single-dose, open label, randomized, three-way crossover, bioequivalence study comparing escitalopram tablets (20 mg) used in clinical studies administered in the fasted state with escitalopram tablets (20 mg) intended for commercial use administered in the fasted and fed state in human volunteers (SCT-PK-04).

The objective of the study was to compare the rate and extent of absorption of 20 mg escitalopram tablets intended for commercial use to 20 mg escitalopram tablets used in clinical studies. The study also assessed the effect of food on the pharmacokinetics of escitalopram tablets intended for commercial use.

This was an open-label, single dose, randomized, three-way crossover, study in 18 healthy young subjects (8 males and 10 females, 18 to 33 years of age). Subjects received each of the following three treatments in a randomized order, separated by an interval of 14 days.

Treatment A: a single oral dose of 20 mg escitalopram tablets intended for commercial use administered in the fasted state (batch # 3395).

Treatment B: a single oral dose of 20 mg escitalopram tablets intended for commercial use administered in the fed state (batch # 3395).

Treatment C: a single oral dose of 20 mg escitalopram tablets (clinical formulation) administered in the fasted state (batch # 99034C).

Subjects who received Treatments A and C were fasted for at least 10 hours prior to dose and for another 4 hours after the dose. Subjects who received Treatment B were fasted for ten hours and then given a standardized high-fat breakfast on the day of dosing. Subjects consumed their breakfast within half an hour and then the drug was administered. All subjects consumed 240 mL of water with each dose.

For Treatment B, a standard high fat (50% of total caloric content of the meal), high calorie (approximately 1000 calories) breakfast was provided and included 2 eggs fried in butter, 2 bacon strips, 2 slices of toast with butter, 4 ounces of hash brown potatoes and 8 ounces of whole milk (i.e., approximately 150 protein calories, 250 carbohydrate calories, 500-600 fat calories).

Blood samples (7mL each) for the determination of escitalopram and its metabolite (s-demethylcitalopram) in plasma were collected from each subject at time 0 (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours.

The concentrations of s-citalopram and s-demethylcitalopram in plasma were determined by a
using 0.5 mL plasma. The limit of quantification was for both s-citalopram and s-demethylcitalopram.

Seventeen subjects completed the study. The results of the study have been summarized in Tables 1 and 2. Based on the 90% confidence interval on log transformed AUC and Cmax, the results of the study indicated that the 20 mg escitalopram tablets intended for commercial use and the 20 mg escitalopram tablets used in clinical studies are bioequivalent.

Fasting: (Cmax 98-115 %, AUC0-inf 95-112 %)

Food did not exert any effect on the pharmacokinetics of escitalopram.

Fed: (Cmax 100-118%, AUC0-inf 99-116 %).

Table 1. **Pharmacokinetic Parameters (Mean ± SD) of Escitalopram Following All Active Treatments**

PK Parameters	*Treatment A (N=17)*	*Treatment B (N=17)*	*Treatment C (N=17)*	*A vs C*		*B vs A*	
				Mean Ratio	*90% CI*	*Mean Ratio*	*90% CI*
C_{max}(ng/mL)	21.1 ± 4.7	23.3 ± 6.7	20.2 ± 5.9	1.04	98-115	1.10	100-118
AUC_{0-t} (ng•hr/mL)	571.8 ± 215.7	607.2 ± 218.8	564.9 ± 234.9	1.01	94-112	1.06	98-116
AUC_{0-inf} (ng•hr/mL)	622.7 ± 224.8	664.0 ± 224.7	613.6 ± 247.1	1.01	95-112	1.06	99-116
				A vs. C P Value		*B vs. A P Value*	
T_{max} (hr)	4.4 ± 1.1	4.8 ± 1.2	5.0 ± 1.5	0.0535		0.2075	
T½ (hr)	23.4 ± 6.1	24 ± 5.0	23.6 ± 5.4	0.7974		0.3735	
CL/F (L/hr)	36.2 ± 13.0	33.8 ± 12.6	37.9 ± 15.2	0.3767		0.2072	
Vz/F (L)	1125.1 ± 180.0	1099.5 ± 221.1	1202.4 ± 318.5	0.1963		0.6056	

Treatment A = commercial fasted
B = commercial fed
C = clinical fasted

Table 2 **Pharmacokinetic Parameters (Mean ± SD) of S-DCT Following All Active Treatments**

PK Parameters	*Treatment A*	*Treatment B*	*Treatment C*	*A vs. C*		*B vs. A*	
	(N=17)	*(N=17)*	*(N=17)*	*Mean Ratio*	*90% CI*	*Mean Ratio*	*90% CI*
C_{max}(ng/mL)	3.3 ± 0.7	3.0 ± 0.5	3.1 ± 0.7	1.06	96-115	0.91	93-112
AUC_{0-t} (ng•hr/mL)	250.0 ± 60.5	228.6 ± 46.9	239.3 ± 79.9	1.04	93-127	0.91	79-108
AUC_{0-inf} (ng•hr/mL)	353.1 ± 56.2	338.0 ± 53.7	334.8 ± 77.3	1.05	95-113	0.96	88-105
				A vs. C P Value		*B vs. A P Value*	
T_{max} (hr)	20.7 ± 15.0	26.2 ± 14.0	20.7 ± 12.7	0.8968		0.2066	
T½ (hr)	58.0 ± 13.7	57.1 ± 10.5	60.7 ± 13.1	0.3083		0.7297	

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Figure . *Plasma Concentration (Mean±SD) of Escitalopram* Following Administration of 20 mg commercial tablet (fed & fasted) and 20 mg Tablet Used in Clinical Studies in Healthy Young Male and Female Subjects.

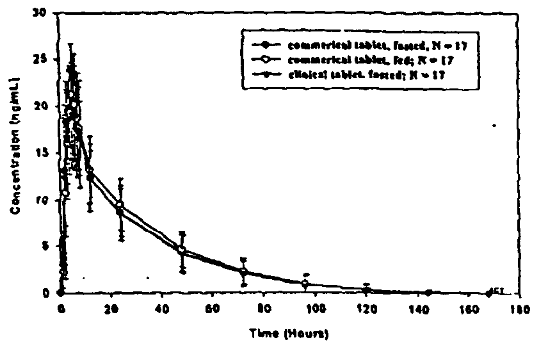

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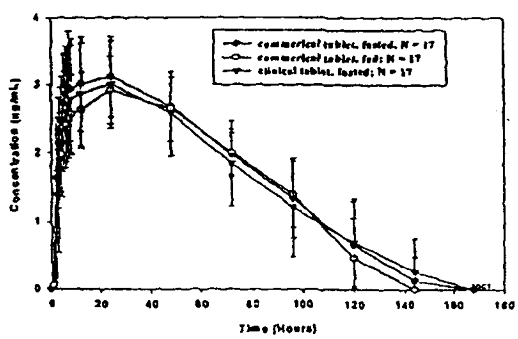
Figure . Plasma Concentration (mean±SD) of S-DCT after Administration of 20 mg Commercial Tablet (fed & fasted) and 20 mg Tablet Used in Clinical Studies in Healthy Young Male and Female Subjects



Study #2

Title: An open, single-dose (20mg), randomized, four-way crossover study in healthy volunteers, investigating bioequivalence of four different formulations of Lu 26-054:5 and 20mg tablets, Lundbeck marketing formulation; 10 mg tablets, Lundbeck clinical formulation; and 10mg tablets, Forest clinical formulation (Study# GCP98113)

The objective of the study was to demonstrate bioequivalence of four different formulations of escitalopram, administered as a single dose of 20mg. This was a single-centre, open-label, four-way crossover study in 16 healthy men (18 to 45 years of age, 4 subjects per sequence). Each treatment was separated by a washout period of 2 weeks. The following formulations were used in this study:

Treatment A - Lundbeck (HLu) marketing formulation, 4x5 mg tablets, batch no. PD 1286.

Treatment B - HLu marketing formulation. 1x20mg tablet, batch no. PD 1293.

Treatment C - HLu clinical formulation, 2x10mg tablets, batch no. PD 1282

Treatment D: Forest (FRX) clinical formulation, 2x10 mg tablets, batch no. R 268.

The bioequivalence was tested between the following treatments:

Treatment A (test) versus Treatment C (reference)

Treatment B (test) versus Treatment C (reference)

Treatment C (test) versus Treatment D (reference)

Blood samples (7mL each) for the determination of escitalopram and its metabolite (s-demethylcitalopram) in serum were collected from each subject at time 0, 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours. The concentrations of citalopram and s-demethylcitalopram in serum were determined by a

using 1 mL serum. The limit of quantification was for both escitalopram and s-demethylcitalopram.

The results of this study have been summarized in Tables 3 and 4. Based on the 90% confidence interval on log transformed AUC and Cmax, the results of the study indicated that all four formulations of escitalopram tablets are bioequivalent.

The study showed that H.Lundbeck escitalopram market formulations (5 and 20 mg tablets) were bioequivalent to the H.Lundbeck escitalopram clinical formulation (10 mg tablet). Furthermore, the H.Lundbeck clinical formulation (10 mg tablet) was bioequivalent to the Forest escitalopram clinical formulation (10 mg tablet).

Table ~~6-24:~~3 Pharmacokinetic Parameters of Escitalopram and S-DCT Following Single Dose Administration of H/Lu Marketing 4x5 mg Tablet, H/Lu Marketing 1 x 20 mg Tablet, Lundbeck Clinical 2 x 10 mg Tablet and Forest Clinical 2 x 10 mg Tablet in Young Healthy Male Subjects

Parameter	H/Lu Marketing 4 x 5 mg Tablet (n = 15)	H/Lu Marketing 1 x 20 mg Tablet (n = 14)	H/Lu Clinical 2 x 10 mg tablet (n = 15)	Forest Clinical 2 x 10 mg tablet (n = 15)
ESCITALOPRAM				
C_{max} (ng/mL)	19.2 ± 4.1	20.0 ± 4.2	19.3 ± 3.4	19.6 ± 4.2
T_{max} (hours)	2.3 ± 0.7	2.1 ± 0.7	2.6 ± 0.8	2.8 ± 1.1
AUC_{0-t} (ng•hr/mL)	470.7 ± 147.0	463.6 ± 110.3	464.2 ± 110.0	498.6 ± 148.9
$AUC_{0-\infty}$ (ng•hr/mL)	522.6 ± 151.5	513.5 ± 110.9	510.0 ± 110.6	546.9 ± 151.2
t½ (hours)	24.2 ± 4.2	25.2 ± 4.0	24.1 ± 3.3	25.4 ± 3.8
CL/F (L/hr)	41.5 ± 12.5	40.7 ± 9.1	41.0 ± 9.0	39.5 ± 11.8
Vz/F (L)	1386 ± 223	1450 ± 237	1405 ± 275	1403 ± 291
S-DEMETHYLCITALOPRAM				
C_{max} (ng/mL)	3.7 ± 0.8	3.5 ± 0.7	3.6 ± 0.7	3.5 ± 0.7
T_{max} (hours)	18.9 ± 11.4	13.5 ± 10.6	18.7 ± 13.2	15.2 ± 11.5
AUC_{0-t} (ng•hr/mL)	277.5 ± 43.1	265.4 ± 34.1	264.8 ± 44.4	273.5 ± 41.9
$AUC_{0-\infty}$ (ng•hr/mL)	366.3 ± 52.5	364.1 ± 37.2	357.0 ± 42.8	367.2 ± 45.6
t½ (hours)	53.6 ± 7.8	55.4 ± 6.0	53.1 ± 6.8	54.9 ± 8.1
MR	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2

Table ~~6-25:~~4 Relative Bioequivalence of Escitalopram and S-Demethylcitalopram Using Different Escitalopram Treatments in Healthy Young Male Subjects

Parameter	Escitalopram Mean Ratio	Escitalopram 90% Confidence Intervals	S-Demethylcitalopram Mean Ratio	S-Demethylcitalopram 90% Confidence Intervals
Comparison of H/Lu Marketing 4x5 mg Tablet (Test, Treatment A) and H/Lu Clinical 2 x 10 mg Tablet (Reference, Treatment C)				
C_{max}	1.021	94.7 – 110.1	0.961	92.5 – 99.9
$AUC_{0-\infty}$	0.997	94.3 – 105.5	0.976	93.4 – 102.0
AUC_{0-t}	1.011	94.9 – 107.8	0.945	90.5 – 98.8
Comparison of H/Lu Marketing 1x20mg Tablet (Test, Treatment B) and H/Lu Clinical 2 x 10 mg Tablet (Reference, Treatment C)				
C_{max}	0.962	89.2 – 103.7	0.992	95.4 – 103.1
$AUC_{0-\infty}$	0.995	94.0 – 105.3	0.970	92.8 – 101.3
AUC_{0-t}	1.004	94.2 – 106.9	0.979	93.7 – 102.3
Comparison of H/Lu Clinical 2 x 10 mg Tablet (Test, Treatment C) and Forest Clinical 2 x 10 mg Tablet (Reference, Treatment D)				
C_{max}	0.980	90.9 – 105.7	1.023	98.4 – 106.4
$AUC_{0-\infty}$	1.027	97.0 – 108.7	1.028	98.4 – 107.5
AUC_{0-t}	1.024	96.1 – 109.1	1.044	99.9 – 109.1

Figure 3 Mean Plasma Escitalopram Concentrations (ng/mL) Following Administration of Four Different Formulations of Escitalopram Tablets in Healthy young Male Subjects

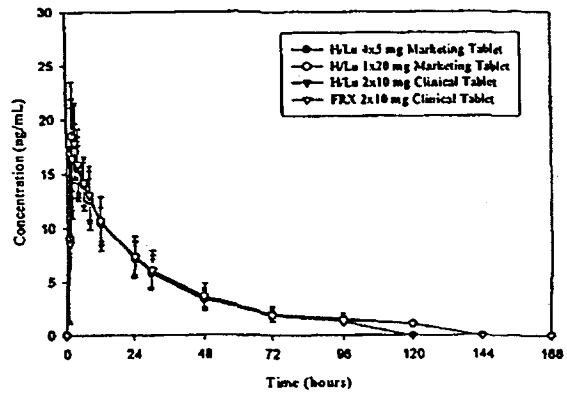
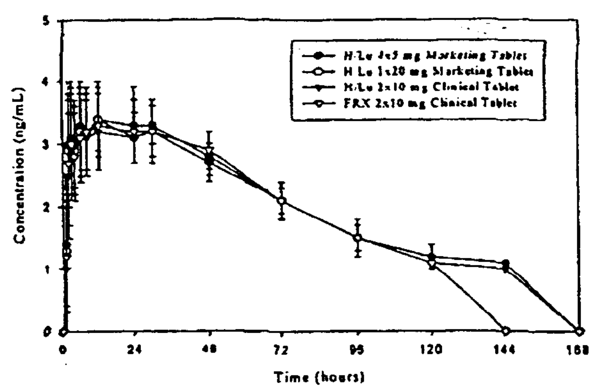


Figure 4 Mean Plasma S-DCT Concentrations (ng/mL) Following Administration of Four Different Formulations of Escitalopram Tablets in Healthy young Male Subjects.



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Study #3

Title: A single-dose, cross-over, open label pharmacokinetic study comparing racemic citalopram (40 mg tablet with S-citalopram 20 mg tablet in human volunteers) (Study GCP # 98106).

The objective of this study was to compare the pharmacokinetics of S-CT, R-CT and the metabolites demethylcitalopram (S-DCT and R-DCT) and didemethylcitalopram (S-DDCT and R-DDCT) following a single oral dose of a 40 mg racemic citalopram tablet or a single oral dose of a 20 mg S-citalopram tablet to healthy male and female subjects. The secondary objective was to examine whether interconversion occurs from S-CT to R-CT in humans.

The study was a single-centre, Phase I, single dose, open-label, randomised study with a two-sequence, two-treatment, two-period cross-over design. The study was originally planned to include 24 healthy volunteers (I2 males and 12 females), aged between 18 and 45 years. Due to delayed results of a toxicity study the clinical protocol was amended to include only male subjects and more female subjects were not enrolled in the study. At that time 9 females had already been enrolled and had received a single dose of study medication (5 racemic citalopram, 4 S-citalopram). More male subjects were enrolled in order to obtain a sample size of 24 for statistical comparisons. There was a 21-day washout period between two treatments.

Blood samples from each subject were drawn at time 0,1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours after dosing. Urine samples were collected from 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, and then at 24 hours interval till 168 hours. Plasma samples were assayed for R-citalopram, S-citalopram, R-demethylcitalopram, S-demethylcitalopram, R-didemethylcitalopram and S-didemethylcitalopram using a validated LC/MS/MS method. The limit of quantification for citalopram and its metabolites using 0.5 mL of plasma was [redacted] . In urine the limit of quantification was [redacted] .

Pharmacokinetics of S-CT:

Following 40 mg racemic citalopram (CT) and 20 mg escitalopram (S-CT), the pharmacokinetic parameters (Cmax, AUC, t1/2 and CL) for S-citalopram were comparable in male subjects. The Cmax of S-CT following CT and S-CT was 21.1 ± 5.5 ng/mL and 18.8 ± 4.5 ng /mL, respectively. The tmax was 3 hours following the administration of CT or S-CT. The AUC(0-inf) of S-CT following CT and S-CT was 685 ± 376 ng*hr/mL and 637 ± 356 ng*hr /mL, respectively. The half-life of S-CT was 26 hours following the administration of CT or S-CT (Table 5).

The AUC of S-DCT was approximately 2 times less than the AUC of S-CT, whereas the half-life of S-DCT was twice than the half-life of S-CT (Table 5). S-didemethylcitalopram (S-DDCT) levels were below quantification limits.

The renal clearance of S-CT was approximately 43 mL/min following the administration of CT or S-CT. About 8% of S-CT was excreted unchanged in the urine. The renal clearance of S-DCT was approximately 113 mL/min following the administration of CT or S-CT. About 10% of S-DCT was excreted unchanged in the urine (Table 7).

Based on Cmax and AUC(0-inf) values of escitalopram, the 20 mg escitalopram tablet was found to be bioequivalent to the 40-mg racemic CT tablet in healthy male subjects. The 90% confidence interval for Cmax and AUC(0-inf) was within 80-125% (Table 8).

Pharmacokinetics of R-CT and comparison with S-CT following administration of 40 mg CT:

Following 40 mg CT, the AUC(0-inf) of R-CT (1312 ± 446 ng*hr/mL) was twice than S-CT (685 ± 376 ng*hr/mL). The half-life of R-CT (47 hours) was 21 hours longer than S-CT (26 hours). The AUC of R-DCT was 1.3 times higher than the AUC of S-DCT, whereas the half-life of R-DCT (88 hours) was 33 hours longer than the half-life of S-DCT (55 hours). (Tables 5-6).

Gender Effect:

The sample size of females in the study was small (5 racemic CT and 4 S-CT). The pharmacokinetic parameters of various isomers of CT in females have been summarized in Tables 9-10.

The results of the study indicated that there was no interconversion, i.e., the S-CT was not converted into R-CT. This conclusion is based on the fact that following the administration of S-CT, the analytical method did not detect R-CT.

Mean pharmacokinetic parameters for male subjects are summarised in Tables 2 and 3.

Table 5. Pharmacokinetic parameters (mean ± SD) for S-CT and S-DCT in male subjects

Treatment	S-CT 40 mg CT (n = 24)	S-CT 20 mg S-CT (n = 24)	S-DCT 40 mg CT (n = 24)	S-DCT 20 mg S-CT (n = 23)
C_{max} (ng/mL)	21.1 ± 5.5	18.8 ± 4.5	3.5 ± 1.2	3.4 ± 1.0
C_{max} (nmol/L)	65.0 ± 17.0 ^{e}	58.0 ± 13.9 ^{e}	11.3 ± 3.9 ^{f}	11.0 ± 3.2 ^{f}
t_{max} (hr)	3.2 ± 2.4	3.0 ± 1.5	14.2 ± 9.7	14.0 ± 11.3
AUC_{0-t} (ng·hr/mL)	621 ± 336	575 ± 319	243 ± 94 ^{d}	236 ± 75
AUC_{0-t} (nmol·hr/L)	1914 ± 1036 ^{e}	1772 ± 983 ^{e}	783 ± 303 ^{d,f}	760 ± 242 ^{f}
AUC_{0-inf} (ng·hr/mL)	685 ± 376	637 ± 356	349 ± 81 ^{d}	335 ± 78
AUC_{0-inf} (nmol·hr/L)	2112 ± 1159 ^{e}	1964 ± 1097 ^{e}	1124 ± 261 ^{d,f}	1079 ± 251 ^{f}
$t_{1/2}$ (hr)	26.3 ± 10.8 ^{a}	26.7 ± 10.9 ^{a}	55.6 ± 13.4 ^{b,d}	58.5 ± 14.6 ^{b}
CL/F (L/hr)	36.4 ± 16.0	39.6 ± 18.0	na	na
V_z/F (L)	1196 ± 260	1331 ± 355	na	na
F_{rel} ^{c}	na	0.93 ± 0.09	na	0.97 ± 0.12

na: not applicable

^{a}: $t_{1/2}$ derived using measurable data (at least 4 time points) from 12 or 24 hours up to 169 hours after dosing.

^{b}: $t_{1/2}$ derived using measurable data (at least 4 time points) up to 169 hours after dosing.

^{c}: Relative bioavailability: AUC_{0-inf} (20 mg S-CT) / AUC_{0-inf} (40 mg CT).

^{d}: AUC_{0-t}, AUC_{0-inf} and $t_{1/2}$ only determined for 23 subjects.

^{e}: Conversion factor for CT: 1 ng/mL = 3.0826 nmol/L. ^{f}: Conversion factor for DCT: 1 ng/mL = 3.2220 nmol/L.

Table 6. Pharmacokinetic parameters (mean ± SD) for R-CT, R-DCT and R-DDCT in male subjects

Treatment	R-CT 40 mg CT (n = 24)	R-DCT 40 mg CT (n = 24)	R-DDCT 40 mg CT (n = 5)
C_{max} (ng/mL)	22.7 ± 5.5	2.6 ± 0.9	1.3 ± 0.2
C_{max} (nmol/L)	70.0 ± 17.0 ^{f}	8.4 ± 2.9 ^{g}	4.4 ± 0.7 ^{h}
t_{max} (hr)	3.5 ± 2.0	48.2 ± 28.9	79.2 ± 31.3
AUC_{0-inf} (ng·hr/mL)	1312 ± 446	458 ± 130 ^{d}	410 ± 109 ^{e}
AUC_{0-inf} (nmol·hr/L)	4044 ± 1375 ^{f}	1476 ± 419 ^{d,g}	1384 ± 368 ^{e,h}
$t_{1/2}$ (hr)	47.0 ± 10.7 ^{a}	88.6 ± 24.9 ^{b,d}	189.5 ± 92.9 ^{c,e}
CL/F (L/hr)	17.1 ± 6.2	na	na
V_z/F (L)	1087 ± 205	na	na

na: not applicable

^{a}: $t_{1/2}$ derived using measurable data (at least 6 time points) from 12 or 24 hours up to 168 hours after dosing.

^{b}: $t_{1/2}$ derived using measurable data (at least 3 time points) up to 168 hours after dosing.

^{c}: $t_{1/2}$ derived using measurable data (at least 3 time points) from 72 hours up to 144 hours after dosing.

^{d}: AUC_{0-inf} and $t_{1/2}$ only determined for 20 subjects. ^{e}: AUC_{0-inf} and $t_{1/2}$ only determined for 3 subjects.

^{f}: Conversion factor for CT: 1 ng/mL = 3.0826 nmol/L. ^{g}: Conversion factor for DCT: 1 ng/mL = 3.2220 nmol/L.

^{h}: Conversion factor for DDCT: 1 ng/mL = 3.3744 nmol/L.

Table ~~6-19~~ 7. Mean Pharmacokinetic Parameters (Mean ± SD) of Escitalopram and S-DCT in Urine Following Administration of Either 40 mg Racemic CT or 20 mg escitalopram in Healthy Male Subjects

ESCITALOPRAM		
	40 mg CT (n = 24)	*20 mg Escitalopram (n = 24)*
CL_R (L/hr)	2.5 ± 0.8	2.7 ± 0.8
$Ae_{(0\text{-}168\ hr)}$ (µg)	1590 ± 928	1594 ± 961
% Dose in Urine	7.9 ± 4.6	8.0 ± 4.8
$Ae_{0\text{-}inf}$ (µg)	1682 ± 1119	1659 ± 1080
$t_{1/2}$ (urine) (hr)	28.4 ± 10.9	27.4 ± 6.4
S-DEMETHYLCITALOPRAM		
	40 mg CT (n = 24)	*20 mg Escitalopram (n = 23)*
CL_R (L/hr)	6.8 ± 1.9	6.9 ± 2.1
$Ae_{(0\text{-}168\ hr)}$ (µg)	1973 ± 400	1930. ± 384
% Dose in Urine	9.9 ± 2.0	9.6 ± 1.9
$Ae_{0\text{-}inf}$ (µg)	2232 ± 418	2174 ± 413
$t_{1/2}$ (urine) (hr)	45.9 ± 18.9	44.8 ± 11.1

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Table ~~6-17~~ 8. Relative Bioequivalence Analysis of Escitalopram and S-Demethylcitalopram: Treatment with 20 mg Escitalopram (test) vs. 40 mg Racemic CT (reference)

ESCITALOPRAM		
Parameter	Ratio of Means	90% Confidence Intervals
C_{max} (ng/mL)	0.901	0.850-0.955
$AUC_{0\text{-}t}$ (ng•hr/mL)	0.918	0.880-0.957
$AUC_{0\text{-}\infty}$ (ng•hr/mL)	0.924	0.892-0.956
S-DEMETHYLCITALOPRAM		
Parameter	Ratio of Means	90% Confidence Intervals
C_{max} (ng/mL)	0.937	0.883-0.994
$AUC_{0\text{-}t}$ (ng•hr/mL)	0.948	0.878-1.024
$AUC_{0\text{-}\infty}$ (ng•hr/mL)	0.961	0.922-1.001

Mean pharmacokinetic parameters for female subjects are summarised in Tables 4 and 5.

Table ~~4~~ 9. Pharmacokinetic parameters (mean ± SD) for S-CT and S-DCT in female subjects in dosing period I

Treatment	S-CT: 40 mg CT (n = 5)	S-CT: 20 mg S-CT (n = 4)	S-DCT: 40 mg CT (n = 5)	S-DCT: 20 mg S-CT (n = 4)
C_{max} (ng/mL)	23.7 ± 3.7	27.4 ± 9.5	4.3 ± 1.9	3.8 ± 1.0
C_{max} (nmol/L)	73.1 ± 11.4 [c]	84.5 ± 29.3 [c]	13.9 ± 6.1 [d]	12.2 ± 3.2 [d]
t_{max} (hr)	2.2 ± 0.8	3.0 ± 0.8	15.2 ± 11.8	26.0 ± 16.5
AUC_{0-t} (ng·hr/mL)	587 ± 244	913 ± 340	244 ± 39	284 ± 40
AUC_{0-t} (nmol·hr/L)	1809 ± 752 [c]	2814 ± 1048 [c]	786 ± 126 [d]	915 ± 129 [d]
AUC_{0-inf} (ng·hr/mL)	639 ± 260	976 ± 348	350 ± 39	377 ± 33
AUC_{0-inf} (nmol·hr/L)	1970 ± 801 [c]	3009 ± 1073 [c]	1128 ± 126 [d]	1215 ± 106 [d]
$t_{1/2}$ (hr)	23.5 ± 8.3 [a]	29.2 ± 10.7 [a]	53.1 ± 24.7 [b]	51.3 ± 5.1 [b]
CL/F (L/hr)	35.5 ± 12.9	23.1 ± 9.9	na	na
V_z/F (L)	1086 ± 130	902 ± 241	na	na

na: not applicable

[a]: $t_{1/2}$ derived using measurable data (at least 4 time points) from 12 hours up to 168 hours after dosing.

[b]: $t_{1/2}$ derived using measurable data (at least 4 time points) up to 168 hours after dosing.

[c]: Conversion factor for CT: 1 ng/mL = 3.0826 nmol/L. [d]: Conversion factor for DCT: 1 ng/mL = 3.2220 nmol/L.

Table ~~5~~ 10. Pharmacokinetic parameters (mean ± SD) for R-CT, R-DCT and R-DDCT in female subjects

Treatment	R-CT: 40 mg CT (n = 5)	R-DCT: 40 mg CT (n = 5)	R-DDCT: 40 mg CT (n = 3)
C_{max} (ng/mL)	26.6 ± 5.2	2.9 ± 1.1	1.3 ± 0.4
C_{max} (nmol/L)	82.0 ± 16.0 [d]	9.3 ± 3.5 [e]	4.4 ± 1.3 [f]
t_{max} (hr)	2.8 ± 0.8	45.6 ± 44.4	56.0 ± 13.9
AUC_{0-inf} (ng·hr/mL)	1253 ± 298	385 ± 47 [c]	na
AUC_{0-inf} (nmol·hr/L)	3862 ± 919 [d]	1240 ± 131 [c,e]	na
$t_{1/2}$ (hr)	40.5 ± 12.9 [a]	60.3 ± 23.2 [b,c]	na
CL/F (L/hr)	16.6 ± 3.6	na	na
V_z/F (L)	931 ± 182	na	na

na: not applicable

[a]: $t_{1/2}$ derived using measurable data (at least 7 time points) from 12 hours up to 168 hours after dosing.

[b]: $t_{1/2}$ derived using measurable data (at least 3 time points) up to 168 hours after dosing.

[c]: AUC_{0-inf} and $t_{1/2}$ only determined for 4 subjects. [d]: Conversion factor for CT: 1 ng/mL = 3.0826 nmol/L.

[e]: Conversion factor for DCT: 1 ng/mL = 3.2220 nmol/L. [f]: Conversion factor for DDCT: 1 ng/mL = 3.3744 nmol/L.

Figure ~~6-14~~ 5. Plasma Concentrations of Escitalopram Following Administration of a Single Dose of Either 20 mg Escitalopram or 40 mg Racemic Citalopram Tablets in Young Healthy Male Subjects.

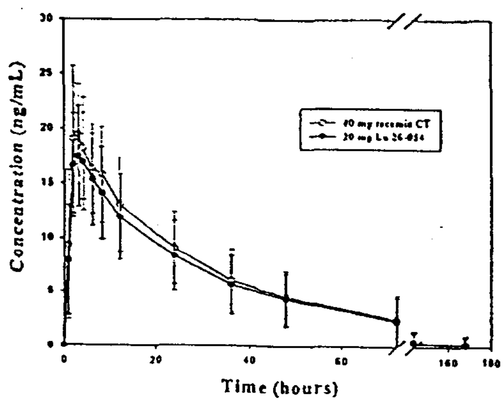
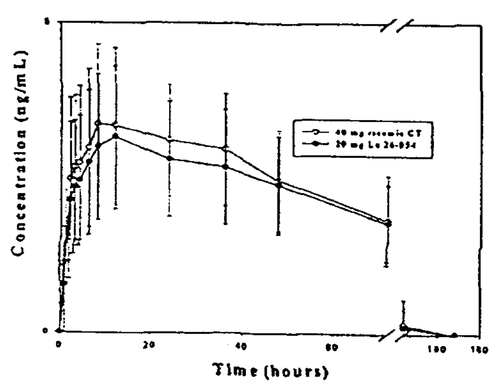


Figure ~~6-15~~ 6. Plasma Concentrations of S-demethylcitalopram Following Administration of a Single Dose of Either 20 mg Escitalopram or 40 mg Racemic Citalopram Tablets in Young Healthy Male Subjects.



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Study # 4

Title: A multiple dose two way crossover double blind study comparing the pharmacokinetics and tolerability of S-citalopram (oral capsules, 10 mg/day and 30 mg/day) and racemic citalopram (oral capsules, 20 mg/day and 60 mg/day) in two panels of human healthy volunteers (study #98107).

The primary objective of this study was to compare the pharmacokinetics of the S-enantiomer of citalopram and its metabolites, following multiple dose administration of Lu 26-054 (S-citalopram) and racemate CT (at two dose levels:10 mg/day Lu 26-054 vs 20 mg/day CT, and 30 mg/day Lu 26-054 vs. 60 mg/day CT) in healthy young subjects. The secondary objective of the study was to determine whether interconversion between S- and R-CT occurs in humans.

This was a single center, Phase I, double blind, randomized, multiple dose two-way crossover study in 36 young healthy subjects (male =18; female=18, age = 18-45 years). Subjects were enrolled into two parallel dosing panels: a low dose panel A (n=18, 9 males and 9 females) and a high dose panel B (n=18, 9 males and 9 females). Each panel was treated during two sequential dosing periods of 24 days, separated by a 14-day washout period. Medication was given orally as encapsulated tablets. Capsules were taken in the morning with 180 mL of water. On the first dosing day and on Day 24 of each treatment period, capsules were taken after overnight fast of 10 hours. Subjects fasted for 4 hours postdosing.

Panel A

Sequence Al:

Treatment 1: CT 20 mg daily for 24 days; 14-day washout; Treatment 2: Lu 26-054 10 mg daily for 24 days (batch #98160J)

Sequence A2:

Treatment I: Lu 26-054 10 mg daily for 24 days; 14-day washout; Treatment 2: CT 20 mg daily for 24 days

Panel B

Sequence B1:

Treatment 1: Titration with racemate-CT 20 mg daily for three days, followed by CT 40 mg daily for three days and 60 mg for 18 days; 14-day washout.

Treatment 2.Titration with Lu 26-054 10 mg daily for three days, followed by Lu 26054 20 mg (batch #98161J) daily for three days and 30 rng Lu 26-054 (batch #98167J) for 18 days.

Sequence B2:

Treatment 1: Titration with Lu 26-054 10 mg daily for three days, followed by Lu 26054 20 mg daily for three days. After the titration period, the subjects received 30 mg Lu 26-054 for 18 days; 14-day washout.

Treatment 2. Titration with CT 20 mg daily for three days, followed by CT 40 mg daily for three days. After the titration period, the subjects received CT 60 mg for 18 days.

Blood samples (6 mL) were obtained in each period for the determination of the S- and R-enantiomers of citalopram and its metabolites DCT and DDCT. The sampling schedule was as follows:

Day 1: pre-dose, 2, 4, 8 and 12 hrs post-dose

Days 2, 10, 16, 21, 22 and 23 hrs pre-dose

Day 24: pre-dose, 1, 2, 3, 4, 6, 8, 12 hrs post-dose

Days 25, 26, 27, 28, *29,* 30, 31, 32, 33, and 34..

Plasma R & S Citalopram, R & S DCT and R & S DDCT concentrations were quantified by LC/MS/MS. The lower limit of quantification for all three moeities [redacted]

Thirty-two subjects completed the study. Four subjects (# 6, 13, 27 and 28) were discontinued during the study; two withdrew due to adverse events and two withdrew their consent. Data from Subjects #6 and 28 were not included in the analysis since data were not available for these subjects during both Periods 1 and 2 at several time points. Data from Subject # 27 were also not included in the analysis since this subject was dropped during Period 2 and cannot serve as his own control. Data from Subject #13 were included in the analysis since this subject was dropped from the study during Period 2 (Day 32), and the concentrations from this subject from the four previous time points (since Day 28) had been below the limit of quantification.

The pharmacokinetic parameters of DDCT were not calculated following the administration of single dose as the plasma levels were fairly low. Also, half-life values for this analyte during the multiple dose were not estimated due to the low plasma levels.

Single Dose:

Bioequivalence analysis (log transformed data) was performed using pooled data from subjects who received 10 mg Lu 26-054 or 20 mg racemic-CT on Day 1, since all subjects also received either of these two treatments in the titration phase for the high dose panel. Bioequivalence was shown for the 10 mg Lu 26-054 (using pooled data from the 10 and 30 mg Lu 26-054 dose groups) compared to the 20 mg racemic-CT (using pooled data from the 20 and 60 mg racemic-CT dose groups); i.e., the 90% confidence intervals for both Cmax and AUC were within 80-125% (Table 11).

Table ~~6-20~~ 11. Relative Bioequivalence Analysis for Escitalopram: Pooled Data from 10 mg and 30 mg Escitalopram vs. Pooled Data from 20 mg and 60 mg racemic CT

ESCITALOPRAM		
Parameter	Ratio of Means	90% Confidence Intervals
C_{max} (ng/mL)	0.942	0.888 - 0.999
AUC_{0-24} (ng•hr/mL)	0.941	0.895 – 0.989
S-DEMETHYLCITALOPRAM		
Parameter	Ratio of Means	90% Confidence Intervals
C_{max} (ng/mL)	0.940	0.886 - 0.998
AUC_{0-24} (ng•hr/mL)	0.914	0.800 – 1.045

Pharmacokinetic parameters using pooled data from subjects who received 10 mg escitalopram treatment (10 mg and 30 mg Lu 26-054 dose groups) and pooled data from subjects who received 20 mg racemic-CT (20 mg and 60 mg racemic-CT dose groups) have been shown in Table 12. No statistically significant differences in the Cmax, Tmax and AUC of S-citalopram or s-desmethylcitalopram were observed between the two treatments in each dose panel (Table 12).

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Table ~~6-21~~ 12. Single Dose Pharmacokinetic Parameters (Mean ± SD) of Escitalopram and S-DCT on Day 1 in a Multiple Dose Study of Escitalopram (10 mg/day and 30 mg/day) and Racemic CT (20 mg/day and 60 mg/day) in Two Panels of Healthy Subjects

ESCITALOPRAM	*Escitalopram Dosage Groups (10 mg)[a]*		*Racemic Citalopram Dosage Groups (20 mg)[a]*	
	10 mg Escitalopram (n=17)	*30 mg Escitalopram (n=16)*	*20 mg racemic CT (n = 17)*	*60 mg racemic CT (n=16)*
C_{max} (ng/mL)	9.5 ± 3.0	8.6 ± 2.4	10.1 ± 3.0	9.0 ± 1.9
T_{max} (hours)	4.1 ± 2.1	4.3 ± 2.4	3.8 ± 2.2	4.3 ± 2.4
AUC_{0-24} (ng•hr/mL)	138.1 ± 37.6	136.4 ± 47.9	150.2 ± 48.3	140.6 ± 38.4
S-DEMETHYLCITALOPRAM	*Escitalopram Dosage Groups (10 mg)[a]*		*Racemic Citalopram Dosage Groups (20 mg)[a]*	
	10 mg Escitalopram (n=17)	*30 mg Escitalopram (n=16)*	*20 mg racemic CT (n = 17)*	*60 mg racemic CT (n=16)*
C_{max} (ng/mL)	1.6 ± 0.4	1.5 ± 0.5	1.7 ± 0.6	1.5 ± 0.5
T_{max} (hours)	12.0 ± 4.9	15.2 ± 7.9	12.6 ± 5.2	15.1 ± 7.0
AUC_{0-24} (ng•hr/mL)	28.6 ± 11.0	27.3 ± 12.7	34.3 ± 11.1	27.6 ± 12.1

[a] On Day 1, all subjects in the 10 mg and 30 mg escitalopram received 10 mg escitalopram and those in the 20 mg racemic CT and 60 mg racemic CT groups received 20 mg escitalopram

Multiple Dose:

Following multiple dosing, both S-CT and S-DCT (10 mg escitalopram vs 20 mg racemic-CT) were bioequivalent (Table 13). When 30 mg escitalopram was compared with 60 mg racemic-CT, S-CT was not bioequivalent but S-DCT met the bioequivalence criteria (Table 13). Mean pharmacokinetic parameters of S-citalopram and its metabolite S-demethylcitalopram have been summarized in Table 14.

Peak concentrations for Lu 26-054 were achieved at approximately 3-4 hours for all dose groups. Steady state was achieved after 10 days of dosing. No statistically significant differences in pharmacokinetic parameters were observed between the two treatments in each dose panel. The mean oral clearance values ranged between 30-38 L/hr for all treatments. Based on Cmax and AUC values, S-DCT levels were approximately 35% of S-CT. Based on the Cmax and AUC values, the S-DDCT levels were approximately 2-4% to that of S-CT.

Table ~~6-22~~ 13. Relative Bioequivalence of Escitalopram: 10 mg Escitalopram vs. 20 mg racemic CT and 30 mg Escitalopram vs. 60 mg racemic CT

ESCITALOPRAM				
	10 mg Escitalopram (test) vs. 20 mg racemic CT (reference)		*30 mg Escitalopram (test) vs. 60 mg racemic CT (reference)*	
Parameter	Ratio of Means[a]	90% Confidence Intervals	Ratio of Means[a]	90% Confidence Intervals
C_{max} (ng/mL)	0.861	0.818-0.907	0.837	0.795-0.882
AUC_{0-24} (ng•hr/mL)	0.879	0.837-0.923	0.845	0.789-0.906
S-DEMETHYLCITALOPRAM				
	10 mg Escitalopram (test) vs. 20 mg racemic CT (reference)		*30 mg Escitalopram (test) vs. 60 mg racemic CT (reference)*	
Parameter	Ratio of Means	90% Confidence Intervals	Ratio of Means	90% Confidence Intervals
C_{max} (ng/mL)	0.908	0.857-0.962	0.877	0.830-0.927
AUC_{0-24} (ng•hr/mL)	0.891	0.850-0.934	0.882	0.826-0.941

[a] antilogarithm of the difference of the least squares means for log-transformed parameter

Table ~~6-23~~ 14. Pharmacokinetic Parameters at Steady State (Mean ± SD) of Escitalopram and S-DCT Following Multiple Dose Administration of Escitalopram (10 mg/day and 30 mg/day) and Racemic CT (20 mg/day and 60 mg/day) in Two Panels of Healthy Volunteers

ESCITALOPRAM				
	Escitalopram Dosage Groups		*Racemic Citalopram Doses*	
	10 mg Escitalopram (n=17)	*30 mg Escitalopram (n=16)*	*20 mg racemic CT (n = 17)*	*60 mg racemic CT (n=16)*
C_{max} (ng/mL)	20.6 ± 10.3	64.4 ± 33.7	24.1 ± 12.5	78.1 ± 44.7
T_{max} (hours)	3.9 ± 1.8	4.1 ± 2.7	3.5 ± 1.1	3.5 ± 1.6
AUC_{0-24} (ng•hr/mL)	360.2 ± 218.7	1100.9 ± 733.6	410.9 ± 255.9	1363.7 ± 1043.6
$t_{1/2}$ (hours)	29.0 ± 11.9	32.5 ± 14.2	27.9 ± 10.8	29.9 ± 14.4
CL/F (L/hr)	34.9 ± 14.2	37.8 ± 19.2	30.6 ± 12.8	32.7 ± 16.7
Vz/F (L)	1254.7 ± 223.8	1461.0 ± 432.5	1074.0 ± 234.3	1135.5 ± 334.3
S-DEMETHYLCITALOPRAM				
	Escitalopram Dosage Groups		*Racemic Citalopram Dosage Groups*	
	10 mg Escitalopram (n=17)	*30 mg Escitalopram (n=16)*	*20 mg racemic CT (n = 17)*	*60 mg racemic CT (n=16)*
C_{max} (ng/mL)	7.4 ± 1.1	19.4 ± 4.4	8.2 ± 1.2	21.8 ± 3.3
T_{max} (hours)	7.5 ± 2.8	6.0 ± 2.0	6.2 ± 2.5	6.6 ± 2.6
AUC_{0-24} (ng•hr/mL)	152.0 ± 22.7	396.3 ± 87.9	171.1 ± 29.4	444.5 ± 71.5
$t_{1/2}$ (hours)	50.2 ± 12.3	54.1 ± 21.7	45.5 ± 12.5	46.2 ± 18.0

Pharmacokinetics of R-CT following administration of 20 mg and 60 mg racemic CT:

On day 1, the Cmax, Tmax and AUC(0-24) of R-CT were comparable with the Cmax, Tmax and AUC(0-24) of S-CT following 20 mg and 60 mg racemic CT administration. The ratio of S to R enantiomer of AUC(0-24) was 0.83 for both doses.

The multiple dosing of racemic CT, however, resulted in higher plasma levels of R-CT than S-CT. The ratio of S to R enantiomer for Cmax and AUC(0-24) was about 0.6 and 0.65, respectively. The half-life of R-CT (52 hrs) was about 24 hours longer than the half-life of S-CT (28 hrs). The oral clearance of R-CT is about 50% of S-CT (14 vs 31 L/hr).

For DCT, on day 1, the ratio of S to R enantiomer for AUC(0-24) following 20 mg and 60 mg racemic CT administration was 3.2 and 7.7, respectively. Following multiple dosing, the ratio of S to R enantiomer was approximately 0.65 for both Cmax and AUC. The half-life of R-DCT (78 hours) was about 32 hours longer than the half-life of S-DCT (45 hours). Based on Cmax and AUC values, R-DCT levels were approximately 30% of racemic-RCT. A majority of the plasma R-DDCT concentrations were below the limit of quantification.

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Table 14A

~~Panel 10~~ - **Single dose pharmacokinetic parameters (mean ± SD) of the S- and R-enantiomer of CT on day 1.**

S-ENANTIOMER OF CT				
	Lu 26-054 Dosage Groups		*Citalopram Dosage Groups*	
	10 mg Lu 26-054 group (n=17) *10 mg Lu 26-054*	*30 mg Lu 26-054[a] group (n=16)* *10 mg Lu 26-054*	*20 mg CT group (n = 17)* *20 mg CT*	*60 mg CT[a] group (n=16)* *20 mg CT*
C_{max} (ng/mL)	9.5 ± 3.0	8.6 ± 2.4	10.1 ± 3.0	9.0 ± 1.9
C_{max} (nM) [b]	29.3 ± 9.2	26.5 ± 7.4	31.1 ± 9.2	27.7 ± 5.6
T_{max} (h)	4.1 ± 2.1	4.3 ± 2.4	3.8 ± 2.2	4.3 ± 2.4
AUC_{0-24} (ng·h/mL)	138.1 ± 37.6	136.4 ± 47.9	150.2 ± 48.3	140.6 ± 38.4
AUC_{0-24} (nM·h) [b]	425.3 ± 115.8	420.1 ± 147.5	462.6 ± 148.8	433.0 ± 118.3

R-ENANTIOMER OF CT				
	Lu 26-054 Dosage Groups		*Citalopram Dosage Groups*	
	10 mg Lu 26-054 group (n=17) *10 mg Lu 26-054*	*30 mg Lu 26-054[a] group (n=16)* *10 mg Lu 26-054*	*20 mg CT group (n = 17)* *20 mg CT*	*60 mg CT[a] group (n=16)* *20 mg CT*
C_{max} (ng/mL)	NC[c]	NC	10.9 ± 2.3	9.8 ± 1.4
C_{max} (nM) [b]	NC	NC	33.6 ± 7.1	30.2 ± 4.3
T_{max} (h)	NC	NC	4.4 ± 2.6	5.0 ± 2.5
AUC_{0-24} (ng·h/mL)	NC	NC	183.7 ± 34.7	170.1 ± 27.4
AUC_{0-24} (nM·h) [b]	NC	NC	565.8 ± 106.9	523.9 ± 84.4

a) Due to the titration design of the study, all subjects in the 30 mg Lu 26-054 and 60 mg CT groups received 10 mg Lu 26-054 and 20 mg CT, respectively, on day 1; b) conversion factor to convert ng/mL to nM = 3.08, 3.22, 3.37 for CT, DCT and DDCT, respectively; c) not calculated.

Table 14B

~~Panel 12~~ - **Single dose pharmacokinetic parameters (mean ± SD) of the S- and R-enantiomer of DCT on day 1.**

S-DEMETHYLCITALOPRAM				
	Lu 26-054 Dosage Groups		*Citalopram Dosage Groups*	
	10 mg Lu 26-054 group (n=17) *10 mg Lu 26-054*	*30 mg Lu 26-054[a] group (n=16)* *10 mg Lu 26-054*	*20 mg CT group (n = 17)* *20 mg CT*	*60 mg CT[a] group (n=16)* *20 mg CT*
C_{max} (ng/mL)	1.6 ± 0.4	1.5 ± 0.5	1.7 ± 0.6	1.5 ± 0.5
C_{max} (nM) [b]	5.2 ± 1.3	4.8 ± 1.6	5.5 ± 1.9	4.8 ± 1.6
T_{max} (h)	12.0 ± 4.9	15.2 ± 7.9	12.6 ± 5.2	13.1 ± 7.0
AUC_{0-24} (ng·h/mL)	28.6 ± 11.0	27.3 ± 12.7	34.3 ± 11.1	27.6 ± 12.1
AUC_{0-24} (nM·h) [b]	92.1 ± 35.4	87.9 ± 40.9	110.4 ± 35.7	88.9 ± 39.0

R-DEMETHYLCITALOPRAM				
	Lu 26-054 Dosage Groups		*Citalopram Dosage Groups*	
	10 mg Lu 26-054 group (n=17) *10 mg Lu 26-054*	*30 mg Lu 26-054[a] group (n=16)* *10 mg Lu 26-054*	*20 mg CT group (n = 17)* *20 mg CT*	*60 mg CT[a] group (n=16)* *20 mg CT*
C_{max} (ng/mL)	NC[c]	NC	0.7 ± 0.7	0.4 ± 0.6
C_{max} (nM) [b]	NC	NC	2.3 ± 2.3	1.3 ± 1.9
T_{max} (h)	NC	NC	18.0 ± 6.3 (n = 10)	17.3 ± 7.5 (n = 6)
AUC_{0-24} (ng·h/mL)	NC	NC	10.8 ± 11.5	3.6 ± 5.2
AUC_{0-24} (nM·h) [b]	NC	NC	34.8 ± 37.0	11.6 ± 16.7

a) Due to the titration design of the study, all subjects in the 30 mg Lu 26-054 and 60 mg CT groups received 10 mg Lu 26-054 and 20 mg CT, respectively; b) conversion factor to convert ng/mL to nM = 3.08, 3.22, 3.37 for CT, DCT and DDCT, respectively; c) not calculated.

Table 14c

~~Panel 14~~ - Pharmacokinetic parameters at steady state (mean ± SD) of the S- and R-enantiomer of CT after multiple dose administration of Lu 26-054 (10 mg/day and 30 mg/day) and CT (20 mg/day and 60 mg/day)

S-ENANTIOMER OF CT				
	Lu 26-054 Dosage Groups		*Citalopram Doses*	
	10 mg Lu 26-054 (n=17)	*30 mg Lu 26-054 (n=16)*	*20 mg CT (n = 17)*	*60 mg CT (n=16)*
C_{max} (ng/mL)	20.6 ± 10.3	64.4 ± 33.7	24.1 ± 12.5	78.1 ± 44.7
C_{max} (nM) [b]	63.4 ± 31.7	198.4 ± 103.8	74.2 ± 38.5	240.5 ± 137.7
T_{max} (h)	3.9 ± 1.8	4.1 ± 2.7	3.5 ± 1.1	3.5 ± 1.6
AUC_{0-24} (ng·hr/mL)	360.2 ± 218.7	1100.9 ± 733.6	410.9 ± 255.9	1363.7 ± 1043.6
AUC_{0-24} (nM·hr) [b]	1109.4 ± 673.6	3390.8 ± 2259.5	1265.6 ± 788.2	4200.2 ± 3214.3
$t_{1/2}$ (h)	29.0 ± 11.9	32.5 ± 14.2	27.9 ± 10.8	29.9 ± 14.4
CL/F (L/h)	34.9 ± 14.2	37.8 ± 19.2	30.6 ± 12.8	32.7 ± 16.7
Vz/F (L)	1254.7 ± 223.8	1461.0 ± 432.5	1074.0 ± 234.3	1135.5 ± 334.3
R-ENANTIOMER OF CT				
	Lu 26-054 Dosage Groups		*Citalopram Doses*	
	10 mg Lu 26-054 (n=17)	*30 mg Lu 26-054 (n=16)*	*20 mg CT (n = 17)*	*60 mg CT (n=16)*
C_{max} (ng/mL)	NC[a]	NC[a]	39.6 ± 11.6	123.2 ± 33.5
C_{max} (nM) [b]	NC	NC	122.0 ± 35.7	379.5 ± 103.2
T_{max} (h)	NC	NC	4.7 ± 2.1	4.1 ± 1.9
AUC_{0-24} (ng·hr/mL)	NC	NC	771.3 ± 236.5	2362.6 ± 796.3
AUC_{0-24} (nM·h) [b]	NC	NC	2375.6 ± 728.4	7276.8 ± 2452.6
$t_{1/2}$ (h)	NC	NC	52.8 ± 11.2	51.2 ± 9.8
CL/F (L/h)	NC	NC	14.0 ± 3.8	14.2 ± 5.0
Vz/F (L)	NC	NC	1030.0 ± 215.8	997.3 ± 219.5

a) NC - not calculated

b) conversion factor to convert ng/mL to nM = 3.08 (CT)

Table 14D

~~Panel 16~~ - Pharmacokinetic parameters at steady state (mean ± SD) of the S- and R-enantiomer of DCT after multiple dose administration of Lu 26-054 (10 mg/day and 30 mg/day) and CT (20 mg/day and 60 mg/day)

S-DEMETHYLCITALOPRAM				
	Lu 26-054 Dosage Groups		*Citalopram Dosage Groups*	
	10 mg Lu 26-054 (n=17)	*30 mg Lu 26-054 (n=16)*	*20 mg CT (n = 17)*	*60 mg CT (n=16)*
C_{max} (ng/mL)	7.4 ± 1.1	19.4 ± 4.4	8.2 ± 1.2	21.8 ± 3.3
C_{max} (nM) [b]	23.8 ± 3.5	62.5 ± 14.2	26.1 ± 3.9	70.2 ± 10.6
T_{max} (h)	7.5 ± 2.8	6.0 ± 2.0	6.2 ± 2.5	6.6 ± 2.6
AUC_{0-24} (ng·h/mL)	152.0 ± 22.7	396.3 ± 87.9	171.1 ± 29.4	444.5 ± 71.5
AUC_{0-24} (nM·h) [b]	489.4 ± 73.1	1276.1 ± 283.0	550.9 ± 94.7	1431.3 ± 230.2
$t_{1/2}$ (h)	50.2 ± 12.3	54.1 ± 21.7	45.5 ± 12.5	46.2 ± 18.0
R-DEMETHYLCITALOPRAM				
	Lu 26-054 Dosage Groups		*Citalopram Dosage Groups*	
	10 mg Lu 26-054 (n=17)	*30 mg Lu 26-054 (n=16)*	*20 mg CT (n = 17)*	*60 mg CT (n=16)*
C_{max} (ng/mL)	NC[a]	NC[a]	11.9 ± 2.6	33.8 ± 6.5
C_{max} (nM) [b]	NC	NC	38.3 ± 8.4	108.8 ± 20.9
T_{max} (h)	NC	NC	8.3 ± 2.5	6.9 ± 2.6
AUC_{0-24} (ng·h/mL)	NC	NC	252.9 ± 60.8	704.3 ± 160.0
AUC_{0-24} (nM·h) [b]	NC	NC	814.3 ± 195.8	2267.8 ± 515.2
$t_{1/2}$ (h)	NC	NC	81.2 ± 23.6	76.1 ± 13.8

a) NC - not calculated

b) conversion factor to convert ng/mL to nM = 3.22 (DCT)

Gender Effect:

Comparison of the Lu 26-054 pharmacokinetic parameters in male and female subjects revealed no statistically significant gender effects for any of the four treatments though females have higher plasma levels (Table 15).

In subjects receiving 10 mg Lu 26-054 the mean Cmax and AUC values were 36% and 50% higher in females than males, whereas in subjects receiving 20 mg citalopram the mean Cmax and AUC values were 35% and 50% higher in females than males.

In subjects receiving 30 mg Lu 26-054 the mean Cmax and AUC values were 19% and 30% higher in females than males, whereas in subjects receiving 60 mg citalopram the mean Cmax and AUC values were 26% and 33% higher in females than males.

With the exception of the 30 mg dose group in which a significantly higher Tmax (5.1 hrs) was observed in the females compared to the males (2.9 hrs), no other statistically significant differences were observed in the other dose groups for Tmax.

For S-DCT, the Cmax and AUC values were not statistically different between male and female subjects in all dose groups except for the 20 mg racemic-CT dose group in which significantly higher Cmax (26%) and AUC (32%) values were observed for the females compared to the males (Table 16).

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Table ~~8.10~~ 15: Comparison of Pharmacokinetic Parameters of Lu 26-054 Between Male and Female In a Multiple Dose Two-Way Crossover Double Blind Study (Study 98107)

	Males	Females
10 mg Lu 26-054 (males, n = 8; females, n = 9)		
C_{max} (ng/mL)	17.3 ± 6.6	23.6 ± 12.4
T_{max} (hours)	3.6 ± 2.0	4.1 ± 1.6
AUC_{0-24} (ng·hr/mL)	284.4 ± 135.4	427.5 ± 262.3
$t_{1/2}$ (hours)	25.0 ± 7.1	32.5 ± 14.5
CL/F (L/hr)	40.4 ± 13.2	30.0 ± 14.0
Vz/F (L)	1346.7 ± 244.5	1172.9 ± 178.6
30 mg Lu 26-054 (males, n = 7; females, n = 9)		
C_{max} (ng/mL)	58.1 ± 35.6	69.3 ± 33.5
T_{max} (hours)	2.9 ± 0.7	5.1 ± 3.3
AUC_{0-24} (ng·hr/mL)	943.4 ± 747.4	1223.3 ± 742.7
$t_{1/2}$ (hours)	30.1 ± 16.4	34.4 ± 12.9
CL/F (L/hr)	44.2 ± 21.2	32.8 ± 17.0
Vz/F (L)	1538.9 ± 397.3	1400.3 ± 472.2
20 mg rac-CT (males, n = 8; females, n = 9)		
C_{max} (ng/mL)	20.3 ± 7.66	27.4 ± 15.4
T_{max} (hours)	3.4 ± 1.2	3.6 ± 1.1
AUC_{0-24} (ng·hr/mL)	326.3 ± 139.9	486.2 ± 316.7
$t_{1/2}$ (hours)	25.0 ± 8.4	30.5 ± 12.5
CL/F (L/hr)	35.0 ± 12.0	26.7 ± 13.0
Vz/F (L)	1157.4 ± 235.0	999.9 ± 219.8
60 mg rac-CT (males, n = 7; females, n = 9)		
C_{max} (ng/mL)	67.9 ± 44.0	86.1 ± 46.2
T_{max} (hours)	3.1 ± 1.5	3.8 ± 1.8
AUC_{0-24} (ng·hr/mL)	1148.0 ± 1030.2	1531.4 ± 1083.5
$t_{1/2}$ (hours)	26.1 ± 13.4	32.9 ± 15.3
CL/F (L/hr)	38.3 ± 17.9	28.2 ± 15.5
Vz/F (L)	1185.6 ± 303.6	1096.6 ± 369.5

Table ~~8.11~~ 16: Comparison of Pharmacokinetic Parameters of S-Demethylcitalopram Between Male and Female In a Multiple Dose Two-Way Crossover Double Blind Study (Study 98107)		
	Males	Females
10 mg Lu 26-054 (males, n = 8; females, n = 9)		
C_{max} (ng/mL)	6.8 ± 1.0	8.0 ± 1.06
T_{max} (hours)	7.5 ± 3.3	7.4 ± 2.4
AUC_{0-24} (ng·hr/mL)	138.3 ± 19.1	164.2 ± 19.0
$t_{1/2}$ (hours)	46.6 ± 11.4	53.4 ± 12.9
30 mg Lu 26-054 (males, n = 7; females, n = 9)		
C_{max} (ng/mL)	19.2 ± 3.8	19.5 ± 5.0
T_{max} (hours)	6.0 ± 2.2	6.0 ± 2.0
AUC_{0-24} (ng·hr/mL)	381.4 ± 71.0	407.9 ± 101.7
$t_{1/2}$ (hours)	49.3 ± 14.9	57.8 ± 26.0
20 mg rac-CT (males, n = 8; females, n = 9)		
C_{max} (ng/mL)	7.2 ± 0.8	9.1 ± 0.7
T_{max} (hours)	6.5 ± 2.9	6.0 ± 2.2
AUC_{0-24} (ng·hr/mL)	146.2 ± 18.1	193.2 ± 16.6
$t_{1/2}$ (hours)	43.8 ± 9.0	47.0 ± 15.3
60 mg rac-CT (males, n = 7; females, n = 9)		
C_{max} (ng/mL)	21.5 ± 4.3	22.0 ± 2.6
T_{max} (hours)	6.6 ± 2.5	6.7 ± 2.8
AUC_{0-24} (ng·hr/mL)	426.6 ± 84.0	458.4 ± 61.6
$t_{1/2}$ (hours)	43.1 ± 18.0	48.6 ± 18.7

Interconversion of S-enantiomer to R-enantiomer:

Measurable (low) plasma concentrations of R-citalopram were observed for several subjects who received 30 mg Lu 26-054. This was expected since a small percentage of R-citalopram (approximately 2%) is present in the Lu 26-054 drug substance and finished product. Also, small amounts of R-CT were observed in the pre-dose Day 1 samples suggesting a carry-over effect at steady state. Overall there was no evidence for interconversion from the S- to the R- enantiomer.

Conclusion:

In this multiple dose two-way crossover double blind study, S-CT was rapidly absorbed, with peak plasma concentrations occurring at approximately 3-4 hours for all dose groups. No statistically significant differences were observed in the Tmax values for both S-CT and S-DCT in both dose panels. The 90% confidence intervals for both S-CT and S-DCT following multiple dose administration of 10 mg S-CT and 20 mg racemic-CT were within 80-125% indicating that 10 mg S-CT is bioequivalent with 20 mg racemic-CT. Following the administration of 30 mg S-CT and 60 mg racemic-CT, the 90% confidence intervals were within 80-125% only for S-DCT but the 90% confidence intervals for S-CT was slightly (79%) outside of this interval for both Cmax and AUC.

The half-life values for S-CT (28 hours) were lower than those of R-CT (52 hours). S-Demethylcitalopram and s-didemethylcitalopram levels were approximately 30-35% and 2-4% those of the parent compound, respectively. No statistically significant gender differences were observed in this study. There appeared to be no interconversion of S-citalopram to R-citalopram.

Figure ~~6-18~~ 7. Mean Plasma Concentrations of Escitalopram Following Multiple Dose Administration of Escitalopram (10 mg/day and 30 mg/day) and Racemic Citalopram (20 mg/day and 60 mg/day) in Two Panels of Healthy Subjects.

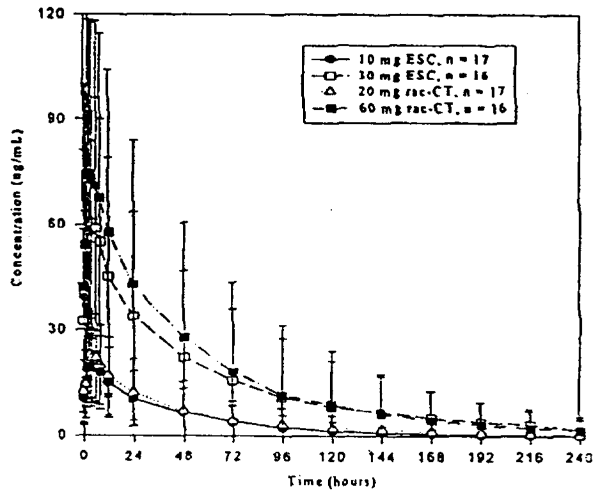
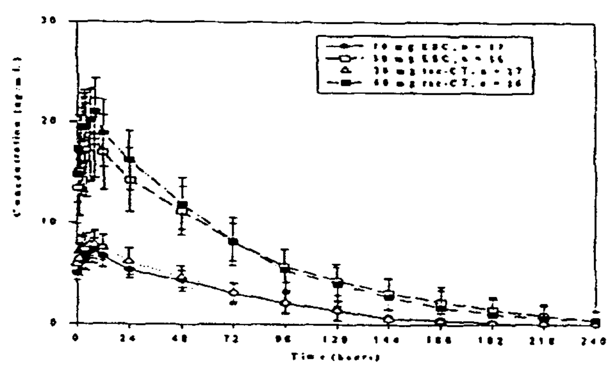


Figure ~~6-19~~ 8. Mean Plasma Concentrations of S-Demethylcitalopram Following Multiple Dose Administration of Escitalopram (10 mg/day and 30 mg/day) and Racemic Citalopram (20 mg/day and 60 mg/day) in Two Panels of Healthy Subjects.



Study #5

Title: A multiple dose pharmacokinetic study of Lu 26-054 in healthy elderly and young subjects (SCT-PK-05).

The primary objective of this study was to determine the pharmacokinetics of escitalopram (S-CT) and its metabolites, S-demethylcitalopram (S-DCT) and S-didemethylcitalopram (S-DDCT) following multiple-dose administration of escitalopram in healthy elderly and young male and female subjects.

This was an open, multiple-dose study in 18 young (18-35 years, 9 males and 9 females) and 18 elderly (>65 years, 9 males and 9 females) healthy subjects. All subjects received a single 10-mg tablet of escitalopram (batch #99030C) daily for 21 days. Subjects fasted overnight for 10 hours before administration of drug on days 1 and 21. Blood samples (7 mL) were collected at frequent intervals over a 24-hour period after a single dose on Day 1, at 0.0 hour on Days 8, 10 and 15, at frequent intervals over a 24-hour period on Day 21 and at 48, 72, 96, 120, 144, 168, and 192 hours post-day 21 dose for the determination of S-CT, S- DCT and S-DDCT. Plasma concentrations of S-CT. S-DCT and S-DDCT were determined by LC/MS/MS method. The lower limit of quantification of escitalopram and its metabolites in plasma was

After Day 1 dosing, though the Tmax was one hour longer in the elderly (6.2 ± 1.1 h) as compared to young subjects (5.1 ± 1.5 h), both Cmax and AUC for escitalopram were comparable between the two groups (Table 17). For S-DCT, there were no statistically significant differences in Tmax, Cmax and AUC values between the elderly and the young subjects (Table 17).

Following multiple dosing on Day 2 I, the Tmax of S-CT between the elderly and young subjects was comparable (Table 18). However, the Cmax was approximately 32% and the AUC(0-inf) was 50% higher in the elderly compared to the young subjects. The half-life in the elderly was also longer compared to the young subjects (41.0 vs. 27.3 h). For S-DCT, the Cmax, AUC and t½ values were 45% higher for the elderly compared to the young subjects (Table 18). Steady state was achieved by the end of one week of dosing. The accumulation ratio was 4.6 ± 1.2 and 3.3 ± 0.7 in the elderly and the young, respectively.

S-DDCT levels were barely higher than the detectable levels (0.5 ng/mL) to estimate pharmacokinetic parameters. Following a single dose, the highest concentration achieved was 0.52 ng/mL in a female subject. Following multiple dosing, the highest concentration achieved was 3.3 ng/mL in an eldely subject.

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Table ~~6-16~~. Pharmacokinetic Parameters (Mean ± SD) of Escitalopram and S-DCT Following a Single Dose (Day 1) Administration of S-Citalopram Tablet (10 mg) in Healthy Elderly and Young Subjects

ESCITALOPRAM			
	Elderly (n=18)	Young (n=18)	p-value
T_{max}(h)	6.2 ± 1.1	5.1 ± 1.5	0.011
C_{max}(ng/mL)	12.0 ± 2.7	12.3 ± 3.3	0.804
$AUC_{(0-24)}$(ng•hr/mL)	180.1 ± 35.9	176.6 ± 51.2	0.815
S-DEMETHYLCITALOPRAM			
T_{max}(h)	14.2 ± 8.2	11.2 ± 7.3	0.234
C_{max}(ng/mL)	1.6 ± 0.5	1.8 ± 0.5	0.181
$AUC_{(0-24h)}$ (ng•hr/mL)	28.4 ± 9.5	33.9 ± 10.0	0.080

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Table ~~6-10~~. Pharmacokinetic Parameters (Mean±SD) of Escitalopram and S-demethylcitalopram Following a 21-day Administration of Escitalopram Tablets (10 mg/day) in Healthy Elderly and Young Subjects

ESCITALOPRAM			
	Elderly (n=17)	Young (n=18)	p-value
T_{max}(h)	5.5 ± 1.5	4.8 ± 1.6	0.153
C_{max}(ng/mL)	30.0 ± 12.7	22.7 ± 7.5	0.033
$AUC_{(0-\infty)}$ (ng•hr/mL)	535.3 ± 221.9	362.2 ± 146.0	0.008
t½(h)	41.0 ± 11.5	27.3 ± 9.0	0.000
CL_{SS}/F(L/hr)	21.6 ± 8.6	32.2 ± 14.0	0.010
V_Z/F(L)	1195.6 ± 346.0	1175.7 ± 418.8	0.936
S-DEMETHYLCITALOPRAM			
T_{max}(h)	6.8 ± 5.1	6.4 ± 2.1	0.734
C_{max}(ng/mL)	8.9 ± 3.6	6.1 ± 2.3	0.008
t½(h)	68.4 ± 19.6	46.8 ± 12.3	0.000
$AUC_{(0-\infty)}$ (ng•hr/mL)	177.2 ± 62.5	119.2 ± 43.8	0.002

Effect of Gender:

Table 19 summarizes the mean pharmacokinetic parameters of escitalopram following administration of escitalopram tablets (10 mg) in male and female volunteers for 21 days. Maximum plasma concentrations were achieved at around 5.9 hours in male subjects. This was longer than the Tmax in female subjects (4.1 h). Both the Cmax (30.3 vs. 23.0 ng/mL), and AUC (506 vs 401 ng*hr/mL) were higher in females than males. The difference in the Cmax and AUC between male and female subjects disappeared when these parameters were normalized based on body weight (Table 19). There was no difference in half-life values between male and female subjects.

There was no statistical difference in the pharmacokinetic parameters of S-DCT between male and female subjects (Table 20).

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Table 8.5 Pharmacokinetic Parameters (Mean ± SD) of Escitalopram Following 21 days of Escitalopram Tablets (10 mg/day) in Healthy Male and Female Volunteers.

	Females (n=18*)	Males (n=18)	p value
T_{max}(h)	4.1 ± 1.6	5.9 ± 1.4	0.009
C_{max}(ng/mL)	30.3 ± 11.8	23.0 ± 8.8	0.030
C_{max}(ng/mL)*	27.7 ± 12.9	25.7 ± 9.1	0.535
$T_{1/2}$(h)	33.3 ± 14.5	34.6 ± 9.7	0.707
$AUC_{(0-24h)}$ (ng•hr/mL)	505.8 ± 231.9	400.7 ± 164.4	0.090
$AUC_{(0-24h)}$ (ng•hr/mL)*	464.9 ± 248.8	450.6 ± 175.9	0.813

* Body weight - normalized to 70 kg
*: It did not affect the statistical results when subject 29 was excluded.
Conversion factor to convert ng/mL to nM =3.08

20

Table 8.6 Pharmacokinetic Parameters (Mean ± SD) of S-DCT Following 21 days of escitalopram Tablets (10 mg/day) in Healthy Female and Male Volunteers.

	Female (n=18)	Male (n=18)	p value
T_{max}(h)	6.0 ± 1.5	7.2 ± 5.2	0.353
C_{max}(ng/mL)	8.4 ± 3.2	6.6 ± 3.1	0.062
C_{max}(ng/mL)*	7.6 ± 3.4	7.5 ± 3.5	0.882
$T_{1/2}$(h)	56.8 ± 22.8	58.4 ± 16.1	0.765
$AUC_{(0-24h)}$ (ng•hr/mL)	164.5 ± 62.2	132.0 ± 56.4	0.070
$AUC_{(0-24h)}$ (ng•hr/mL)*	149.7 ± 66.8	150.6 ± 64.2	0.959

* Body weight - normalized to 70 kg
Conversion factor to convert ng/mL to nM =3.22

Figure ~~6-12.~~ 9 Mean Plasma Concentrations (Mean ± SD) of S-Citalopram Following a 21-Day Administration of S-Citalopram Tablets (10 mg/day) in Healthy Young vs. Elderly Subjects.

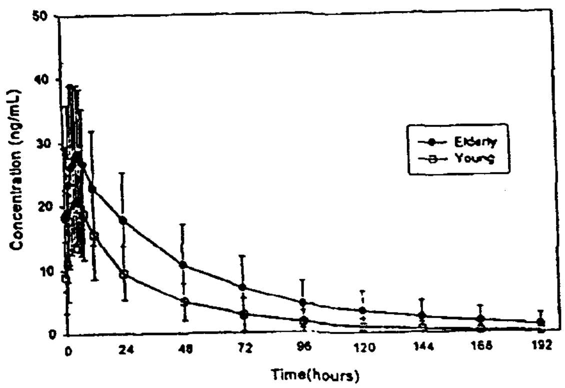
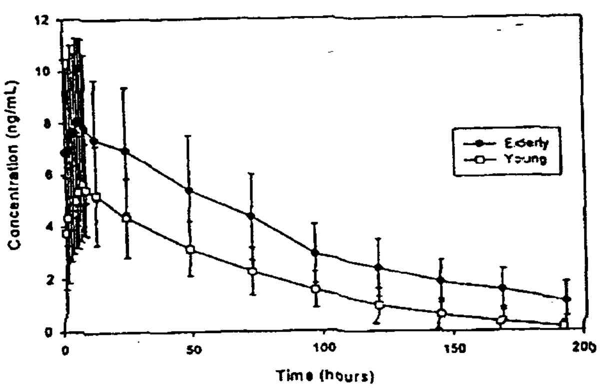


Figure ~~6-13.~~ 10 Mean Plasma Concentrations (Mean ± SD) of S-Demethylcitalopram Following a 21-Day Administration of S-Citalopram Tablets (10 mg/day) in Healthy Young vs. Elderly Subjects.



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Study #6

Title: A Comparison of the Pharmacokinetic Interaction of Metoprolol with Lu 26-054 or Paroxetine in Healthy Young Subjects (Study #SCT-PK-03).

Studies in human liver microsomes have shown that escitalopram undergoes metabolism via the cytochrome P450 (CYP) system. Specifically, the CYP3A4 and CYP2C19 isozymes have been shown to be responsible for the conversion of escitalopram to its principal metabolite, S-DCT. Conversion of S-DCT to S-DDCT, the S-enantiomer of didemethylcitalopram is mediated mainly by CYP2D6. Recently, studies in human liver microsomes have shown that escitalopram, S-DCT, R-CT (R isomer of CT), and R-DCT (R isomer of DCT) are weak or negligible inhibitors of human cytochromes (CYP) 1A2, 2C9, 2C19, 2El and 3A. Furthermore, R-CT, S-CT and S-DCT produce negligible inhibition of CYP2D6.

Paroxetine (Paxil®), a marketed SSRI indicated for the treatment of depression has been shown to be metabolized in part by the CYP2D6 isozyme and is also a potent inhibitor of this isozyme. During the clinical use of either escitalopram or paroxetine, some patients may be receiving other medications concomitantly. One such medication is metoprolol, which is widely used in the treatment of hypertension, angina pectoris and to prevent recurrence of myocardial infarction. CYP2D6 is responsible for the conversion of metoprolol to its primary metabolite, α-hydroxymetoprolol. Concomitant administration of metoprolol with the inhibitors of CYP2D6 may result in an increase in the plasma concentrations of metoprolol.

The objective of this study was to compare the effects of paroxetine (40 mg) with that of escitalopram (20 mg) on the pharmacokineties and pharmacodynamics (blood pressure, pulse and psychomotor assessments) of metoprolol (100 mg) in healthy young subjects.

This was a double blind, parallel, randomized, multiple dose study in young (18-35 years) healthy male and female subjects. A total of 30 subjects entered the study. Subjects took one metoprolol 100 mg tablet on Day 1, followed by a 7-day washout period. Subjects were then randomized (i.e., 14 subjects per group) to receive double blind treatment with either one encapsulated escitalopram 10 mg tablet once daily for 7 days followed by two encapsulated escitalopram 10 mg tablets once daily for 21 days, or one encapsulated paroxetine 20 mg tablet once daily for 7 days followed by two encapsulated paroxetine 20 mg tablets once daily for 21 days. On the last day of either escitalopram or paroxetine dosing, the subjects also took one metoprolol 100 mg tablet concomitantly. Blood samples (10mL each) for determination of metoprolol in plasma were collected from each subject at 0.0 hour (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 12, 24 and 48 hours after 0800 drug administration on Days 1 and 35. Blood samples (10 mL each) for determination of escitalopram, Paroxetine and metabolites in plasma were also collected from each subject at (pre-dose) on Days 8, 15, 22, 29, 33, 34, 35 and 40.

Escitalopram concentrations were determined by [redacted] (0.5 mL plasma). The lower limit of quantification was [redacted] Paroxetine concentrations were measured using [redacted] (0.6 mL plasma). The lower limit of quantification was [redacted] Metoprolol and its metabolite were determined by [redacted] (0.25 mL plasma). The lower limit of quantification was [redacted] ng/mL.

Twenty seven subjects completed the study. The pharmacokinetic parameters of metoprolol have been summarized in Table 21 given with or without escitalopram or paroxetine. Co-administration of metoprolol with escitalopram or paroxetine resulted in increased levels of metoprolol. The Cmax of metoprolol increased by 53% and 120%, following escitalopram or paroxetine administration, respectively. A 2-fold and 4-fold increase in the AUC(0-inf) of metoprolol was observed following escitalopram or paroxetine administration, respectively. The half-life of metoprolol increased by one hour after escitalopram administration, whereas a 2-fold increase in half-life was observed when metoprolol was given with paroxetine.

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Table 21. Mean Pharmacokinetic Parameters (Mean ± SD) of Metoprolol With or Without Either Escitalopram or Paroxetine in Healthy Subjects

EFFECT OF ESCITALOPRAM			
	Metoprolol Alone (Day 1); (N = 15)	*Metoprolol + Escitalopram (Day 35); (N = 15)*	*p-values*
C_{max} (ng/mL)	160.6 ± 81.1	244.1 ± 75.7	0.007
T_{max} (hours)	1.7 ± 0.5	2.1 ± 0.5	0.028
AUC_{0-t} (ng•hr/mL)	953.7 ± 670	1770.1 ± 705.6	0.003
AUC_{0-inf} (ng•hr/mL)	998.8 ± 706.2	1826.6 ± 709.1	0.003
t½ (hours)	3.3 ± 1.3	4.6 ± 1.5	0.014
CL/F (L/hr)	150.7 ± 93.2	63.8 ± 26.8	0.003
Vz/F (L)	607.9 ± 289.2	390 ± 110.3	0.014
EFFECT OF PAROXETINE			
	Metoprolol Alone (Day 1); (N = 12)	*Metoprolol + Paroxetine (Day 35); (N = 12)*	*p-values*
C_{max} (ng/mL)	153.5 ± 69.1	339.6 ± 62.8	0.000
T_{max} (hours)	2.4 ± 0.8	2.3 ± 0.8	0.603
AUC_{0-t} (ng•hr/mL)	1190.6 ± 957.9	4524.9 ± 1350.3	0.000
AUC_{0-inf} (ng•hr/mL)	1250.2 ± 981.9	4739.8 ± 1393.7	0.000
t½ (hours)	3.9 ± 1.7	8.6 ± 1.8	0.000
CL/F (L/hr)	145.2 ± 143	23.3 ± 8.8	0.013
Vz/F (L)	618.9 ± 354.2	273.2 ± 54.1	0.006

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Figure ~~6~~ 11. Mean Metoprolol Concentrations Before (Day 1) and During Escitalopram Coadministration (Day 35) in Young Healthy Male and Female Subjects

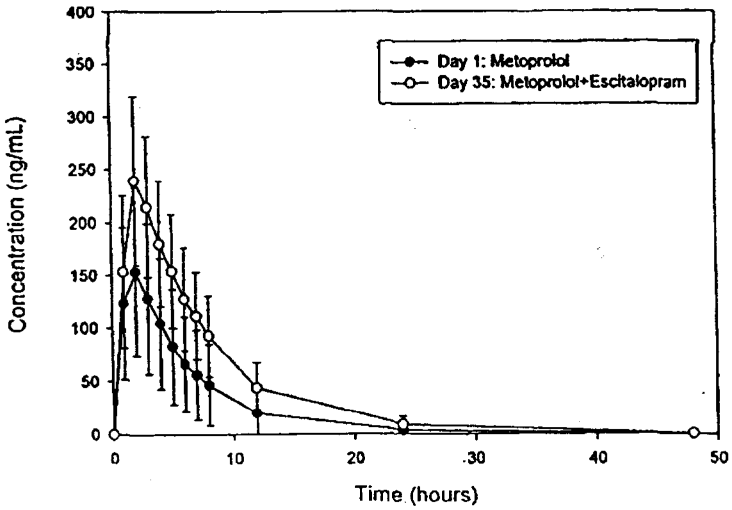
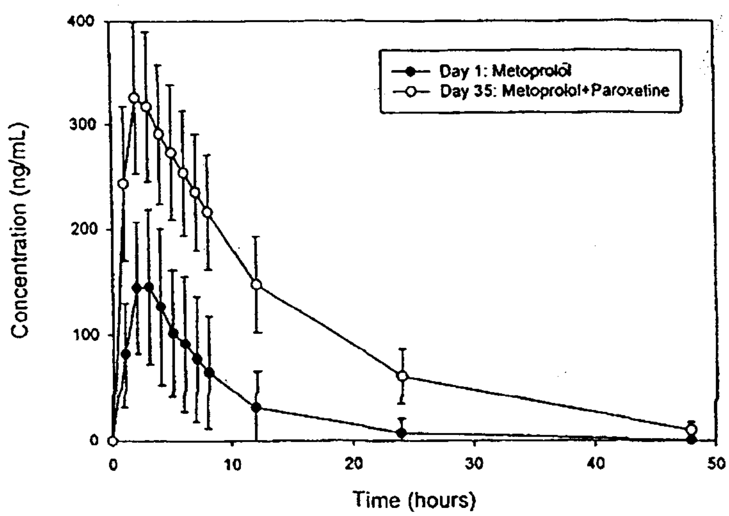


Figure ~~7~~ 12. Mean Metoprolol Concentrations Before (Day 1) and During Paroxetine Coadministration (Day 35) in Young Healthy Subjects



Co-administration of metoprolol with escitalopram or paroxetine resulted in decreased levels of α hydroxy-metoprolol. The pharmacokinetic parameters of α-hydroxymetoprolol have been summarized in Table 22 when given with or without escitalopram or paroxetine. The Cmax of α-hydroxymetoprolol decreased by 36% and 93%, following escitalopram or paroxetine administration, respectively. The AUC(0-t) of α-hydroxymetoprolol decreased by 13% and 94% following escitalopram or paroxetine administration respectively. The half-life of α-hydroxymetoprolol increased approximately by 1.5 hour after escitalopram administration, whereas almost 2-fold increase in half-life of α-hydroxymetoprolol was observed when metoprolol was given with paroxetine.

Following coadministration of metoprolol with escitalopram or paroxetine, plasma concentrations of metoprolol were increased compared to those when metoprolol was administered alone, although the effects of escitalopram were less than that of paroxetine. The decrease in plasma concentrations of α-hydroxymetoprolol were also more pronounced during paroxetine coadministration than with escitalopram. The larger effect of paroxetine on Cmax, AUC, and half-life compared to escitalopram is likely due to the pronounced inhibition by paroxetine of CYP2D6, the isozyme responsible for the metabolism of metoprolol to α-hydroxymetoprolol. The results indicate that paroxetine is much more potent inhibitor of CYP2D6 than escitalopram.

The Sponsor concludes that the subject-rated visual analog scales for alertness, coordination, confusion, and anxiety showed no clinically relevant changes in scores obtained when metoprolol was administered alone or concomitantly with either escitalopram or paroxetine despite the observed pharmacokinetic interaction between a single dose of metoprolol and multiple doses of escitalopram or paroxetine. Neither concomitant escitalopram nor paroxetine treatment affected the metoprolol induced changes in blood pressures and pulse rates. Concomitant use of escitalopram and metoprolol did not affect the overall safety profile of either drug.

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Table 22. Mean Pharmacokinetic Parameters (Mean ± SD) of α-Hydroxymetoprolol With or Without Either Escitalopram or Paroxetine in Healthy Subjects

EFFECT OF ESCITALOPRAM			
	Metoprolol Alone (Day 1) (N = 15)	*Metoprolol + Escitalopram (Day 35); (N = 15)*	*p-values*
C_{max} (ng/mL)	65.9 ± 28.3	42.1 ± 19.1	0.012
T_{max} (hours)	2.2 ± 1.4	3.6 ± 1.6	0.017
AUC_{0-t} (ng•hr/mL)	672.5 ± 232.1	559.1 ± 230.9	0.190
$AUC_{0-\infty}$ (ng•hr/mL)	747.7 ± 230.7	651.6 ± 247.8	0.281
t½ (hours)	7.3 ± 2.2	8.9 ± 1.9	0.055
EFFECT OF PAROXETINE			
	Metoprolol Alone (Day 1) (N = 12)	*Metoprolol + Paroxetine (Day 35); (N = 12)*	*p-values*
C_{max} (ng/mL)	51.2 ± 29.8	3.5 ± 3.1	0.000
T_{max} (hours)	2.5 ± 1.2	8.1 ± 15.1[a]	0.299
AUC_{0-t} (ng•hr/mL)	553.5 ± 220.3	34 ± 34	0.000
$AUC_{0-\infty}$ (ng•hr/mL)	636 ± 223.5	153 ± 36.1[b]	0.003
t½ (hours)	8.3 ± 3.1	14.8 ± 5.1[b]	0.013

[a] N=9 (α-hydroxymetoprolol concentrations were undetectable in 3 subjects after coadministration of paroxetine and metoprolol)
[b] N=3 (t½ and extrapolated AUC values could be estimated for only 3 subjects from the elimination phase of their plasma concentration profiles)

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Figure 13. Mean α-Hydroxymetoprolol Concentrations Before (Day 1) and During Escitalopram Coadministration (Day 35) in Young Healthy Male and Female Subjects

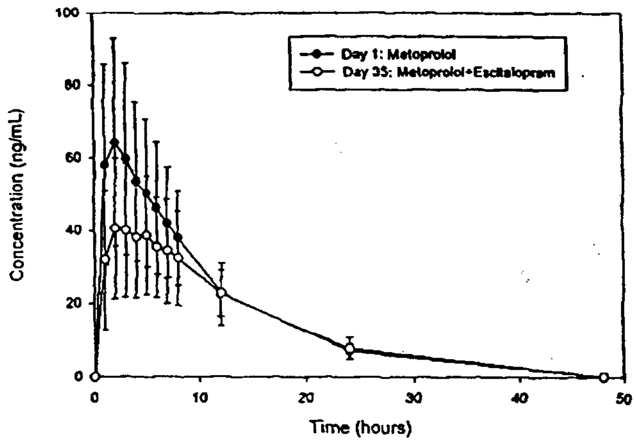
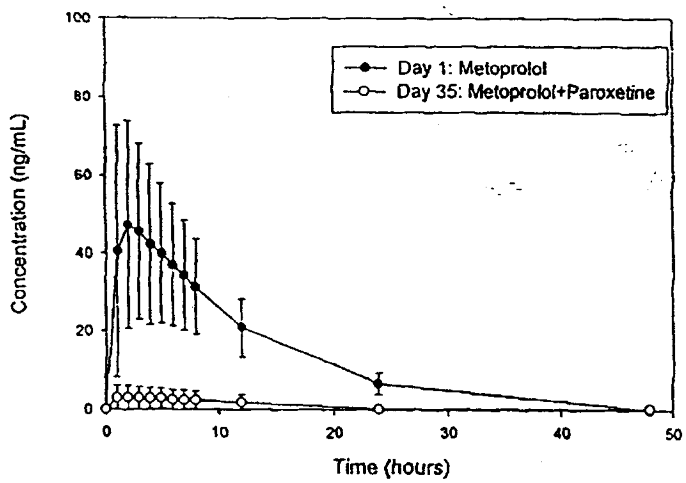


Figure 14. Mean α-Hydroxymetoprolol Concentrations Before (Day 1) and During Paroxetine Coadministration (Day 35) in Young Healthy Subjects



Study #7

Title: A comparison of the pharmacokinetic interaction of Lu 26-054 or fluoxetine with desipramine in healthy young subjects (Study# SCT-PK-01).

The primary objective of this study was to compare the effects of escitalopram and fluoxetine on desipramine pharmacokinetics in humans. A secondary objective was to compare the effects of escitalopram and fluoxetine on psychomotor function (as rated by the visual analog scale and Pittsburgh Sleep Quality Index) in healthy subjects when each drug was administered alone or concomitantly with desipramine.

This was a single center, double blind, parallel, multiple dose, randomized study in 40 young (18-35 years old) healthy male and female subjects. Subjects took one desipramine 50-mg tablet on Day 1, followed by a 7-day washout period. Subjects were then randomized (20 subjects per group) to receive double blind treatment with either one encapsulated escitalopram 10 mg tablet once daily for 7 days followed by two encapsulated escitalopram 10 mg tablets once daily for 21 days or one encapsulated fluoxetine 20 mg tablet once daily for 7 days followed by two encapsulated fluoxetine 20 mg tablets once daily for 21 days. On the last day of either escitalopram or fluoxetine dosing, the subjects also took one desipramine 50 mg tablet concomitantly. Blood samples (10mL each) for the determination of desipramine in plasma were collected from each subject at time 0, 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96, 120 hours after drug administration on Days 1 and 35. Blood samples (10 mL each) for the determination of escitalopram, fluoxetine and its metabolite norfluoxetine in plasma were collected from each subject at (pre-dose) on Days 9, 15, 22, 29, 33, 34, 35 and 42.

Escitalopram concentrations were determined by 0.5 mL plasma). The lower limit of quantification was Fluoxetine and norfluoxetine concentrations were measured using (1 mL plasma). The lower limit of quantification was ng/mL. Desipramine concentrations were determined by (0.2 mL plasma). The lower limit of quantification was .

Thirty nine subjects completed the study. Table 23 summarizes the pharmacokinetic parameters of desipramine on Day I (alone) and on Day 35 in combination with either escitalopram or fluoxetine. Coadministration of desipramine with fluoxetine or escitalopram resulted in increased Cmax and AUC values of desipramine as compared to desipramine alone. Fluoxetine increased desipramine

Cmax by 83% and AUC by 311% (Day 1 vs. Day 35 values). Fluoxetine increased the half-life of desipramine from 25 hours to 67 hours, almost a 3-fold increase. Escitalopram increased desipramine Cmax by 41% and AUC by 107% (Day 1 vs. Day 35 values). The half-life of desipramine increased by 8 hours (20.1 vs. 28.3 hrs) when given with escitalopram. Overall, the results of the study suggested that fluoxetine is much more potent inhibitor of CYP2D6 than escitalopram.

Significant decrease in alertness and coordination (as measured by visual analog scales [VAS]) as well as increases in nausea, drowsiness, and lightheadedness were noted by subjects after a single dose of desipramine. Despite the higher concentrations of desipramine following coadministration with either fluoxetine or escitalopram, there were no differences observed between the change in VAS scores from the first dose of desipramine (Day 1) and at Day 35 when desipramine was coadministered with either fluoxetine or escitalopram.

The Pittsburgh Sleep Quality Index (PSQI), a subjective estimate of the subject's sleep quality over the previous month, was administered at Day -1 (baseline) and Day 34 (following 27 days of either fluoxetine or escitalopram treatment. No differences were observed between the change in scores from baseline and at Day 34 between the escitalopram and fluoxetine treatment groups (PSQI scores indicated good sleep quality for both treatment groups).

Table 23. Pharmacokinetic Parameters (Mean ± SD) of Desipramine on Day 1 (Alone) and on Day 35 in Combination with Either Escitalopram or Fluoxetine

EFFECT OF ESCITALOPRAM		
	Desipramine Alone (Day 1); (n = 20)	*Desipramine + Escitalopram (Day 35); (n = 20)*
C_{max} (ng/mL)	20.9 ± 7.9	29.5 ± 7.8
T_{max} (hours)	6.3 ± 1.7	6.9 ± 4.3
AUC_{0-t} (ng•hr/mL)	517.1 ± 313.9	1016.2 ± 660.7
$AUC_{0-\infty}$ (ng•hr/mL)	587.3 ± 387.2	1218.3 ± 1023.4
t½ (hours)	20.1 ± 13.1	28.3 ± 17.5
CL/F (L/hr)	122.3 ± 74.2	62.0 ± 36.2
Vz/F (L)	2778.2 ± 1190.2	1907.3 ± 606.3
EFFECT OF FLUOXETINE		
	Desipramine Alone (Day 1); (n = 19)	*Desipramine + Fluoxetine (Day 35); (n = 19)*
C_{max} (ng/mL)	19.7 ± 9.6	36.0 ± 5.2
T_{max} (hours)	6.9 ± 2.1	7.9 ± 4.1
AUC_{0-t} (ng•hr/mL)	660.6 ± 612.7	2279.6 ± 369.9
$AUC_{0-\infty}$ (ng•hr/mL)	804.6 ± 844.0	3305.3 ± 771.7
t½ (hours)	24.8 ± 17.3	66.9 ± 15.6
CL/F (L/hr)	120.6 ± 81.1	15.9 ± 3.7
Vz/F (L)	2911.3 ± 1173.4	1474.0 ± 202.5

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Figure ~~6-1~~ 15. Mean Desipramine Concentrations Before (Day 1) and During Escitalopram Coadministration (20 mg/day, Day 35) in Young Healthy Male and Female Volunteers

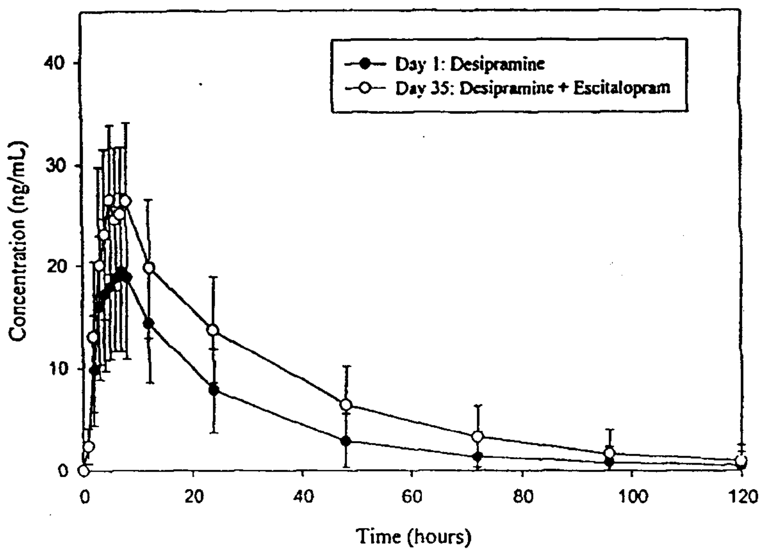
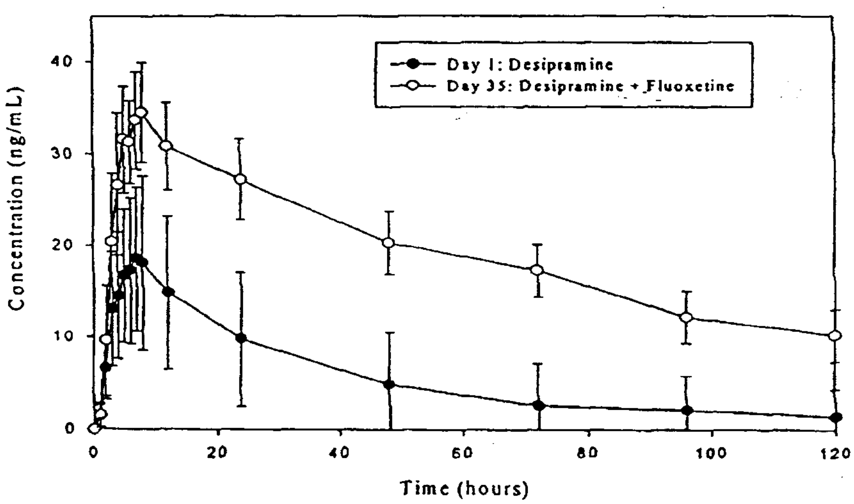


Figure ~~6-2~~ 16. Mean Desipramine Concentrations Before (Day 1) and During Fluoxetine Coadministration (40 mg/day, Day 35) in Young Healthy Male and Female Volunteers



Study #8

Title: A pharmacokinetic study of the combined administration of escitalopram and ritonavir in healthy young subjects (SCT PK 02).

The primary objective of this study was to evaluate the pharmacokinetic interaction of a single dose of ritonavir (600 mg) and a single dose of escitalopram (20 mg) in healthy young subjects.

This was a single center, open label, randomized, three-way crossover study in 21 healthy young subjects (22-34 years; 10 females and 11 males). Subjects received each of the following treatments in a randomized order, separated by an interval of 14 days:

1) a single dose of 600-mg ritonavir (6x100mg capsules)
2) a single dose of a 20-mg escitalopram tablet
3) co-administration of a single dose of 600 mg ritonavir and a single dose of a 20 mg escitalopram tablet.

Blood samples from each subject were taken at time 0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144 and 168 hours after drug administration on Days 1, 15 and 29. Plasma samples were assayed for R-citalopram, S-citalopram, R-demethylcitalopram, S- demethylcitalopram, R-didemethylcitalopram and S-didemethylcitalopram using a [redacted] method. The limit of quantification for escitalopram and its metabolites using 0.5 mL of plasma was [redacted]

Eighteen subjects completed the study. The results of the study have been summarized in Tables 23 and 24. The results of the study indicated that coadministration of ritonavir did not affect the pharmacokinetics of escitalopram. The Cmax of escitalopram was 20.9 ng/mL and 20.3 ng/mL in the absence and presence of ritonavir, respectively. There was no statistically significant difference in the AUC (659 vs 607 ng*hr/mL) when escitalopram was administered with or without ritonavir. The half-life of escitalopram (t½) was similar when escitalopram was administered alone (21.9 hours) and with ritonavir (20.9 hours).

The Tmax of S-DCT was approximately 20 hours when escitalopram was administered alone. Following coadministration with ritonavir, the Tmax was significantly longer (36 hours). The Cmax, AUC and T1/2 of S-DCT were not affected by ritonavir coadministration. The levels of S-didemethylcitalopram were below the quantification limit.

Escitalopram had no effect on the pharmacokinetics of ritonavir (Table 24).

Table 23. **Pharmacokinetic Parameters (Mean ± SD) of Escitalopram and S-DCT Following Administration of Escitalopram 20 mg Tablet With or Without Ritonavir**

ESCITALOPRAM	*Without Ritonavir (n = 18)*	*With Ritonavir (n = 18)*	*P value*
C_{max} (ng/mL)	20.9 ± 4.1	20.3 ± 4.0	0.714
T_{max} (hours)	4.3 ± 1.6	4.6 ± 1.3	0.172
AUC_{0-t} (ng•hr/mL)	562.7 ± 197.7	617.5 ± 198.3	0.805
$AUC_{0-\infty}$ (ng•hr/mL)	607.4 ± 203.8	658.9 ± 203.5	0.256
t½ (hours)	21.9 ± 5.6	20.9 ± 4.5	0.101
CL/F (L/hr)	37.0 ± 13.6	33.4 ± 10.9	0.086
Vz/F (L)	1079.0 ± 166.2	947.6 ± 141.0	0.001

S-DEMETHYLCITALOPRAM	*Without Ritonavir (n = 18)*	*With Ritonavir (n = 18)*	*P value*
C_{max} (ng/mL)	3.2 ± 0.7	3.1 ± 0.8	0.418
T_{max} (hours)	20.3 ± 10.2	36.3 ± 14.2	0.000
AUC_{0-t} (ng•hr/mL)	227.7 ± 65.7	227.1 ± 76.5	0.972
$AUC_{0-\infty}$ (ng•hr/mL)	322.0 ± 62.9	324.0 ± 63.4	0.881
t½ (hours)	52.8 ± 12.0	52.0 ± 13.6	0.770

Table 24. **Pharmacokinetic Parameters of Ritonavir Following Administration of 600 mg Ritonavir With or Without Escitalopram**

	Without Escitalopram (n = 18)	*With Escitalopram (n = 18)*	*P value*
C_{max} (µg/mL)	19.1 ± 7.3	16.5 ± 8.9	0.198
T_{max} (hours)	6.7 ± 2.7	6.8 ± 2.3	0.793
AUC_{0-t} (µg•hr/mL)	170.8 ± 71.7	158.4 ± 100.1	0.597
$AUC_{0-\infty}$ (µg•hr/mL)	187.2 ± 91.3	167.5 ± 105.1	0.468
t½ (hours)	5.0 ± 3.7	6.0 ± 6.3	0.486
CL/F (L/hr)	3.8 ± 1.5	6.5 ± 11.1	0.240
Vz/F (L)	23.2 ± 8.2	37.1 ± 43.6	0.159

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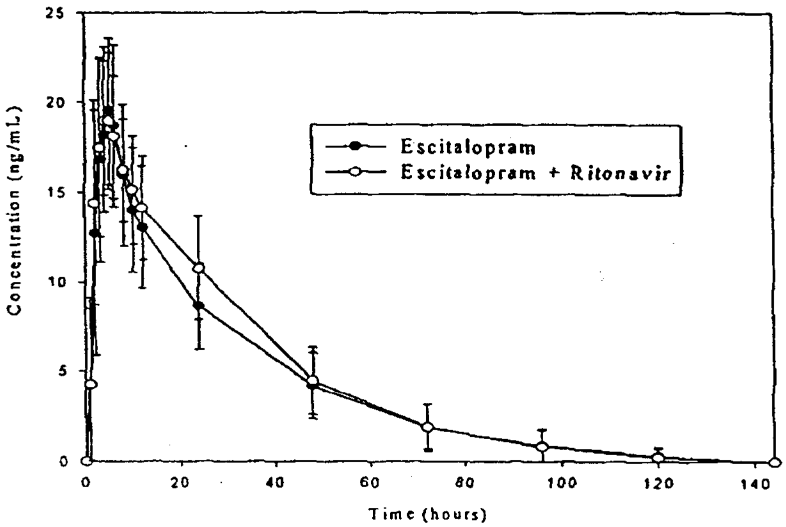
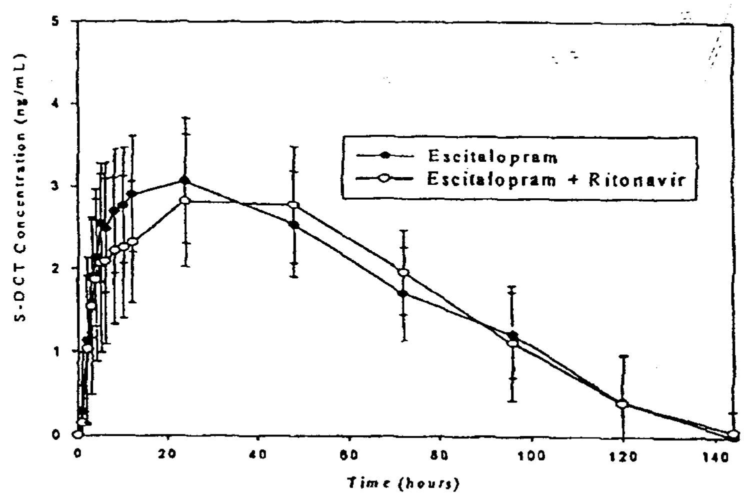
Figure ~~63~~. **Plasma Concentrations of Escitalopram when Administered Alone (20 mg) or in Combination with Ritonavir (600 mg) in Young Healthy Male and Female Subjects**



18
Figure ~~6-4~~. **Plasma Concentrations of S-Demethylcitalopram when Escitalopram was Administered Alone (20 mg) or in Combination with Ritonavir (600 mg) in Young Healthy Male and Female Subjects**

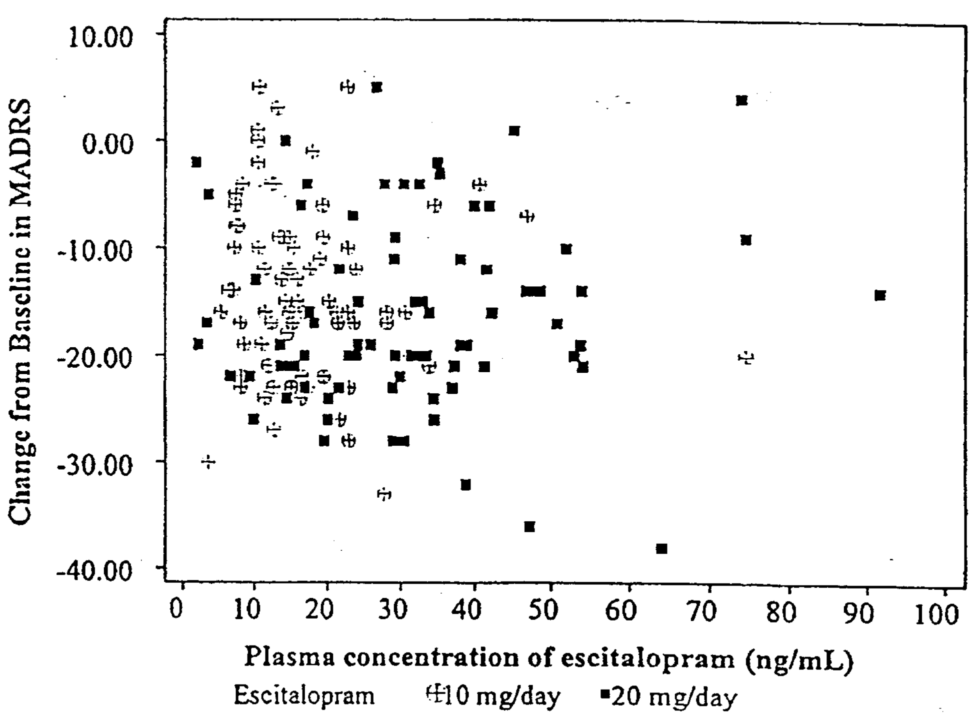


Study #9

In an attempt to establish a relationship between plasma concentration and efficacy (change in Montgomery Asberg Depression Rating Scale (MADRS) score from baseline), data from 155 escitalopram treated patients (77 on 10 mg/day and 78 on 20 mg/day escitalopram dose) were evaluated. One blood sample was taken from each patient within 27 hours after the final dose of escitalopram at the end of week 8 (Study SCT-MD-01). No relationship between plasma concentration and efficacy (change in MADRS score from baseline) was found (Pearson correlation coefficient = -0.43) over the dose range of 10 to 20 mg of escitalopram.

An E_{max} model evaluated by this reviewer also failed to establish any relationship between plasma concentration and change in MADRS score.

[redacted]. MADRS Change from Baseline versus Escitalopram Concentration



Dissolution

The dissolution of escitalopram oxalate tablets was performed using one of two methods: 1) in 800 mL of buffer, pH = 1.5 at 37°C using Apparatus 1 (baskets) rotating at 100 rpm. 2) in 900 mL of 0.1 N HCl at 37°C using Apparatus 2 (paddles) rotating at 50 rpm.

The Sponsor also used three media at different pH. The dissolution of escitalopram tablets was comparatively rapid in 0.1N HCl and buffer at pH 4.5 as compared to buffer at pH 6.8.

FDA's proposed dissolution method and specification for escitalopram oxalate tablets for all three strengths is as follows:

[redacted]

Q = [redacted] 30 minutes.

Table 6-34. *Dissolution Profile for Escitalopram* Oxalate 5 mg Tablets Used in Bioavailability Studies Method B

% Dissolved	
Lot Number	PD 1286
Date of Dissolution	
Method Used	B
Time (Limit)	
10 minutes	
Mean	99
%RSD	6.7
Minimum	
Maximum	
20 minutes	
Mean	103
%RSD	5.3
Minimum	
Maximum	
30 minutes	
Mean	103
%RSD	5.1
Minimum	
Maximum	

<u>Method B:</u>
Dissolution medium: [redacted]
Apparatus:
Analytical method: [redacted]

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Waiver Request for In Vivo Bioequivalence Study:

The Sponsor is requesting a waiver of evidence of *in vivo* bioequivalence between the 10 mg escitalopram commercial tablets and 10 mg escitalopram tablets used in clinical studies based upon the product characteristics, bioavailability/bioequivalence data and *in vitro* dissolution data as described below. The commercial formulation used in the bioequivalence study was manufactured at Forest Laboratories, Ireland (the proposed primary manufacturing site) while the clinical formulation batch was manufactured at [redacted]

Product Characteristics:

The escitalopram oxalate product intended for marketing (i.e., commercial formulation) in the U.S. is an immediate release tablet and will be available in 5, 10 and 20 mg strengths. The 5, 10 and 20 mg commercial formulation tablets are compositionally proportional.

The 20 mg commercial and clinical formulations contain the same ingredients and the same core tablet weight with the following exceptions: the magnesium stearate was [redacted] and the tablet shape was changed from oval to round. The two formulations (20 mg tablets) are bioequivalent in vivo. Since the 10 mg commercial formulation has half the amount of active ingredient and is also half of the weight as the Forest 20 mg tablet, the Forest commercial 10 mg tablet is likely to be bioequivalent to the Forest 10 mg clinical tablet.

Comparative Dissolution:

The escitalopram tablets used in the clinical studies were manufactured by [redacted] . whereas those intended for commercial use are manufactured by Forest Laboratories, Ireland. The dissolution profiles of the 5, 10 and 20 mg escitalopram tablets used in the clinical studies were compared to those of the corresponding commercial lots (Table 6-38 through 6-46) and were comparable. By 30 minutes, the dissolution was [redacted] in all three media.

Based on the following facts that:

1. The 20 mg commercial tablet is bioequivalent to the 20 mg clinical tablet.
2. The 10 and 20 mg clinical tablets are dose proportional in vivo (up to 30 mg).
3. The 10 mg commercial formulation is proportional to the 20 mg commercial formulation.
4. The dissolution profiles of the 10 mg clinical and 10 mg commercial tablets are similar.

Therefore, a waiver for bioequivalence study between the 10 mg commercial and 10 mg clinical tablets is granted.

Panel 5. Composition of Escitalopram Commerical Tablets

STRENGTH	5 mg		10 mg		20 mg	
INGREDIENTS (CORES)	mg/Tab	% w/w	mg/Tab	% w/w	mg/Tab	% w/w
Escitalopram Oxalate						
Talc USP						
Microcrystalline Cellulose [redacted] Colloidal Silicon Dioxide [redacted]						
Croscarmellose Sodium [redacted]						
Magnesium Stearate [redacted]						
Total Core Weight						
[redacted]						
Total Coated Tablet Weight (mg)						

Note: Tab = tablet

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6.6 Drug Formulations

The escitalopram development program described in this NDA included 8 pharmacokinetic/bioavailability studies and two phase III clinical studies performed by Forest Laboratories or H. Lundbeck. The tablet formulations described in this section were used in the completed pharmacokinetic and clinical studies.

6.6.1 Finished Product

The escitalopram oxalate formulations intended for marketing in the U.S. are immediate release tablet formulations available in 5, 10 and 20 mg strengths. The round, white to off-white, coated tablets differ in size and in the markings on the tablet indicating tablet strength.

6.6.2 Formulation Development

Table 6-27 through Table 6-29 lists the formulations for the 10, 20 and 30 mg escitalopram tablets, respectively used in the clinical studies. The tables contain the compositional codes for each tablet formulation, the batch numbers corresponding to the formulations, and the composition of each formulation. Table 6-32 describes the formulation and manufacturing changes for each tablet strength investigated during the development program.

At the early stage of drug product development, escitalopram tablet cores contained Talc USP, Microcrystalline Cellulose NF/Colloidal Silicon Dioxide NF (Prosolv SMCC 90), Croscarmellose Sodium NF, Colloidal Silicon Dioxide NF and Magnesium Stearate, NF. The tablets (Compositional Code D, Table 6.24) were white to off-white in color and were compressed to a standard oval shape at a running weight of 200 mg. This formulation was used in a single dose study evaluating the bioequivalence of 20 mg escitalopram to that of 40 mg racemic CT (Study 98106)[11].

The next batch of tablets (Compositional Codes A, E and H, Table 6-27 through Table 6-29, respectively) contained the same ingredients as the above tablets with a nominal increase in the amount of Talc (—), Croscarmellose Sodium (—) and a decrease in Magnesium Stearate (—). The tablet cores are white to off white; oval shaped and had an average weight of — or all doses (10 mg, 20 mg and — strengths). These formulations were used in a multiple dose study assessing the bioequivalence of 10 and 30 mg escitalopram tablets to 20 and 60 mg racemic CT (Study 98107)[12].

The investigational drug product used in the next phase of pharmacokinetic and clinical studies (Compositional Codes B, C and F, Table 6-27 and Table 6-28) was a film-coated tablet containing similar tablet core ingredients that were used in the initial single and multiple dose pharmacokinetic studies (Studies SCT-PK-01, -02, -03, -04, -05, and SCT-MD-01). In addition to the tablet core ingredients listed above, the film coated tablets contained Hydroxypropyl Methyl Cellulose/ —— , Titanium Dioxide USP and —— Polyethylene Glycol — The lot numbers of this formulation used in the listed pharmacokinetic and clinical studies are presented in Table 6-32. A pharmacokinetic study (Study 98113) in young healthy subjects using a tablet lot with this formulation (10 mg tablet, Compositional Code C) showed that this tablet was bioequivalent to the 10 mg Lundbeck clinical formulations[13].

The drug product manufactured by Forest for commercial purposes (Compositional Code G, Table 6-28) is similar in formulation, composition and color to that of the investigational drug product used in clinical studies with the exception of the shape and tablet weight. There is a slight increase in magnesium stearate from —— to optimize the compression process. The tablet weighs — This formulation was used in the pharmacokinetic study (Study SCT-PK-04) evaluating the bioequivalence of 20 mg escitalopram tablets (Compositional Code F) used in the clinical studies and the 20 mg escitalopram tablets intended for commercial use[9]. This study showed that all calculated 90% confidence intervals for escitalopram (C_{max} and AUC) fell within the acceptance criterion of 80 – 125% demonstrating bioequivalence of these products.

6.6.3 Composition

Table 6-27 lists by study the tablet lots of escitalopram oxalate used in clinical bioavailability/bioequivalence, pharmacokinetic and the phase III depression studies. The table provides the protocol number, tablet strength and manufacturing lot number. Table 6-32 lists the tablet formulations by strength and lot number.

The final (commercial) Forest Laboratories formulation of escitalopram tablets (Compositional Code G) consists of escitalopram oxalate —), Talc — — w/w), Microcrystalline Cellulose — Colloidal Silicon Dioxide — — Croscarmellose Sodium — — , Magnesium Stearate — , w/w), ——), Titanium Dioxide — , Macrogol w/w). The total weight of this tablet is — This differs from the H. Lundbeck A/S clinical formulation (Compositional Code I) in that the latter is proportional compositionally; i.e., all the ingredients (including inert) increase proportionally with increasing dose.

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In-Vitro metabolism of escitalopram

Transformation of escitalopram (S-CT), the pharmacologically active S-enantiometer of citalopram,to S-desmethyl-CT (S-DCT), and of S-DCT to S-didesmethyl-CT (S-DDCT), was studied in human liver microsomes and in expressed CYPs. Biotransformation of the R-enantiomer (R-CT) was studied in parallel. S-CT was transformed to S-DCT by CYP2C19 (K_m = 69 μM), CYP2D6 (K_m = 29 μM) and CYP3A4 (K_m = 588 μM). After normalization for hepatic abundance, relative contributions to net intrinsic clearance were: 37% for CYP2C19, 28% for CYP2D6, and 35% for CYP3A4. At 10 μM S-CT in liver microsomes, S-DCT formation was reduced to 60% of control by 1 μM ketoconazole, and to 80-85% of control by 5 μM quinidine or 25 μM omeprazole. S-DDCT was formed from S-DCT only by CYP2D6; incomplete inhibition by quinidine in liver microsomes indicated participation of a non-CYP pathway. Based on established index reactions, S-CT and S-DCT were negligible inhibitors (IC_{50} > 100 μM) of CYP1A2, 2C9, 2C19, 2E1, and 3A, and weakly inhibited CYP2D6 (IC_{50} = 70-80 μM). R-CT and its metabolites, studied using the same procedures, had properties very similar to the corresponding S-enantiomers. Thus S-CT, biotransformed by three CYP isoforms in parallel, is unlikely to be affected by drug interactions or genetic polymorphisms. S-CT and S-DCT also are unlikely to cause clinically important drug interactions via CYP inhibition.

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RESULTS

Inhibition studies

In all systems the positive control inhibitors produced the expected degree of inhibition of their respective index reactions (Table 1).

CYP1A2. R- and S-CT and metabolites all were negligible inhibitors of phenacetin O-deethylation, the index reaction for CYP1A2. None of these compounds produced 50% inhibition. The mean IC_{50} for α-naphthoflavone was 0.2 μM, and the mean IC_{50} for fluvoxamine was 0.3 μM.

CYP2C9. R-CT, S-CT, R-DCT, and S-DCT were weak inhibitors of CYP2C9, represented by tolbutamide hydroxylation, with less than 50% inhibition produced even at 250 μM. R-DDCT and S-DDCT produced a moderate degree of inhibition, with IC_{50} values of 30.7 (±6.3) μM and 25.7 (±8.0) μM, respectively. Sulfaphenazole was a strong inhibitor (IC_{50}=1.3 μM), and the SSRI fluvoxamine also was a moderately strong inhibitor (IC_{50}=9.4 μM).

CYP2C19. R- and S-CT were very weak inhibitors, with less than 50% inhibition of S-mephenytoin hydroxylation even at 100 μM. R- and S-DCT also were weak inhibitors. R- and S-DDCT were moderate inhibitors, with mean IC_{50} values of 18.7 μM and 12.1 μM, respectively. Omeprazole was a strong inhibitor of CYP2C19, as was the SSRI fluvoxamine (see Table 2).

CYP2D6. Only R-DCT had potentially important inhibiting potency versus CYP2D6, represented by dextromethorphan O-demethylation. The mean IC_{50} was 25.5 (±2.1) μM. This is very close to the inhibitory potency of sertraline, and is consistent with clinical data suggesting that racemic citalopram and sertraline have comparably weak CYP2D6 inhibitory potency. The SSRI paroxetine was at least an order of magnitude more potent (IC_{50}=2.6 μM) than R-DCT as a CYP2D6 inhibitor (see Table 2). Fluoxetine and norfluoxetine (mean IC_{50} 2.0 and 2.7 μM, respectively) also were strong CYP2D6 inhibitors.

CYP3A. CT and metabolites all were very weak or negligible inhibitors of CYP3A, as indicated by triazolam hydroxylation. None of the compounds (at 100 μM) produced more than 50% inhibition. Fluvoxamine and nefazodone were moderately strong inhibitors.[16,30]

CYP2E1. CT and metabolites were weak or negligible inhibitors of chlorzoxazone 6-hydroxylation, producing less than 20% inhibition at 250 μM.

Enzyme kinetic studies: liver microsomes

The mean K_m for biotransformation of R-CT to R-DCT was higher than for S-CT (256 vs 165 μM)(Figure 1). Using the V_{max}/K_m ratio ("intrinsic clearance") as an approximation of metabolic activity at low substrate concentrations, the mean ratio for S-CT exceeded that for R-CT (6.1 vs. 4.9 μL/min/mg protein), but the difference was not statistically significant based on Student's paired t-test.

The mean K_m for biotransformation of R-DCT to R-DDCT was higher than for S-DCT (108 vs. 72 μM) (Figure 2). Based on the V_{max}/K_m ratio, intrinsic clearance for S-DCT was slightly higher than for R-DCT (1.32 vs. 1.17 μL/min/mg protein). Furthermore intrinsic clearances for DCT formation from R- or S-CT both were higher than clearances for transformation of DDCT from R- or S-DCT.

Enzyme kinetic studies: individual human cytochromes.

Table 3 shows enzyme kinetic values for formation of DCT from R- and S-CT by heterologously-expressed human CYP2C19, 2D6, and 3A4 (Figure 3). Consistent with prior studies of racemic CT[1], CYP2D6 had the highest affinity (lowest K_m), CYP3A4 had the lowest affinity, and CYP2C19 fell in between. This was true for both R-CT and S-CT. V_{max}/K_m ratios corresponding to each of the isoforms were higher for S-CT than for R-CT.

After normalization for estimated relative abundance of the three individual CYP isoforms, CYP3A accounted for 46% of net intrinsic clearance of R-CT, CYP2C19 for 33%, and CYP2D6 for 21%. For S-CT, CYP3A accounted for 35% of net clearance, CYP2C19 for 37%, and CYP2D6 for 28% (Figure 4)(Table 4).

Figure 5 show the biotransformation of R-DCT and S-DCT to DDCT by heterologously-expressed CYP2D6. K_m values (12.4 and 16.8 μM, respectively; Table 3) were lower than the high-affinity components of the reaction in liver microsomes.

Chemical inhibition of CT and DCT biotransformation in microsomes.

At 10 μM of R- or S-CT, ketoconazole reduced reaction velocity to 55-60% of control, quinidine to 80% of control, and omeprazole to 80-85% of control (Figure 6). When the R- and S-CT concentration was increased to 100 μM, the degree of inhibition by ketoconazole increased, while inhibition by quinidine decreased (Figure 6). These findings are consistent with the data from heterologously-expressed CYP isoforms.

Quinidine (5 μM) reduced formation of DDCT from R-DCT or S-DCT by only 50%, whereas the same concentration of quinidine reduced formation of R-DCT and S-DCT to less than 10% of control values in heterologously-expressed CYP2D6.

DISCUSSION

R-CT, S-CT, R-DCT, and S-DCT are weak or negligible inhibitors of human cytochromes (CYP) 1A2, 2C9, 2C19, 2E1, and 3A in human liver microsomes. R- and S-CT also are weak or negligible inhibitors of CYP2D6. The R isomer of DCT is a weak to moderate inhibitor of CYP2D6, comparable in potency to sertraline. R- and S-DDCT are moderate inhibitors of CYP2C9 and 2C19. However this is unlikely to be of clinical importance due to the low plasma levels of DDCT achieved clinically.

Transformation clearance of S-CT to DCT in liver microsomes is higher than that of R-CT, accounting for the trend to higher plasma levels of R-CT during clinical use of racemic citalopram, and the shorter elimination half-life of S-CT.[5-7] Formation clearance of DCT from CT exceeds elimination clearance of DCT to DDCT. Since plasma levels of DCT do not exceed those of CT during clinical use of racemic citalopram, the findings suggest that another metabolic pathway (in addition to formation of DDCT), or another mechanism of elimination, may contribute to DCT clearance.[31, 32]

Studies with heterologously-expressed human CYP isoforms indicate that CYP2D6, -2C19, and -3A all contribute to formation of DCT from R- or S-CT, with CYP3A accounting for 35-46% of net intrinsic clearance. The contribution of CYP3A is predicted to increase at higher concentrations of CT, while the contribution of CYP2D6 is predicted to decrease. This was verified by studies of chemical inhibition of this reaction in liver microsomes by index inhibitors. As in the case of liver microsomes, intrinsic clearance of S-CT by the three CYP isoforms was higher than that of R-CT.

CYP2D6 was the only identified CYP isoform mediating formation of DDCT from R- or S-DCT. However, these were high-affinity (low K_m) reactions in expressed CYP2D6, with K_m values lower than the high-affinity component in liver microsomes. Furthermore, the reaction was incompletely inhibited by quinidine (5 μM) in liver microsomes. This again suggests participation of some other process mediating net biotransformation of DCT.[31, 32]

Thus S-CT (escitalopram) is biotransformed to its principal demethylated metabolite by three distinct human CYP isoforms in parallel. As such, impaired activity of any one of these isoforms, due to a drug interaction or a genetic "*slow metabolizer*" polymorphism, is unlikely to have a large effect on net metabolic clearance. S-CT and its metabolites are weak or negligible inhibitors of *human* CYP *isoforms*, indicating that clinically important drug interactions due to impaired CYP activity are unlikely.[33-36]

TABLE 1

IN VITRO SYSTEMS FOR EVALUATING

CYP INHIBITORY ACTIVITY OF

CITALOPRAM STEREOISOMERS AND METABOLITES

CYP isoform	Substrate (with concentration)	Product	Index inhibitor (mean±SE IC_{50})
1A2	Phenacetin (100 μM)	Acetaminophen	α-Naphthoflavone (0.2±0.05 μM)
2C9	Tolbutamide (100 μM)	Hydroxytolbutamide	Sulfaphenazole (1.3±0.04 μM)
2C19	S-mephenytoin (25 μM)	4'-Hydroxymephenytoin	Omeprazole (4.2±0.08 μM)
2D6	Dextromethorphan (25 μM)	Dextrorphan	Quinidine (0.43±0.05 μM)
2E1	Chlorzoxazone (50 μM)	6-Hydroxychlorozoxazone	Diethydithio-carbamate* (16.6±3.2 μM)
3A	Triazolam (250 μM)	α-Hydroxytriazolam	Ketoconazole (0.07±0.01 μM)

*Preincubated with microsomes prior to addition of substrate.

TABLE 2

IC_{50} VALUES VERSUS

S-MEPHENYTOIN HYDROXYLATION (CYP2C19) or

DEXTROMETHORPHAN O-DEMETHYLATION (CYP2D6)

Compound	IC_{50} (mean±SE), μM S-mephenytoin* hydroxylation	dextromethorphan* O-demethylation
Index inhibitor		
	Omeprazole:	Quinidine:
	4.2 (±0.8)	0.43 (±0.5)
Citalopram and metabolites		
R-CT	186 (±26)	126 (±16)
S-CT	>250	73 (±5)
R-DCT	77.4 (±8.1)	25.5 (±2.1)
S-DCT	>250	78 (±5)
R-DDCT	18.7 (±4.0)	81 (±11)
S-DDCT	12.1 (±1.9)	121 (±13)
SSRI comparator	Fluvoxamine: 0.62 (±0.08)	Paroxetine: 2.6 (±0.3)
		Sertraline: 29.9 (±4.5)
		Desmethylsertraline: 81 (±12)

*Concentration = 25 μM

TABLE 3

KINETIC ANALYSIS OF BIOTRANSFORMATION OF CITALOPRAM AND DESMETHYCITALOPRAM ENANTIOMERS BY HETEROLOGOUSLY-EXPRESSED HUMAN CYTOCHROMES

Transformation reaction	Cytochromes: CYP2C19	CYP2D6	CYP3A4
R-CT to DCT			
V_{max}	1.65	2.18	2.15
K_m	77	47	454
V_{max}/K_m	2.13	4.63	0.47
Abundance-adjusted relative V_{max}/K_m	32.9%	20.7%	46.3%
S-CT to DCT			
V_{max}	2.52	2.73	3.19
K_m	69	29	588
V_{max}/K_m	3.63	9.54	0.54
Abundance-adjusted relative V_{max}/K_m	36.9%	28.1%	34.9%
R-DCT to DDCT			
V_{max}		0.63	
K_m		12.4	
V_{max}/K_m		5.04	
S-DCT to DDCT			
V_{max}		0.58	
K_m		16.8	
V_{max}/K_m		3.44	

Units are: V_{max}, picoMoles/min/picoMole P450
K_m, μM
V_{max}/K_m: nanoliters/min/picoMole P450
Relative V_{max}/K_m: % of total

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Comments to the Medical Reviewer

1. Please evaluate the effect of coadministration of escitalopram and metoprolol on blood pressure and heart rate.

2. Escitalopram produced negligible inhibitory effect on 2D6 in vitro. However, in-vivo studies with CYP2D6 substrates (metoprolol and desipramine) indicated that escitalopram has inhibitory effect on CYP2D6. Co-administration of escitalopram (20 mg/day for 21 days) with metoprolol (single dose of 100 mg) or desipramine (single dose of 50 mg) increased the AUC of metoprolol by 82% and desipramine by 100%.

Since in-vivo study is more clinically relevant than in-vitro study, therefore, from in-vivo study it has been concluded that escitalopram will have inhibitory effect on CYP2D6 substrates. Please ensure that

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Recommendation:

This NDA as submitted is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

The Sponsor's request for the waiver of in vivo bioequivalence study between the 10 mg escitalopram commercial tablets and 10 mg escitalopram tablets used in clinical studies based upon the product characteristics and in vitro dissolution data is granted.

FDA's proposed dissolution method and specification for all three strengths of escitalopram oxalate tablets is as follows:

[redacted]

Please convey the labeling comments, dissolution method and specification, and the recommendation to the Sponsor.

Iftekhar Mahmood, Ph. D.
Division of Pharmaceutical Evaluation I

RD/FT initialed by Raman Baweja, Ph. D. ____________________

OCPB briefing: November 20, 2001

CC: NDA 21-323
HFD-120, HFD-860 (Mahmood, Baweja, Mehta).

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