CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Escitalopram Oxalate-Lexapro	PRIMARY REVIEWER: Andre Jackson
	TYPE: SNDA
NDA: 21323/S-30/S30-Tablets	STRENGTH: 5 mg, 10 mg and 20 mg
NDA: 21365/S-20/S21-Oral Solution	STRENGTH: 5 mg/5ml
APPLICANT: Forest Laboratories	Submission Date: May 22, 2008

INDICATIONS: Depression

Review of Three Pharmacokinetic studies in Adolescent Children 12-17 Years for Lexapro

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STUDY CIT-PK-07 COMPARISON OF CITALOPRAM PHARMACOKINETICS IN ADULTS AND PEDIATRICS FOLLOWING A 40 MG DOSE

INTRODUCTION

Citalopram (CIT) is a bicyclic phthalein derivative which pharmacologically is characterized as a selective and potent inhibitor of the neuronal uptake of serotonin (5-HT) in the central nervous system. Escitalopram, the pure S-enantiomer of CIT, is primarily responsible for the serotonin reuptake inhibition produced by CIT. The bioavailability of citalopram is nearly complete with negligible first-pass metabolism. The predominant metabolite of CIT in humans is demethylcitalopram (DCT). Compared to CIT, this metabolite is present in lower concentrations and is relatively inactive as a serotonin reuptake inhibitor (SRI). The half-lives of CIT and DCT in normal healthy volunteers are approximately 35 and 60 hours, respectively. Another less predominant metabolite,

didemethylcitalopram (DDCT), has a half-life of 100 hours and is even less active than DCT as an SRI. Elimination of citalopram is predominantly hepatic (87%).

PURPOSE OF THE STUDY

The primary objective of this study was to evaluate the pharmacokinetics of citalopram, DCT (demethylcitalopram), and DDCT (didemethylcitalopram) and their enantiomers in pediatric patients with depression (compared to adult patients with depression), following titration to a dose of 40 mg daily from a starting dose of 20 mg daily. The secondary objectives were to assess the safety and efficacy of citalopram in pediatric patients.

Since the S-enantiomer of CIT is responsible for activity only R-citalopram, S-citalopram, S-demethyl-citalopram and S-didemethylcitalopram will be reported in this review.

METHODS

The study was a 4 week, open-label, parallel groups, multiple-dose, dose-escalating study. The study was done in a single group of pediatric patients from 10-17 years of age for comparison with the adult patients 21-45 yrs of age.

The patients received racemic citalopram at a starting dose of 20 mg daily for one week and then received citalopram 40 mg daily for 3 weeks.

Blood and urine samples for pharmacokinetic analysis were collected throughout the study.

Demographics:

	Adult N=12	Pediatric N=13	All Patients N=25
Age, years			
Mean	36	14.2	24.7
Standard Deviation	6.4	1.9	12.0
Min – Max	21, 44	10, 17	10, 44
Weight, kg			
Mean	77.6	62.3	69.6
Standard Deviation	14.95	11.69	15.2
Min – Max	55.8, 102.5	41.2, 78.2	41.2, 102.5
Height, cm			
Mean	172.8	165.9	169.2
Standard Deviation	12.3	12.8	12.8
Min – Max	157.0, 193.0	146.0, 191.7	146.0, 193.0

Twenty-three (23) of the 25 patients who were enrolled completed the study. Two patients #01131, 16 years old (unable to establish reliable venous access on Day 1) and #02105, an adult (lost to follow-up on Day 20) did not complete the study.

Blood Sampling and Collection Procedure

Twenty-four (24) blood samples for determination of the concentrations of the enantiomers of citalopram and their metabolites were collected. Seventeen (17) blood samples for determination of the concentration of the enantiomers of citalopram and their metabolites were collected for the patient under 12 years of age.

Day 1: 0.0 hour (pre-dose) and 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0 hours post-dose
Day 2: 24.0 hours (post-dose)
Day 8: 0.0 hour (pre-dose)
Day 27: 0.0 hour (pre-dose)
Day 28: 0.0 hour (pre-dose), and 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, and 12.0 hours postdose.
Days 29, 30, 32, 34, and 35: 24.0, 48.0, 96.0, 144.0, and 168.0 hours post the Day 28 final drug dose.

For the patient under 12 years of age only 17 blood samples were collected, for a total of 145 mL of blood (including 60 mL for pre-study, Day 8, and post-study clinical analysis), at the following timepoints:
Day 1: 0.0 hour (pre-dose) and 1.0, 2.0, 4.0, 8.0, and 12.0 hours post-dose
Day 2: 24 hours post dose

Day 8: 0.0 hour (pre-dose)
Day 28: 0.0 hour (pre-dose), and 1.0, 2.0, 4.0, 8.0, and 12.0 hours post-dose.
Days 29, 30, and 32: 24.0, 48.0, and 96.0, hours post the Day 28 final drug dose.

DATA ANALYSIS

The area under the plasma concentration time curve (AUC0-t and AUC0-∞), maximum plasma concentration (Cmax), time of maximum plasma concentration (Tmax), and elimination half-life (t½) were obtained from the plasma concentrations as described below. The areas under the plasma concentration versus time curves up to the last measurable concentration (AUC0-t) were estimated by numerical integration using the linear trapezoidal rule

$$AUC_{0-t} = \sum_{i=2}^{n} 0.5 \ (C_i + C_{i-1}) \ (t_i - t_{i-1})$$

where Ci was the plasma concentration at the corresponding sampling time point ti. The values of the elimination rate constant (λz) for citalopram, DCT, R-CT, escitalopram, R-DCT and S-DCT were determined by a non-compartmental analysis. A regression analysis was performed on the terminal linear phase of the semi-logarithmic plots of individual plasma concentration time-data.

STATISTICAL EVALUATION

Pharmacokinetic Parameters
Estimates of mean values obtained for pharmacokinetic parameters were compared between age groups and between genders using standard statistical procedures. Statistical analyses were performed with the Statistical Analyses System (SAS) version 6.12 for the UNIX system microcomputer using the General Linear Models procedure (GLM).
Analysis of variance (ANOVA) was performed on the pharmacokinetic parameters including Cmax, AUC0-24 and Tmax after the initial doses, and Cmax, AUCss, Tmax, t½, Vz/F, CL/F and Ae0-24 after the final dose. AUC and Cmax were log-transformed in the analysis of variance.

Analytical
DETAILED STUDY REPORTS
ASSAY VALIDATION
Analytical- The assay for citalopram was a chiral assay.

Parameter	R-citalopram	S-citalopram	S-demethyl-citalopram	S-didemethylcitalopram
Method	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS
Concentration Range	3.75-75 ng/ml	3.75-75 ng/ml	3.75-75 ng/ml	3.75-75 ng/ml
Number of Freeze-thaw	3	3	3	3
Benchtop Stability at RT	2 hrs	2 hrs	2 hrs	2 hrs
Long term at –30° C	27 months	27 months	27 months	27 months
Extraction Recovery	(b) (4)			

WITHIN STUDY RESULTS:
Study Dates: August 9, 1999 to November 11, 2000
Total Storage: 15 months

Parameter	R-Citalopram	S-Citalopram	S-demethyl-citalopram	S-didemethylcitalopram
Method	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS
Sensitivity/LOQ	1 ng/ml	1 ng/ml	1 ng/ml	1 ng/ml
Linearity (Standard curve samples)	1-150 ng/ml	1-150 ng/ml	1-150 ng/ml	1-150 ng/ml
Quality Control (QC) Samples	3.75 ng/ml 15 ng/ml 75 ng/ml	3.75 ng/ml 15 ng/ml 75 ng/ml	3.75 ng/ml 15 ng/ml 75 ng/ml	3.75 ng/ml 15 ng/ml 75 ng/ml
Precision of Standards (%CV)	1.8% @ 1 ng/ml 2.5% @ 150	1.7% @ 1 ng/ml 2.4% @ 150	4.2% @ 1 ng/ml 2.0% @ 150	1.9% @ 1 ng/ml 2.7% @ 150

	ng/ml	ng/ml	ng/ml	ng/ml
Precision of QC Samples (%CV)	5.7% @3.75 ng/ml 6.3% @ 75 ng/ml	7.9% @3.75 ng/ml 7.3% @ 75 ng/ml	7.7% @3.75 ng/ml 8.2% @ 75 ng/ml	6.3% @3.90 ng/ml 7.0% @ 78 ng/ml
Accuracy of Standards (%)	99% @ 1 ng/ml 99% @ 150 ng/ml	99.4% @ 1 ng/ml 99.7% @ 150 ng/ml	99% @ 1 ng/ml 99% @ 150 ng/ml	99% @ 1 ng/ml 99% @ 150 ng/ml
Accuracy of QC Samples (%)	98% @ 1 ng/ml 99% @ 75 ng/ml	96% @ 1 ng/ml 99% @ 75 ng/ml	97% @ 1 ng/ml 97% @ 75 ng/ml	96.5@3.9 ng/ml 98%@78 ng/ml

RESULTS

Table 1. Incidence of Treatment Emergent Adverse Events (≥3 patients)

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Preferred Term	Adult (N=12) n (%)	Pediatric (N=13) n (%)
Patients with at least one TEAE	12 (100)	10 (76.9)
Headache	5 (41.7)	3 (23.1)
Nausea	2 (16.7)	3 (23.1)
Fatigue	1 (8.3)	3 (23.1)
Rhinitis	3 (25.0)	1 (7.7)
Decreased Appetite	1 (8.3)	2 (15.4)
Dry Mouth	2 (16.7)	1 (7.7)
Insomnia	1(8.3)	2 (15.4)
Lightheaded feeling	3 (25)	0 (0)

The adverse events appeared to be comparable in adults and pediatric populations.

PHARMACOKINETIC RESULTS

In general, none of the patients had detectable concentrations of didemethylcitalopram during the 24 hour period after the initial dose of 20 mg citalopram and the concentrations for didemethylcitalopram in the steady state were too low to estimate the pharmacokinetic parameters. Therefore, the pharmacokinetic parameters for didemethylcitalopram were not calculated.

The PDR reports, " At steady state, the concentrations of citalopram's metabolites, DCT and DDCT, in plasma are approximately one-half and one-tenth, respectively, that of the parent drug. *In vitro* studies show that citalopram is at least 8 times more potent than its metabolites in the inhibition of serotonin

reuptake, suggesting that the metabolites evaluated do not likely contribute significantly to the antidepressant actions of citalopram. In addition Escitalopram is at least 100-fold more potent than the R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. For this review results for S and R citalopram will be presented.

Pharmacokinetics

SINGLE DOSING

Figure 1. Plasma Concentrations (mean±SD) of Escitalopram after a Single Dose Administration of 20 mg Citalopram in Pediatric vs. Adult Patients

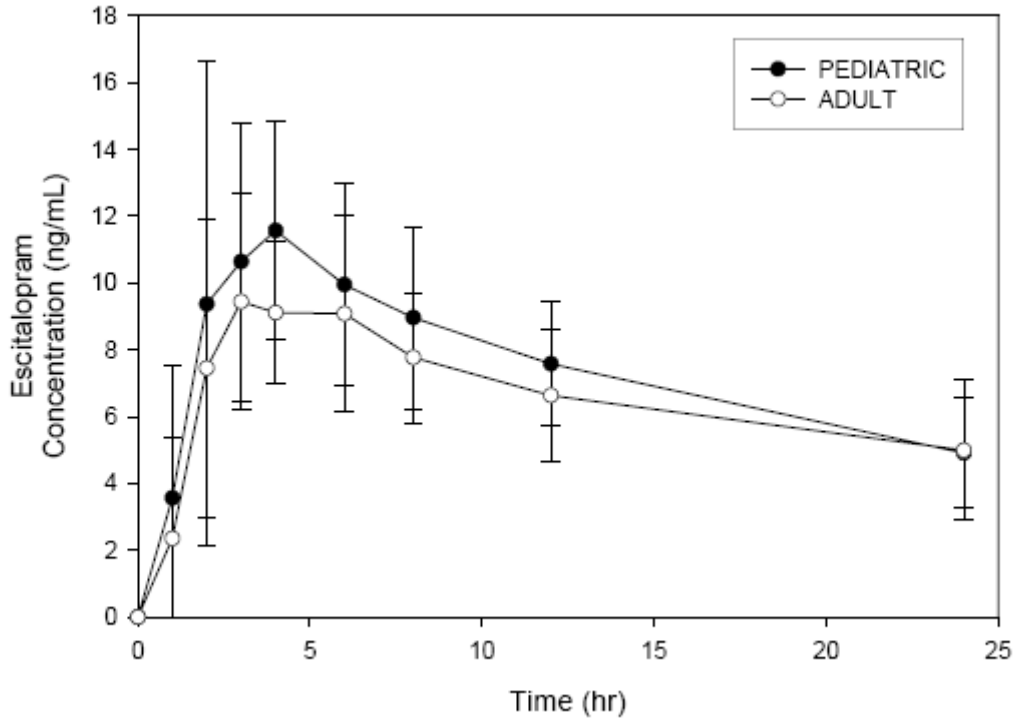


Figure 2. Plasma Concentrations (mean±SD) of R-citalopram after a Single Dose Administration of 20 mg Citalopram in Pediatric vs. Adult Patients.

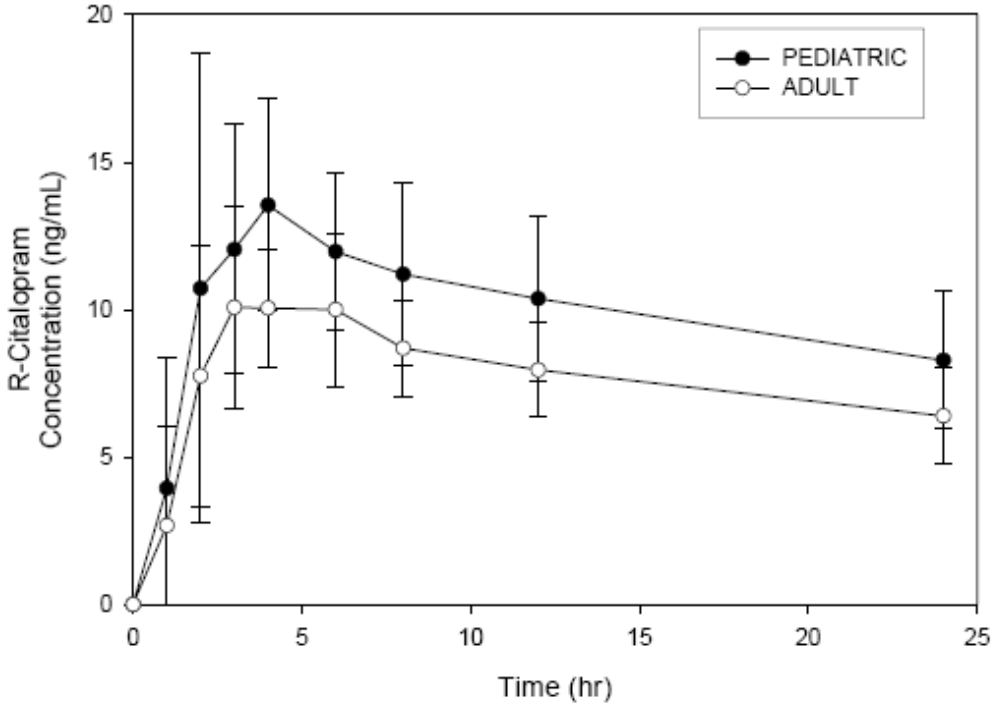


Figure 3. Plasma Concentrations (mean±SD) of Escitalopram after a Single Dose Administration of 20 mg Citalopram in Male vs. Female Patients.

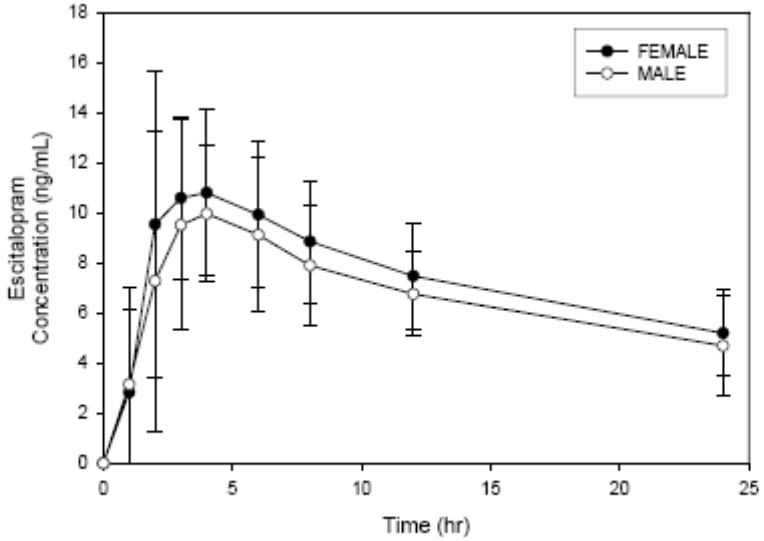


Figure 4. Plasma Concentrations (mean±SD) of R-citalopram after a Single Dose Administration of 20 mg Citalopram in Male vs. Female Patients.

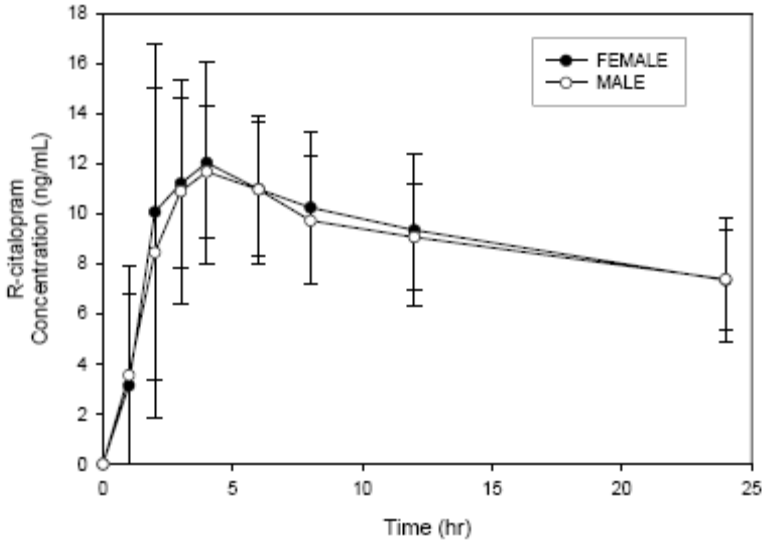


Table 1. Pharmacokinetic Parameters (Mean ± SD) Escitalopram following a Single Dose of 20 mg Citalopram in Adult and Pediatric Patients.

Escitalopram			
PK Parameters	Adult (N=11)	Pediatric (N=12)	p-value
C_{max} (ng/mL)	11.2 ± 2.8	13.1 ± 4.4	0.149
T_{max} (hr)	3.4 ± 1.8	3.5 ± 1.4	0.809
AUC_{0-24} (hr* ng/mL)	157.4 ± 41.2	179.4 ± 52.2	0.196

Table 2. Pharmacokinetic Parameters (Mean ± SD) of Escitalopram following a Single Dose of 20 mg Citalopram in Female and Male Adult and Pediatric Patients.

Escitalopram			
PK Parameters	Female (N=12)	Male (N=11)	p-value
C_{max} (ng/mL)	12.9 ± 3.6	11.4 ± 4.0	0.168
T_{max} (hr)	3.5 ± 1.6	3.3 ± 1.6	0.809
AUC_{0-24}(hr* ng/mL)	178.0 ± 49.5	158.9 ± 45.6	0.232

MULTIPLE DOSING

Figure 5. Plasma Concentrations (mean±SD) of Escitalopram after a Multiple Dose Administration of 40 mg/day Citalopram in Pediatric vs. Adult Patients.

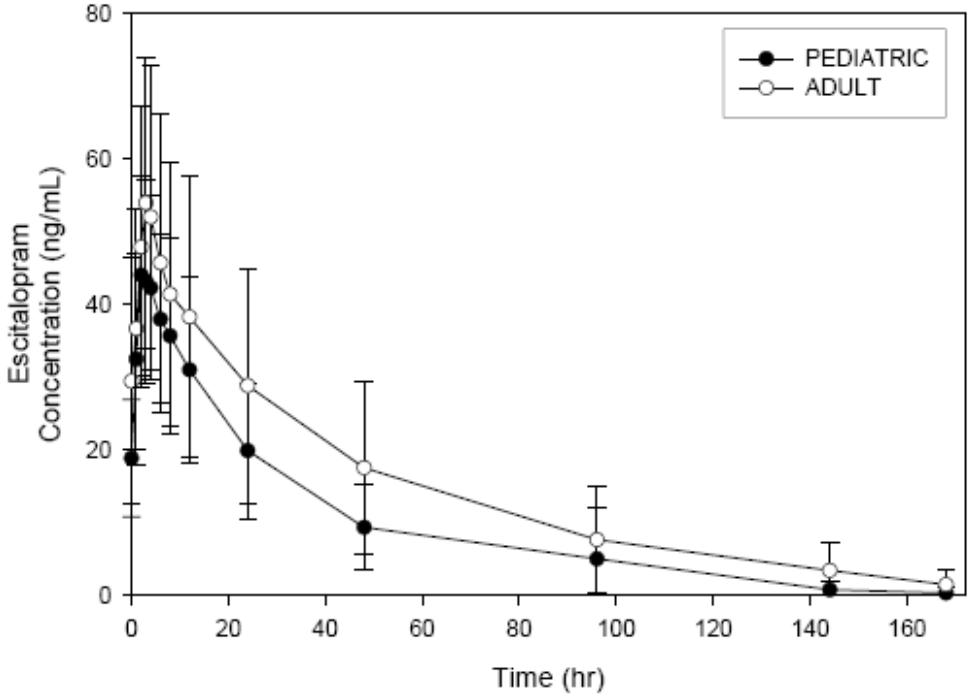


Figure 6. Plasma Concentrations (mean±SD) of R-citalopram after a Multiple Dose Administration of 40 mg/day Citalopram in Pediatric vs. Adult Patients.

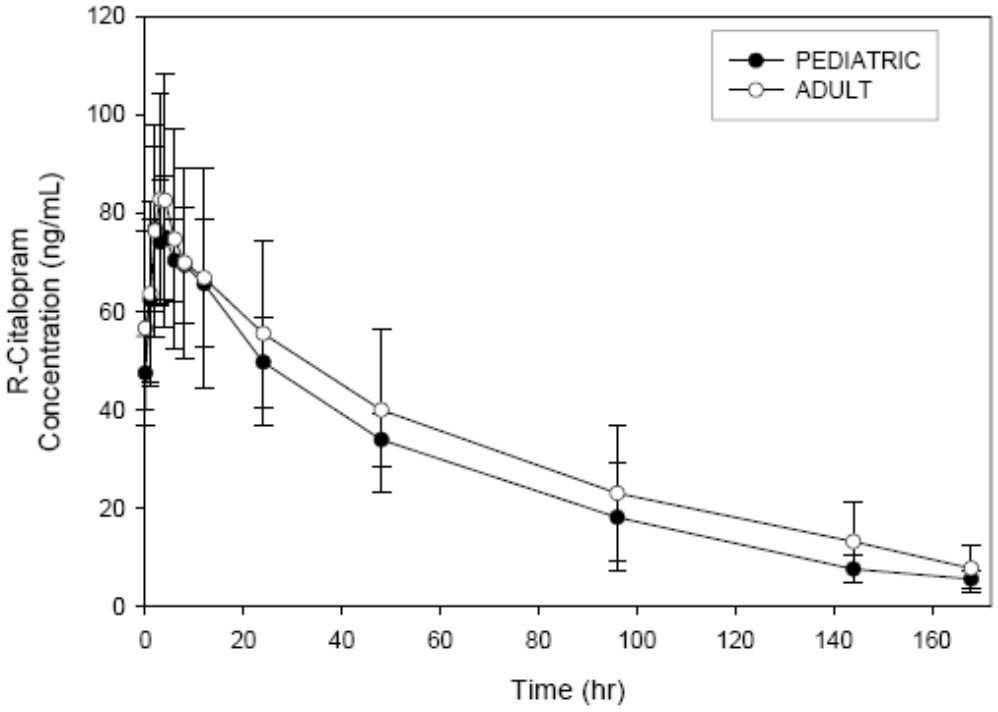


Table 3. Pharmacokinetic Parameters (Mean ± SD) of Escitalopram following Multiple Dose Administration of 40 mg/day Citalopram in Adult and Pediatric Patients

Escitalopram			
PK Parameters	Adult (N=11)	Pediatric (N=12)	p-value
C_{max} (ng/mL)	57.2 ∀ 21.2	47.1 ± 13.9	0.327
T_{max} (hr)	2.8 ± 0.6	2.6 ± 1.3	0.524
AUC_{ss} (hr* ng/mL)	935.7 ± 434.9	745.2 ± 270.8	0.447
$t_{1/2}$ (hr)	31.4 ± 9.8	27.9 ± 12.6	0.524
CL/F (L/hr)	52.9 ± 24.1	60.2 ± 21.5	0.622
Vz/F (L)	2151.9 ± 707.8	2465.4 ± 1672.5	0.687
Ae_{0-24} (mg)	3.5[a] ± 2.4	2.3[a] ± 1.3	0.190

Table 4. Pharmacokinetic Parameters (Mean ± SD) of Escitalopram following Multiple Dose Administration of 40 mg/day Citalopram in Female and Male Patients.

Escitalopram			
PK Parameters	Female (N=12)	Male (N=11)	p-value
C_{max} (ng/mL)	54.1 ± 15.7	49.6 ± 20.9	0.578
T_{max} (hr)	2.8 ± 0.8	2.6 ± 1.3	0.887
AUC_{ss}(hr* ng/mL)	880.3 ± 312.5	778.3 ± 418.5	0.432
$t_{1/2}$ (hr)	30.5 ± 11.9	28.5 ± 11.0	0.807
CL/F (L/hr)	51.0 ± 18.1	62.9 ± 26.0	0.278
Vz/F (L)	2111.1 ± 826.1	2538.4 ± 667.0	0.514
Ae_{0-24} (mg)	3.0[a] ± 1.8	2.9[a] ± 2.2	0.864

Table 5. Individual and Mean Pharmacokinetic Parameters of R-citalopram after Administration of a Single dose of 20 mg and Multiple Daily Dose of 40 mg/day Citalopram.

				Single Dose			Multiple Dose						
AGE	SUBJECT	SITE	SEX	T_{max} hour	C_{max} ng/mL	AUC_{0-24} hr*ng/mL	Ae_{0-24} mg	C_{max} ng/mL	T_{max} hour	$t_{1/2}$ hour	AUC_{ss} hr*ng/mL	Vz/F L	CLss/F L/hr
Pediatric	26	1	M	2.0	15.3	261.6	8.2	84.7	1.0	43.1	1418.5	1751.7	28.2
Pediatric	26	2	M	4.0	13.2	248.0	5.3	61.2	4.0	65.8	1038.7	3657.2	38.5
Pediatric	27	2	M	2.0	11.3	175.0	4.6	72.5	1.0	43.9	1350.1	1877.1	29.6
Pediatric	28	1	M	4.0	11.5	189.6	3.3	66.4	3.0	35.6	1372.8	1497.3	29.1
Pediatric	28	2	M	4.0	11.2	168.4	NA	73.9	6.0	49.4	1563.7	1824.2	25.6
Pediatric	29	1	M	2.0	22.5	328.0	5.2	106.5	2.0	40.6	1974.5	1186.4	20.3
Pediatric	29	2	F	4.0	11.2	170.8	3.6	77.6	1.0	39.5	1537.6	1482.5	26.0
Pediatric	30	1	M	4.0	12.5	196.6	4.9	70.3	6.0	38.0	1371.2	1599.5	29.2
Pediatric	30	2	F	3.0	15.9	256.1	NA	68.8	4.0	62.3	1487.3	2416.5	26.9
Pediatric	31	2	F	6.0	15.4	244.7	6.1	91.0	3.0	33.0	1553.8	1224.4	25.7
Pediatric	32	1	F	6.0	14.7	233.4	7.1	84.2	8.0	42.4	1754.4	1395.1	22.8
Pediatric	S1(Child)	1	F	2.0	24.3	401.9	5.5	111.4	2.0	33.5	1913.1	1010.4	20.9
			Mean	3.6	14.9	239.5	5.4	80.7	3.4	43.9	1528.0	1743.5	26.9
			SD	1.4	4.4	69.7	1.5	15.7	2.3	10.5	258.4	708.9	4.8
			Min	2.0	11.2	168.4	3.3	61.2	1.0	33.0	1038.7	1010.4	20.3
			Max	6.0	24.3	401.9	8.2	111.4	8.0	65.8	1974.5	3657.2	38.5
			CV%	40.3	29.2	29.1	27.7	19.4	66.6	23.9	16.9	40.7	17.9

NA: Not Available

ADDENDUM TO STUDY CIT-PK-07-EXCLUSION OF 10 YR OLD SUBJECT

The label for study CIT-PK-07 states an age range of 12-17; however, the study was done in subjects 10-17. To be consistent with the label a female subject age 10 was removed from the data set and the analysis repeated.

Single Dosing

Figure 1. Plasma Concentrations (Mean ± SD) of Escitalopram after a Single Dose Administration of 20 mg Citalopram in Pediatric (excluding 10 year-old female patient) vs. Adult Patients

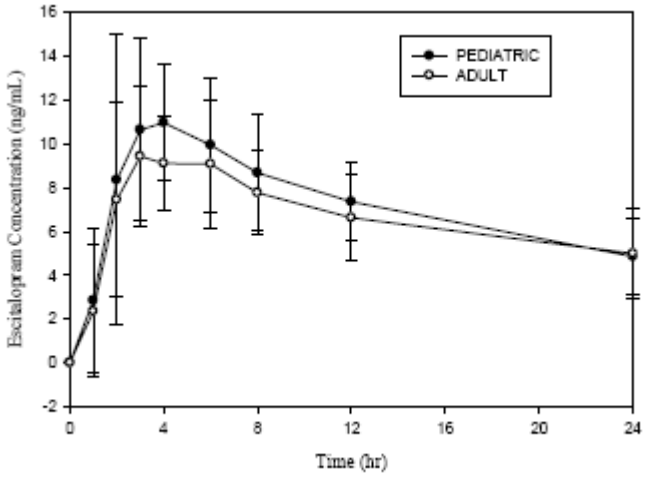


Figure 2. Plasma Concentrations (Mean ± SD) of R-citalopram after a Single Dose Administration of 20 mg Citalopram in Pediatric (excluding 10 year-old female patient) vs. Adult Patients

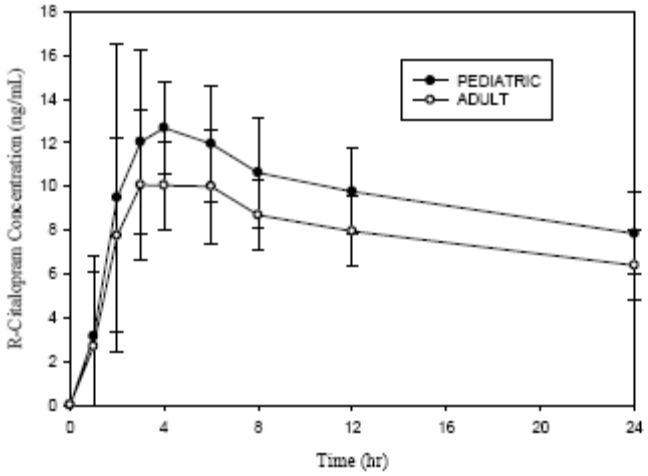


Figure 3. Plasma Concentrations (Mean ± SD) of Escitalopram after a Single Dose Administration of 20 mg Citalopram in Male vs. Female (excluding 10 year-old female) Patients

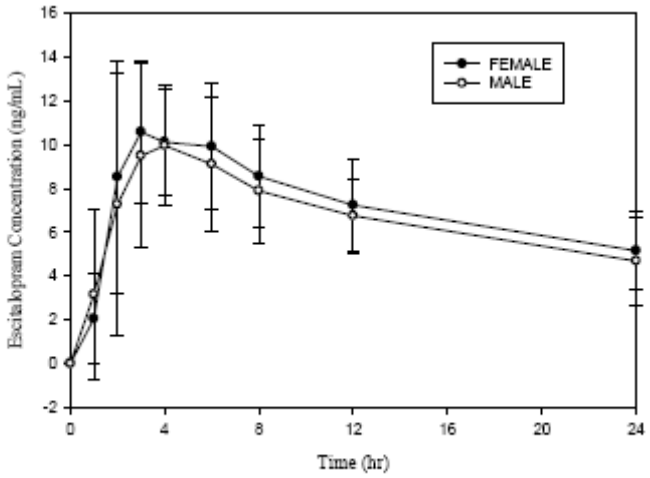


Figure 4. Plasma Concentrations (Mean ± SD) of R-Citalopram after a Single Dose Administration of 20 mg Citalopram in Male vs. Female (excluding 10 year-old female) Patients

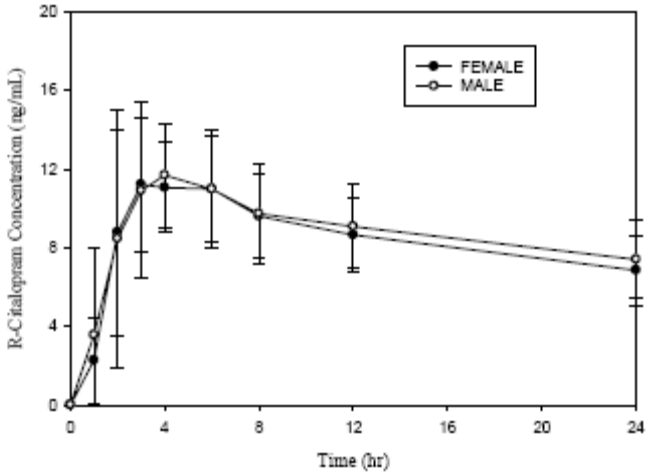


Table 1.	Pharmacokinetic Parameters (Mean ± SD) of Escitalopram following a Single Dose of 20 mg Citalopram in Adult and Pediatric Patients (excluding 10 year-old female patient)		
	Escitalopram		
PK Parameters	Adult (N = 11)	Pediatric (N = 11)	p value
C_{max} (ng/mL)	11.2 ± 2.8	12.4 ± 3.9	0.622
T_{max} (hr)	3.4 ± 1.8	3.6 ± 1.4	0.521
AUC_{0-24} (ng•h/mL)	157.4 ± 41.2	172.2 ± 48.1	0.431

Table 2.	Pharmacokinetic Parameters (Mean ± SD) of Escitalopram following a Single Dose of 20 mg Citalopram in Female and Male Adult and Pediatric Patients (excluding 10 year-old female patient)		
	Escitalopram		
PK Parameters	Female (N = 11)	Male (N = 11)	p value
C_{max} (ng/mL)	12.2 ± 2.7	11.4 ± 4.0	0.264
T_{max} (hr)	3.6 ± 1.6	3.3 ± 1.6	0.787
AUC_{0-24} (ng•h/mL)	170.7 ± 44.6	158.9 ± 45.6	0.599

Multiple Dosing

Figure 5. Plasma Concentrations (Mean ± SD) of Escitalopram after Multiple-Dose Administration of 40 mg Citalopram in Pediatric (excluding 10 year-old female patient) vs. Adult Patients

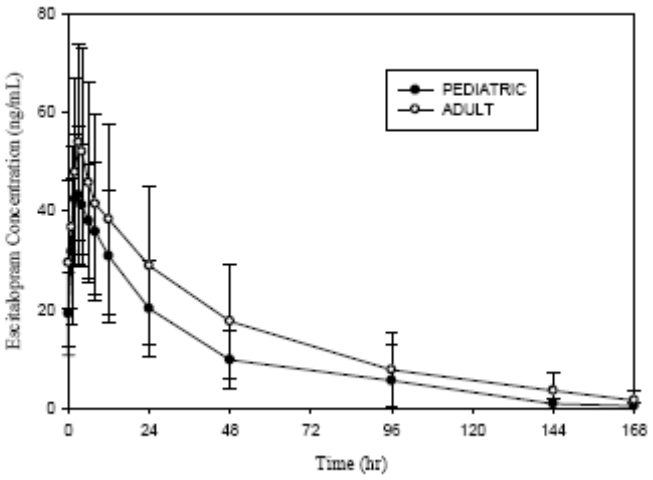


Figure 6. Plasma Concentrations (Mean ± SD) of R-citalopram after Multiple-Dose Administration of 40 mg Citalopram in Pediatric (excluding 10 year-old female patient) vs. Adult Patients

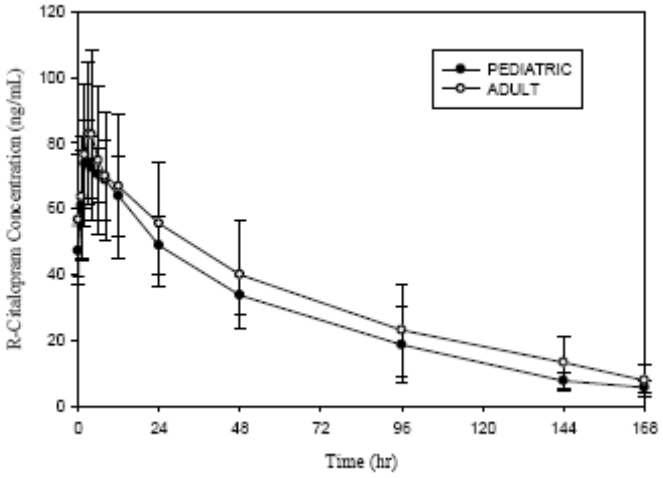


Table 3.	Pharmacokinetic Parameters (Mean ± SD) of Escitalopram following Multiple Dose Administration of 40 mg Citalopram in Adult and Pediatric Patients (excluding 10 year-old female patient)		
	Escitalopram		
PK Parameters	Adult (N = 11)	Pediatric (N = 11)	p value
C_{max} (ng/mL)	57.2 ± 21.2	45.8 ± 13.7	0.293
T_{max} (hr)	2.8 ± 0.6	2.6 ± 1.4	0.384
AUC_{ss} (ng•h/mL)	925.7 ± 434.9	738.5 ± 283.0	0.358
$t_{½}$ (hr)	31.4 ± 9.8	29.1 ± 12.5	0.470
CL/F (L/hr)	26.5 ± 12.1	30.6 ± 11.10	0.358
Vz/F (L)	1075.9 ± 353.9	1297.5 ± 844.9	0.948
Ae_{0-24} (mg)	3.5 ± 2.4	2.3 ± 1.4	0.221

Table 4.	Pharmacokinetic Parameters (Mean ± SD) of Escitalopram following a Multiple Dose Administration of 40 mg Citalopram in Female and Male Patients (excluding 10 year-old female patient)		
	Escitalopram		
PK Parameters	Female (N = 11)	Male (N = 11)	p-value
C_{max} (ng/mL)	53.4 ± 16.2	49.6 ± 20.9	0.511
T_{max} (hr)	2.8 ± 0.8	2.6 ± 1.3	0.217
AUC_{ss} (ng•h/mL)	885.9 ± 327.2	778.3 ± 418.5	0.264
$t_{½}$ (hr)	31.9 ± 11.3	28.5 ± 11.0	0.393
CL/F (L/hr)	23.5 ± 11.7	31.4 ± 13.0	0.264
Vz/F (L)	1012.3 ± 493.8	1269.2 ± 833.5	0.896
Ae_{0-24} (mg)	3.1 ± 1.9	2.9 ± 2.2	0.683

Table 5. Individual and Mean Pharmacokinetic Parameters of R-Citalopram for Pediatric Patients (excluding 10 year old female patient) after Administration of a Single Dose of 20 mg and Multiple Daily Dose of 40 mg/day Citalopram

				Single Dose			Multiple Dose						
AGE	Subject	SITE	SEX	Tmax	Cmax	AUC_{0-24}	Ae_{0-24}	Cmax	Tmax	t½	AUCss	Vz/F	CL/F
				(hr)	(ng/mL)	(ng•h/mL)	(mg)	(ng/mL)	(hr)	(hr)	(ng•h/mL)	(L)	(L/hr)
Pediatric	32	1	F	6.0	14.7	233.4	7.1	84.2	8.0	42.4	1754.4	697.5	11.4
Pediatric	29	2	F	4.0	11.2	170.8	3.6	77.6	1.0	39.5	1537.6	741.3	13.0
Pediatric	30	2	F	3.0	15.9	256.1	NA	68.8	4.0	62.3	1487.3	1208.3	13.4
Pediatric	31	2	F	6.0	15.4	244.7	6.1	91	3.0	33	1553.8	612.2	12.8
Pediatric	26	1	M	2.0	15.3	261.6	8.2	84.7	1.0	43.1	1418.5	875.9	14.1
Pediatric	28	1	M	4.0	11.5	189.6	3.3	66.4	3.0	35.6	1372.8	748.6	14.6
Pediatric	29	1	M	2.0	22.5	328	5.2	106.5	2.0	40.6	1974.5	593.2	10.1
Pediatric	30	1	M	4.0	12.5	196.6	4.9	70.3	6.0	38	1371.2	799.8	14.6
Pediatric	26	2	M	4.0	13.2	248	5.3	61.2	4.0	65.8	1038.7	1828.6	19.3
Pediatric	27	2	M	2.0	11.3	175	4.6	72.5	1.0	43.9	1350.1	958.6	14.8
Pediatric	28	2	M	4.0	11.2	168.4	NA	73.9	6.0	49.4	1563.7	912.1	12.9
			Mean	3.7	14.1	224.7	5.4	77.9	3.5	44.9	1493.0	905.1	13.7
			SD	1.4	3.3	49.6	1.6	12.9	2.3	10.5	239.3	351.5	2.3
			Min	2.0	11.2	168.4	3.3	61.2	1.0	33.0	1038.7	593.2	10.2
			Max	6.0	22.5	328.0	8.2	106.5	8.0	65.8	1974.5	1828.6	19.3
			CV%	38.1	23.8	22.1	29.3	16.6	66.0	23.3	16.0	38.8	16.9

COMMENTS:

No age or gender effects on pharmacokinetic parameters were found for escitalopram. Exclusion of the 10 yr old subject had no impact on the results comparing adults and pediatrics.

STUDY NO. SCT-PK-10-A SINGLE DOSE PHARMACOKINETIC STUDY OF ESCITALOPRAM IN HEALTHY ADOLESCENT AND ADULT SUBJECTS

OBJECTIVE

To assess tolerability and compare the pharmacokinetics of escitalopram, S-enantiomer of the racemic compound citalopram (CIT), following a single dose regimen in healthy adolescents and adults**.**

DESIGN OF STUDY

This was a single-center, open-label, single-dose study in twenty-four (24) subjects. Twelve (12) adolescents and twelve (12) adults received a 10 mg **escitalopram (S-isomer of CIT)** oxalate tablet on Day 1. Subjects were institutionalized for the duration of the study. The study was carried out from June 23, 2002 to June 30, 2002. The parent or guardian of the adolescent subjects accompanied them during the study. Study drug was dosed with 240 mL of water under fasted conditions. Standardized, bland, low-fat meals were provided to all subjects while institutionalized.

Concurrent Medications
No concomitant medication was permitted during the study. Subjects were instructed not to take any drugs for at least 14 days prior to and during the course of the study. They were specifically reminded that this included aspirin, Bufferin®, Excedrin®, Anacin®, ibuprofen, acetaminophen, other over-the-counter analgesics, vitamin preparations, cough syrup, herbal remedies, and homeopathic medicines.

Subject Demographics

Group	Subject No.	Gender	Race	Height (cm)	Weight (kg)	Age (yrs)
Adolescent	1	F	White	154.9	50.9	15
Adolescent	2	F	White	154.9	51.4	15
Adolescent	3	F	Other	162.6	66.4	14
Adolescent	4	F	White	149.9	49.5	12
Adolescent	5	F	Other	152.4	51.8	16
Adolescent	6	F	White	160.0	49.1	14
Adolescent	7	M	White	162.6	69.1	15
Adolescent	8	M	White	162.6	50.5	13
Adolescent	9	M	White	167.6	69.1	14
Adolescent	10	M	White	175.3	88.6	17
Adolescent	11	M	Black	160.0	46.4	15
Adolescent	12	M	Other	172.7	77.3	17
			Mean	161.3	60.0	14.8
			SD	7.8	13.7	1.5
			Range	149.9-175.3	46.4-88.6	12-17
Adult	21	F	White	172.7	81.8	27
Adult	22	F	White	162.6	70.0	33
Adult	23	F	Other	160.0	66.4	30
Adult	24	F	Other	154.9	63.6	34
Adult	25	F	White	154.9	54.1	29
Adult	26	F	White	157.5	63.6	35
Adult	27	M	White	172.7	71.8	28
Adult	28	M	White	185.4	75.5	29
Adult	29	M	White	160.0	73.6	35
Adult	30	M	Black	175.3	55.9	22
Adult	31	M	White	167.6	60.9	23
Adult	32	M	White	177.8	72.7	35
			Mean	166.8	67.5	30.0
			SD	10.0	8.2	4.6
			Range	154.9-185.4	54.1-81.8	22-35

ANALYTICAL

Since the plasma concentrations of R-citalopram, R-demethylcitalopram, and Rdimethylcitalopram, and S-didemethylcitalopram levels were below the lower limit of quantitation (BLOQ) of the analytical assay in all subjects (BLOQ of 1 ng/mL), their validation will not be reported.

The study was carried out from June 23, 2002 to June 30, 2002.
Analysis August 2002
Total Storage 60 days

Parameter	S-Citalopram	S-demethyl-citalopram
Method	LC/MS/MS	LC/MS/MS
Sensitivity/LOQ	1 ng/ml	1 ng/ml

Linearity (Standard curve samples)	1-150 ng/ml	1-150 ng/ml
Quality Control (QC) Samples	3.00 ng/ml 30 ng/ml 120 ng/ml	3.00 ng/ml 30 ng/ml 120 ng/ml
Precision of Standards (%CV)	1.7% @ 1 ng/ml 1.1% @ 150 ng/ml	1.0% @ 1 ng/ml 1.6% @ 150 ng/ml
Precision of QC Samples (%CV)	2.4% @3.00 ng/ml 2.3% @ 120 ng/ml	1.7% @3.00 ng/ml 2.0% @ 120 ng/ml
Accuracy of Standards (%)	100% @ 1 ng/ml 99.7% @ 150 ng/ml	99% @ 1 ng/ml 99% @ 150 ng/ml
Accuracy of QC Samples (%)	99% @ 3 ng/ml 99% @ 120 ng/ml	97% @ 3.00 ng/ml 101% @ 120 ng/ml

Blood Sample Collection

Blood samples for the determination of S-citalopram, R-citalopram, S-demethylcitalopram, R-demethylcitalopram, S-didemethylcitalopram and R-didemethylcitalopram concentrations were collected following dosing on Day 1 at 0.0-hour (pre-dose), 1, 2, 3, 4, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours post dose.

PHARMACOKINETIC DATA ANALYSIS

Pharmacokinetic parameters were estimated using WinNonlin (version 3.3). The following parameters were determined from the plasma concentrations of escitalopram: the area under the plasma concentration versus time curve (AUC0-t and AUC0-∞), maximum plasma concentration (Cmax), time of maximum plasma concentration (Tmax), elimination half-life (T½), oral clearance (CL/F) and apparent volume of distribution (Vz/F). The following parameters were estimated for the metabolites: Cmax, Tmax, AUC0-t,AUC0-∞ and T½.

Maximum plasma concentration (Cmax) and the time of maximum concentration (Tmax) for escitalopram and its metabolites were determined by observation. The first-order rate constant, λz, describing the terminal decline in plasma was estimated by WinNonlin (version 3.3) using log-linear regression of the terminal

linear phase of the mean plasma concentration-time curves. A minimum of 3 points in the terminal phase were required to define λz.

RESULTS

ADVERSE EVENTS

The incidence of adverse events is provided in Table 1.

There were no serious adverse events reported. No subject withdrew from the study due to treatment emergent adverse event (TEAE). Seven (29.2%) of the twenty-four subjects, 2 adolescent and 5 adult subjects, reported a total of 10 adverse events. The adverse events reported were nausea, headache, dizziness, vomiting, and diarrhea and they were all mild in intensity.

Table 1 . Incidence of Treatment Emergent Adverse Events (% Subjects)

Preferred Term	*Adolescents (N=12) n (%)*	*Adults (N=12) n (%)*
Subjects with at least one TEAE	2 (16.7)	5 (41.7)
Nausea	0 (0)	3 (25.0)
Headache	0 (0)	1 (8.3)
Diarrhea	0 (0)	2 (16.7)
Dizziness	1 (8.3)	1 (8.3)
Vomiting	1 (8.3)	1 (8.3)

Figure 1. Mean Plasma Concentrations of S-citalopram Following Administration of a Single 10 mg Dose of Escitalopram Oxalate Tablet in Adolescent and Adult Subjects

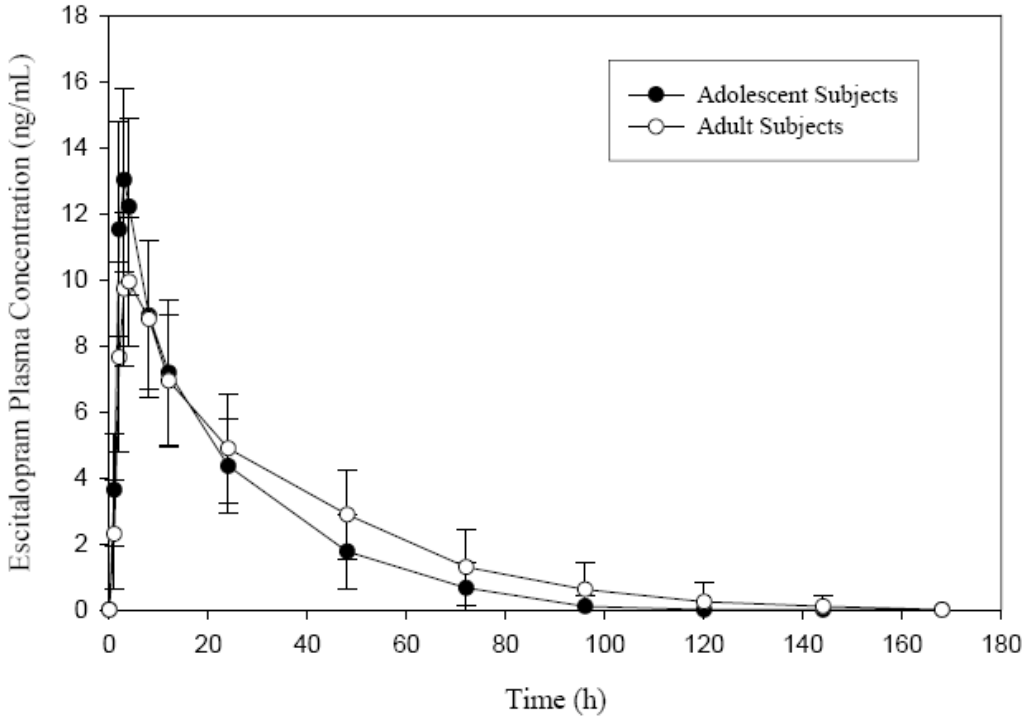


Table 2. Pharmacokinetic Parameters of Escitalopram Following Administration of a Single 10 mg Escitalopram Oxalate Tablet in Healthy Adolescent Subjects

Subject	C_{max} *(ng/mL)*	T_{max} *(h)*	AUC_{0-t} *(ng h/mL)*	$AUC_{0-\infty}$ *(ng h/mL)*	$T_{1/2}$ *(h)*	*CL/F (L/h)*	*Vz/F (L)*
1	11.50	3	197.5	224.9	16.0	44.5	1025.0
2	14.75	3	174.8	232.8	11.9	43.0	739.2
3	11.80	3	191.6	217.0	16.3	46.1	1085.2
4	10.78	2	113.8	143.3	10.6	69.8	1066.9
5	13.86	3	235.2	265.0	15.3	37.7	833.9
6	18.92	3	433.5	467.2	18.8	21.4	581.4
8	16.07	2	410.6	462.4	22.6	21.6	704.3
9	12.79	3	299.1	335.8	22.5	29.8	966.7
10	9.18	3	331.6	381.4	32.2	26.2	1218.6
11	13.61	3	276.8	319.1	16.1	31.3	728.5
12	10.85	4	322.9	379.9	26.5	26.3	1005.7
Mean	13.10	2.9	271.6	311.7	19.0	36.2	905.0
SD	2.76	0.5	100.0	105.0	6.4	14.3	198.5
%CV	21.10	18.5	36.8	33.7	33.9	39.5	21.9
Minimum	9.18	2.0	113.8	143.3	10.6	21.4	581.4
Maximum	18.92	4.0	433.5	467.2	32.2	69.8	1218.6

Table 3. Pharmacokinetic Parameters of Escitalopram Following Administration of a Single 10 mg Escitalopram Oxalate Tablet in Healthy Adult Subjects

Subject	C_{max} *(ng/mL)*	T_{max} *(h)*	AUC_{0-t} *(ng h/mL)*	$AUC_{0-\infty}$ *(ng h/mL)*	$T_{1/2}$ *(h)*	*CL/F (L/h)*	*Vz/F (L)*
21	8.52	3	142.2	171.2	19.4	58.4	1630.9
22	9.98	4	282.9	323.2	23.9	30.9	1066.6
23	11.14	4	269.4	306.6	24.1	32.6	1135.6
24	10.75	4	345.9	402.1	24.7	24.9	884.6
25	13.78	3	546.2	603.2	35.9	16.6	858.8
26	10.92	8	393.9	441.5	29.8	22.6	972.4
27	7.69	2	181.9	360.0	48.4	27.8	1939.8
28	11.91	3	399.8	439.6	27.6	22.7	905.5
29	8.53	4	162.3	194.5	18.7	51.4	1389.5
30	12.33	3	638.1	711.9	44.1	14.0	894.0
31	7.83	8	203.0	260.4	21.6	38.4	1197.8
32	11.32	8	388.8	430.7	28.2	23.2	945.1
Mean	10.39	4.5	329.5	387.1	28.9	30.3	1151.7
SD	1.92	2.2	154.2	157.0	9.4	13.4	340.6
%CV	18.44	48.8	46.8	40.6	32.7	44.1	29.6
Minimum	7.69	2.0	142.2	171.2	18.7	14.0	858.8
Maximum	13.78	8.0	638.1	711.9	48.4	58.4	1939.8

Figure 2. Mean Plasma Concentrations of S-Demethylcitalopram Following Administration of a Single 10 mg Dose of Escitalopram Oxalate Tablet in Adolescent and Adult Subjects

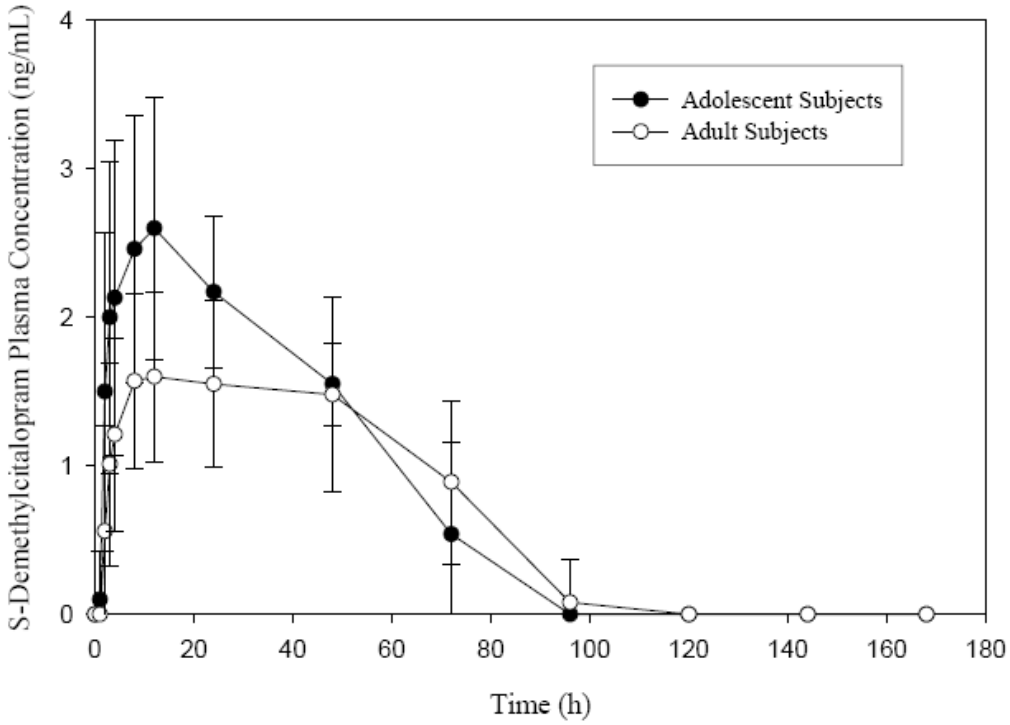


Table 4. Pharmacokinetic Parameters of S-Demethylcitalopram Following Administration of a Single 10 mg Escitalopram Oxalate Tablet in Healthy Adolescent Subjects

Subject	C_{max} *(ng/mL)*	T_{max} *(h)*	AUC_{0-t} *(ng h/mL)*	$AUC_{0-\infty}$ *(ng h/mL)*	$T_{1/2}$ *(h)*
1	3.21	8.0	109.2	198.2	39.5
2	4.31	12.0	141.7	ND	ND
3	2.70	8.0	96.3	171.1	39.0
4	3.20	3.0	110.5	173.3	31.3
5	2.94	12.0	147.0	232.6	48.3
6	3.17	12.0	158.2	261.5	51.9
8	1.92	12.0	113.1	228.2	70.6
9	1.64	24.0	96.2	ND	ND
10	1.34	12.0	49.8	ND	ND
11	3.09	12.0	147.1	216.2	42.7
12	1.71	12.0	73.0	ND	ND
Mean	2.66	11.5	112.9	211.6	46.2
SD	0.90	5.0	33.7	33.0	12.7
%CV	33.82	43.7	29.9	15.6	27.4
Minimum	1.34	3.0	49.8	171.1	31.3
Maximum	4.31	24.0	158.2	261.5	70.6

ND = Not determined

Table 5. Pharmacokinetic Parameters of S-Demethylcitalopram Following Administration of a Single 10 mg Escitalopram Oxalate Tablet in Healthy Adult Subjects

Subject	C_{max} *(ng/mL)*	T_{max} *(h)*	AUC_{0-t} *(ng h/mL)*	$AUC_{0-\infty}$ *(ng h/mL)*	$T_{1/2}$ *(h)*
21	2.37	8.0	81.2	172.3	50.1
22	1.92	12.0	113.2	280.3	92.7
23	1.84	24.0	111.3	ND	ND
24	2.18	24.0	160.9	243.4	57.1
25	1.51	12.0	92.9	589.9	284.7
26	1.84	8.0	107.8	231.5	76.5
27	3.00	48.0	157.2	ND	ND
28	1.43	12.0	90.7	ND	ND
29	1.83	12.0	68.8	ND	ND
30	0.00	0.0	0.0	ND	ND
31	1.65	24.0	97.3	ND	ND
32	1.49	48.0	89.7	ND	ND
Mean	1.76	19.3	97.6	303.5	112.2
SD	0.71	15.2	41.4	164.8	97.8
%CV	40.23	78.8	42.4	54.3	87.2
Minimum	0.00	0.0	0.0	172.3	50.1
Maximum	3.00	48.0	160.9	589.9	284.7

ND = Not determine

COMMENTS:

Following a single 10 mg dose adolescents had a 26% higher Cmax and a 19% lower AUC than adults.

STUDY CIT_PK_13 AN EVALUATION OF THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF CITALOPRAM IN PEDIATRIC AND ADULT SUBJECTS

PURPOSE OF THE STUDY

This study was designed to evaluate the pharmacokinetics of citalopram and its metabolites in pediatric subjects (compared to adult subjects) following a single 20 mg dose.

STUDY PLAN

This was an open-label, parallel, single dose study in 12 pediatric (7 -11 years old) and 12 adult (18 - 35 years old) healthy male and female subjects. Subjects were institutionalized for the entire study. The parent or guardian of the pediatric subject accompanied the institutionalized subject during the study. Subjects received 20 mg of citalopram in a 10 mL oral solution (10mg/5 ml) at 0800 on Study Day 1.

Multiple plasma samples were obtained on Study Day 1. On Study Days 2 through 8, subjects had a single blood draw at 0800 hours.

METHODS

DEMOGRAPHICS

	Adults N=12	Children N=12
Age, years		
Mean	30.3	9.4
Standard Deviation	3.8	1.1
Min – Max	23, 35	7,11
Weight, kg		
Mean	74	34
Standard Deviation	16.43	5.17
Min – Max	52.7, 102.7	26.8, 44.1
Height, cm		
Mean	165.1	137.0
Standard Deviation	12.11	7.28
Min – Max	149.9, 188	127.0, 149.9

Eight adults were Caucasian, and four were non-Caucasian (Black). Ten children were Caucasian, and 2 were non-Caucasian (Black).

Treatment Regimen

On Day 1 subjects received a single 20 mg dose of citalopram in a 10 mL oral solution (10mg/10mL) at 0800 hours. Subjects remained ambulatory or seated

upright and awake for the first four (4) hours following drug administration and did not engage in strenuous activity.

Diet
Subjects were dosed under fasted conditions. During the study, standardized, bland, lowfat meals were provided to all subjects while institutionalized.

Concomitant Medication
No concomitant medication was permitted during the study. Subjects were instructed not to take any drugs for at least 14 days prior to and during the course of the study. They were specifically reminded that this included aspirin, Bufferin®, Excedrin®, Anacin®, ibuprofen, acetaminophen, other over-the-counter analgesics, vitamin preparations, cough syrup, herbal remedies and homeopathic medicines

Blood Sampling and Collection Procedure
Blood samples were collected at the following times.
Day 1, after 0800 drug administration at: 0 hour (pre-dose), 1, 2, 3, 4, 8, and 12 hours (post-dose) Days 2, 3, 4, 5, 6, 7, and 8 at: 24, 48, 72, 96, 120, 144, and 168 hours (post Day 1 dose).

ANALYTICAL

Parameter	R-Citalopram	S-Citalopram	S-demethyl-citalopram	S-didemethyl citalopram
Method	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS
Sensitivity/LOQ	1 ng/ml	1 ng/ml	1 ng/ml	1 ng/ml
Linearity (Standard curve samples)	1-150 ng/ml	1-150 ng/ml	1-150 ng/ml	1-150 ng/ml
Quality Control (QC) Samples	3.75 ng/ml 15 ng/ml 75 ng/ml	3.75 ng/ml 15 ng/ml 75 ng/ml	3.75 ng/ml 15 ng/ml 75 ng/ml	3.75 ng/ml 15 ng/ml 75 ng/ml
Precision of Standards (%CV)	1.0% @ 1 ng/ml 2.3% @ 150 ng/ml	1.4% @ 1 ng/ml 4.3% @ 150 ng/ml	4.6% @ 1 ng/ml 4.6% @ 150 ng/ml	5.3% @ 1 ng/ml 4.0% @ 150 ng/ml
Precision of QC Samples (%CV)	6% @3.75 ng/ml 3.6% @ 75 ng/ml	6.4% @3.75 ng/ml 3.4% @ 75 ng/ml	7.7% @3.75 ng/ml 8.2% @ 75 ng/ml	6.3% @3.90 ng/ml 7.0% @ 78 ng/ml

Accuracy of Standards (%)	99% @ 1 ng/ml 101% @ 150 ng/ml	99.2% @ 1 ng/ml 102% @ 150 ng/ml	99.6% @ 1 ng/ml 99.3% @ 150 ng/ml	99% @ 1 ng/ml 101% @ 150 ng/ml
Accuracy of QC Samples (%)	99% @ 1 ng/ml 94% @ 75 ng/ml	99% @ 1 ng/ml 94% @ 75 ng/ml	97.2% @ 1 ng/ml 94% @ 75 ng/ml	94@3.75 ng/ml 92%@75 ng/ml

DATA ANALYSIS

Plasma concentrations of citalopram, DCT and DDCT were derived from the concentration values for R-CT, escitalopram, R-DCT, S-DCT, R-DDCT, and S-DDCT. The area under the plasma concentration time curve (AUC0-t and AUC0-∞), maximum plasma concentration (Cmax), time of maximum plasma concentration (Tmax), and elimination half-life (T½) were obtained from the plasma concentrations. The areas under the plasma concentration versus time curves up to the last measurable concentration (AUC0-t) were estimated by numerical integration using the linear trapezoidal rule.

STATISTICAL EVALUATION

Pharmacokinetic Parameter

Estimates of mean values obtained for pharmacokinetic parameters were compared statistically between age and gender groups using standard statistical procedures.

Statistical analyses were performed with the Statistical Analyses System (SAS) version 6.12 for the UNIX system microcomputers using the General Linear Models procedure (GLM). Analysis of variance (ANOVA) was performed on all of the pharmacokinetic parameters, including Cmax, AUC, Tmax, T½, and CL/F. AUC and Cmax were logtransformed in the analysis of variance comparison.

RESULTS

Table 1. Incidence of Treatment Emergent Adverse Events

Preferred Term	Adults (N=12) n (%)	Children (N=12) n (%)
Patients with at least one TEAE	7 (58.3)	5 (41.7)
Nausea	5 (41.7)	5 (41.7)
Headache	5 (41.7)	1 (8.3)
Diarrhea	2 (16.7)	2 (16.7)
Dizziness	1 (8.3)	0 (0)
Chills	1 (8.3)	0 (0)
Fever	0 (0)	1 (8.3)
Vomiting	0 (0)	4 (33.3)

Pharmacokinetic data were analyzed for all 24 subjects [12 adults (9 females and 3 males) and 12 children (6 males and 6 females)] who entered the study.

Table 2. Pharmacokinetic Parameters (Mean ± SD) of Citalopram following Administration of 20 mg Citalopram in Healthy Adult and Pediatric Volunteers.

Citalopram			
PK Parameters	Adult (N=12)	Pediatric (N=12)	p
C_{max} (ng/mL)	20.5 ± 4.7	43.8 ± 8.4	0.000
T_{max} (hr)	3.8 ± 0.5	2.9 ± 0.8	0.002
AUC_{0-t} (hr* ng/mL)	805.8 ± 289.9	1110.1 ± 336.5	0.012
AUC_{0-inf} (hr* ng/mL)	871.5 ± 312.4	1161.7 ± 343.4	0.018
$t_{½}$ (hr)	34.2 ± 7.6	26.1 ± 4.0	0.007
CL/F (L/hr)	25.4 ± 8.0	18.3 ± 4.2	0.009
Vz/F (L)	1189.2 ± 234.0	675.0 ± 133.5	0.000

Following a single dose administration of 20 mg citalopram oral solution, a shorter Tmax (24%, i.e., 54 minutes), higher Cmax (2 fold), larger AUC0-t (38%) and AUC0-inf (33%) were observed in children compared to adults (Table 2). These data suggest that the rate of absorption of citalopram was faster and the extent of absorption was higher in children compared to adults. Also, a shorter t½ (24%, i.e., 8 hrs) and smaller CL/F (28%) and Vz/F (43%) were observed in children compared to adults.

OVERALL COMMENT:

The firm has conducted several studies measuring different citalopram moieties which makes a direct comparison between studies related to exposure difficult.

However for study cit-pk-07 the firm did conduct a steady-state study for 3 weeks at 40 mg/day in patients. The graph of AUC0-24 hrs vs percentile for the single dose study showed a slight increase in exposure of S-citalopram for pediatrics 210 ng/mlxhr vs 260 ng/mlxhr Figure 1. However the comparable graph following steady-state dosing at 40mg/day for 3 weeks was reversed Figure 2. The reversal may be due to the fact that the drug has a 35 hr half-life but the single dose measurements were only to 24 hrs. Since the prescribed dosage regimen is multiple dosing, the reviewer has concluded that the increased exposure following single dosing is not relevant. Exposure for children is similar to adults for approximately 75-80% of the subjects (N=24) in the study.

Figure 1. AUC0-24hrs vs. percentile for adults and children in Study 07 following a single 20 mg/day dose.

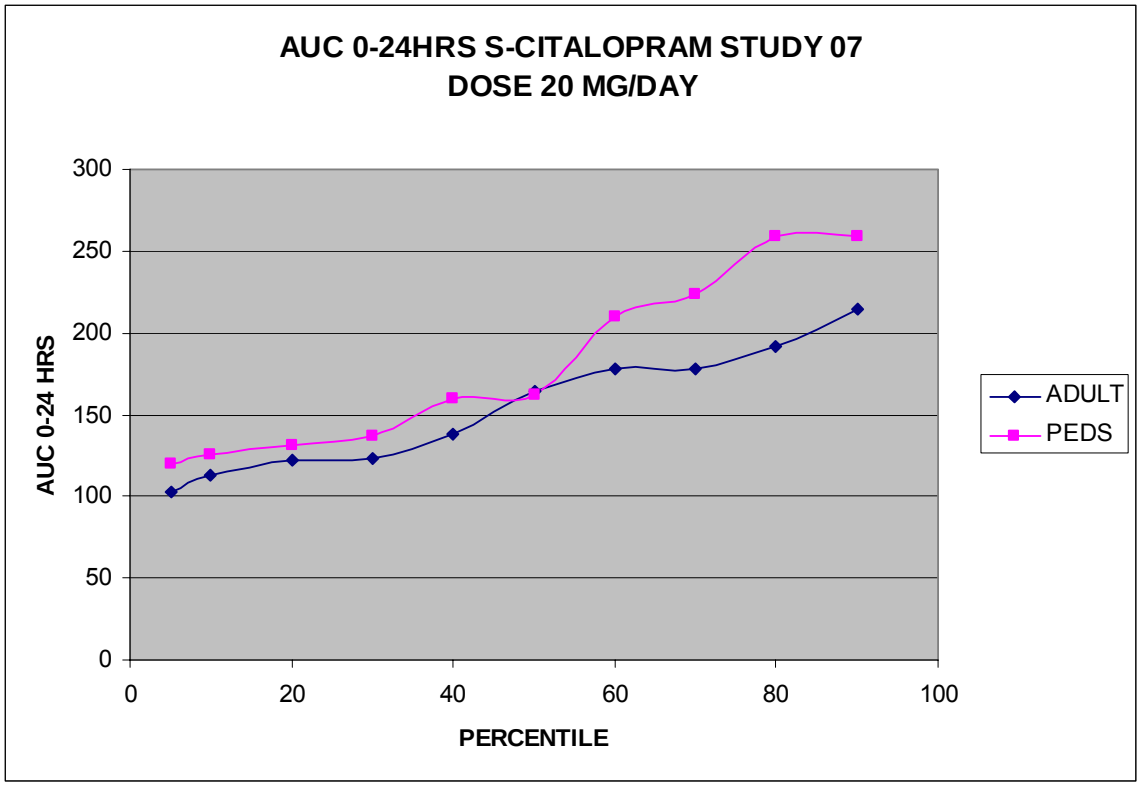
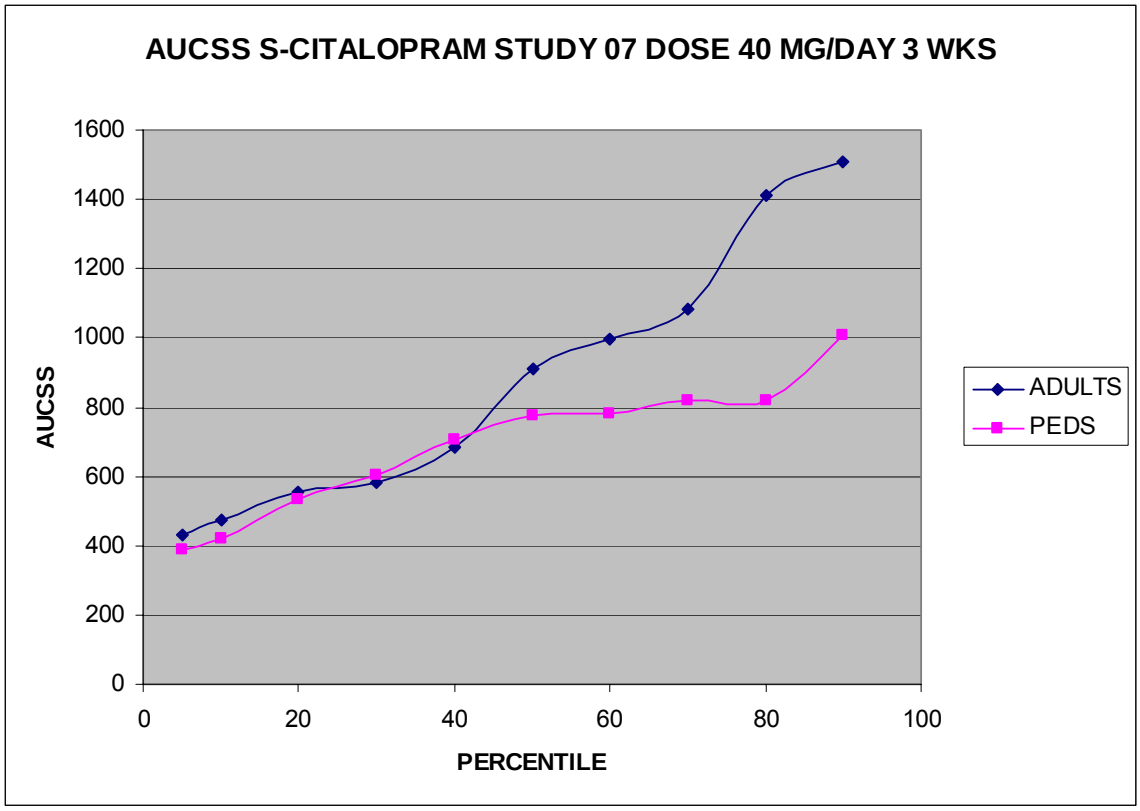


Figure 2. AUCss vs. percentile for adults and children in Study 07 following a single (last dose) 40 mg/day dose for 3 weeks.



SIGNATURES

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RD/FTinitialized by Raman Baweja, Ph.D._____

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cc: NDA 21-323, HFD-860(Mehta, Raman, Baweja, Jackson)
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5 pages withheld immediately after this page as B4 (draft labeling)

LABELING COMMENT:

OCP has proofed the PLR and it is acceptable.

LEXAPRO CURRENT LABEL

(b) (4)

LEXAPRO PLR LABEL

(b) (4)

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/s/

Andre Jackson
2/20/2009 06:42:26 AM
BIOPHARMACEUTICS

Raman Baweja
2/20/2009 10:13:08 AM
BIOPHARMACEUTICS
Review also linked to NDA 21323/S-31, and NDA 21365/S-22.