CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-323

PHARMACOLOGY REVIEW(S)

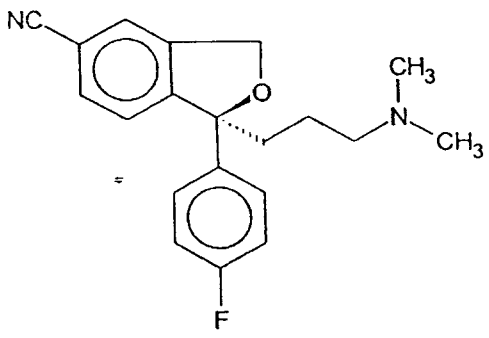
Review and Evaluation of Pharmacology/Toxicology Data
NDA 21,323

Reviewer Name Paul Roney
Division Name DNDP
HFD# 120
Review Completion Date December 3, 2001

Review number Original
IND/NDA number [redacted] NDA 21,323
Serial number/date/type of submission March 23, 2001
Information to sponsor: Yes (X) No ( )
Sponsor (or agent): Forest Laboratories, Inc
Manufacturer for drug substance

Drug:

Code Name: Lu 26-054
Generic Name: S-Citalopram, Escitalopram
Trade Name:
Chemical Name: S-(+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, oxalate
CAS Registry Number: 128196-01-0 (base) 219861-08-2 (oxalate)
Molecular Formula/ Molecular Weight: $C_{20}H_{21}FN_2O$, $C_2H_2O_4$ MW 414.42 (oxalate)
Structure:



Lu 26-054 (base)

Relevant INDs/NDAs: [redacted] (S-Citalopram), NDA 20,822 (Citalopram, racemic)

Drug Class: Selective Serotonin Reuptake Inhibitor (SSRI)

Indication: Depression and Panic Disorder

Clinical formulation: Tablets

Route of administration: Oral

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EXECUTIVE SUMMARY

Escitalopram is the pharmacologically active enantiomer in racemic citalopram, an approved drug for the treatment of depression. Since a full preclinical toxicity battery has been conducted on the racemate, only a series of bridging studies were required to fulfill the preclinical toxicology battery for this New Drug Application. Preclinical studies submitted to support the registration of escitalopram included cardiovascular safety pharmacology studies, repeat dose studies in rats (up to 13 weeks), and teratology studies in rats. The primary toxicology concern identified in the repeat dose studies was cardiotoxicity at 80 mg/kg and above. Cardiotoxicity was not observed with the racemic mixture. This effect was observed at 40 times the maximum human therapeutic dose (on a mg/m^2 basis). The fetotoxicity of escitalopram was comparable to the racemate. It is concluded that this NDA is approvable with respect to pharmacology/toxicology data pending labeling revisions.

PHARMACOLOGY

Mechanism of Action

S-citalopram, the active enantiomer of RS-citalopram (Celexa), is a selective serotonin reuptake inhibitor (SSRI). RS-citalopram was approved for use in the United States for the treatment of depression in July 1998. S-citalopram has a 1700 and 43000 fold greater inhibition of serotonin uptake over norepinephrine and dopamine, respectively (see Figure 1). The S-citalopram is about 130 to 167 times more potent than the R enantomer in inhibiting serotonin uptake (see sponsor Tables 4 and 5). Additional evidence of the specificity of the binding of S-citalopram to the serotonin transporter is its relative lack of binding to other receptor types (see sponsor Table 6).

Inhibition of the accumulation of ^{3}H-labelled amines into rat brain synaptosomes in vitro.

	Citalopram	(+)	(-)	Demethyl-citalopram	(+)	(-)
	Lu 10-171-B	Lu 26-054-O	Lu 26-055-O	Lu 11-109-C	Lu 26-119-O	Lu 26-120-O
5-HT uptake	1.8	1.5	250	14	9.9	65
NA uptake	6100	2500	6900	740	1500	500
DA uptake	40000	65000	54000	28000	34000	25000
Ratio NA/5-HT	3400	1700	28	53	150	7.7
Ratio DA/5-HT	22000	43000	220	2000	3400	380

Results are expressed as IC50-values in nM (logarithmic means).

Figure 1, From Page 9 of Report 68/809

The activity of the metabolites have also been examined. The monodesmethyl metabolite possesses 12 – 14% of the activity of the parent molecule. S-Citalopram inhibits the uptake by binding to the high affinity imipramine site on the serotonin transporter.

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Drug Activity Related to Proposed Indication

In addition to its *in vitro* properties, S-citalopram has been studied in *in vivo* models of depression —— For example, 10 mg/kg/day was effective in the forced swimming test in mice, a model of depression. In addition, 0.4mg/kg sc S-citalopram inhibited ultrasonic vocalizations in mice subjected to footshocks, —— These studies, combined with RS-citalopram's effectiveness in treating depressive disorders, suggest that S-citalopram has the potential to be an effective treatment for depressive disorders and ——

Study	Species	Test	Route	Dose Range (mg/kg)	Effects
4/805	Mouse	Forced Swimming	SC	1-16	S-citalopram increased swimming time at 4 mg/kg; RS-citalopram was effective at 8 mg/kg and above; R-citalopram was ineffective at 32 mg/kg
4/805	Rat	Vocalization	SC	0.25-4	S-citalopram decreased vocalization following shock at 0.5 mg/kg; RS-citalopram was effective at 0.25 to 2 mg/kg; R-citalopram was effective at 4 mg/kg
4/805	Mouse	Aggressive Behavior	SC	Not given	S-citalopram ED50 was 0.1 mg/kg; RS-citalopram ED50 was 0.3 mg/kg; R-citalopram ED50 was >2 mg/kg
105F/808	Rat	Aggressive Behavior	SC	0.25, 0.5, 1; single dose	S-citalopram reduced aggressive behavior at 0.25 mg/kg
105F/808	Rat	Aggressive Behavior	SC	0.5 for 7-14 days	S-citalopram increased aggressive behavior.

Secondary Pharmacological Action

The binding of S-citalopram and its metabolites to a variety of receptors has been examined (see Figure 2, Figure 3, Figure 4, Figure 5, and Figure 6). Relative to its affinity for the serotonin transporter (1-2 nM), s-citalopram has relatively low affinity for other receptors. Pharmacological studies support the serotonin potentiating properties of S-citalopram and indicate that the S-enantiomer is more active than the R-enantiomer (see Figure 7). S-citalopram also decreased the frequency of firing in the dorsal raphe nucleus serotoninergic neurons at doses lower than the RS-enantiomer. R-citalopram was essentially inactive in this system (see Figure 8).

Effects of CT, DCT and Enantiomers on Inhibition of Binding of ^{3}H-Labelled Ligands of Different Receptors in Rat Brain Membranes *in vitro*

Receptor	*Ligand*	*CT*	*S-CT*	*R-CT*	*DCT*	*S-DCT*	*R-DCT*
D-1	^{3}H-SCH 23390	22000	32000	16000	32000	>10000	>10000
D-2	^{3}H-spiperone	33000	>100000	11000	53000	89000	27000
5-HT_{1A}	^{3}H-8-OHDPAT	15000	17000	>100000	41000	31000	>100000
5-HT_2	^{3}H-ketanserin	3300	13000	6300	8700	11000	6700
α1	^{3}H-prazosin	1600	5500	1600	1500	4300	650
α2	^{3}H-idazoxan	18000	20000	12000	23000	39000	16000
β	^{3}H-ihydroalprenolol	>100000	>100000	>100000	>100000	>100000	>100000
H1	^{3}H-mepyramine	350	2100	280	1700	4200	1000
Muscarine	^{3}H-QNB	5600	3800	11000	14000	NT	NT

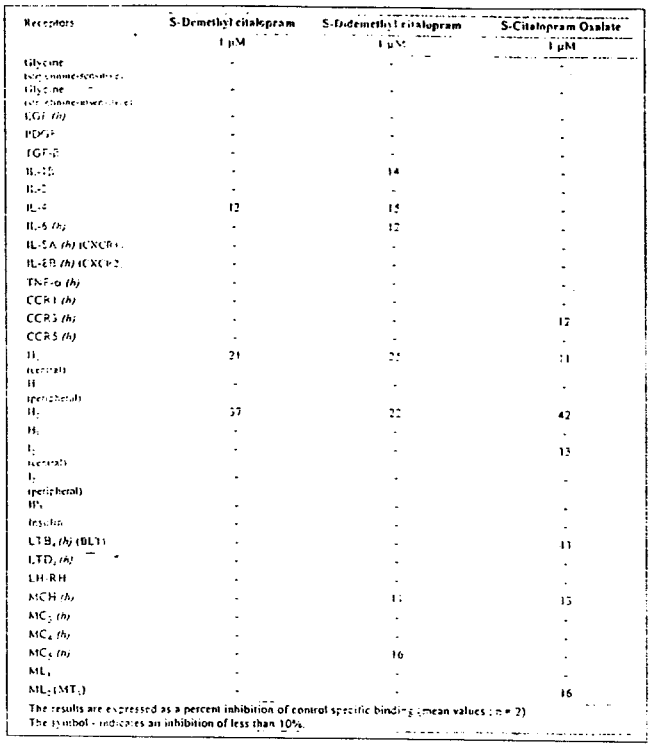
Results are expressed as IC_{50}-values in nM (logarithmic means).
NT = Not Tested

Figure 2, from page 10 of Report 68/809

Receptors	S-Demethyl citalopram	S-Didemethyl citalopram	S-Citalopram Oxalate
	1 µM	1 µM	1 µM
A_1 *(r)*	-	-	-
A_{2A}	-	-	-
α_{1A}	22	12	18
α_{1b}	51	33	40
α_{2A} *(r)*	-	-	-
α_{2b}	-	10	19
α_K *(r)*	-	-	-
AT_1 *(h)*	-	-	-
ANP	-	-	-
BZD (central)	-	-	-
Bombesin (non-selective)	-	-	-
B_1	-	-	-
B_2	-	-	-
CGRP *(h)*	-	-	-
CB_1 *(h)*	19	-	-
CCK_A *(h)* (CCK_1)	-	-	-
C5a *(r)*	-	-	-
CRF_1	-	-	-
D1 *(h)*	13	-	11
D2 *(h)*	-	-	-
D3 *(h)*	-	-	-
D4.4 *(h)*	-	-	-
D5 *(h)*	-	-	15
ET_A *(h)*	16	16	-
ET_B *(h)*	-	12	-
fMLP *(h)*	-	-	-
$GABA_A$	-	-	-
$GABA_B$	11	-	-
GABA transporter	-	-	-
GAL1 *(h)*	-	-	-
GAL2 *(h)*	-	-	-
AMPA	15	-	-
Kainate	-	-	-
NMDA	-	-	-

The results are expressed as a percent inhibition of control specific binding (mean values ; n = 2).
The symbol - indicates an inhibition of less than 10%.

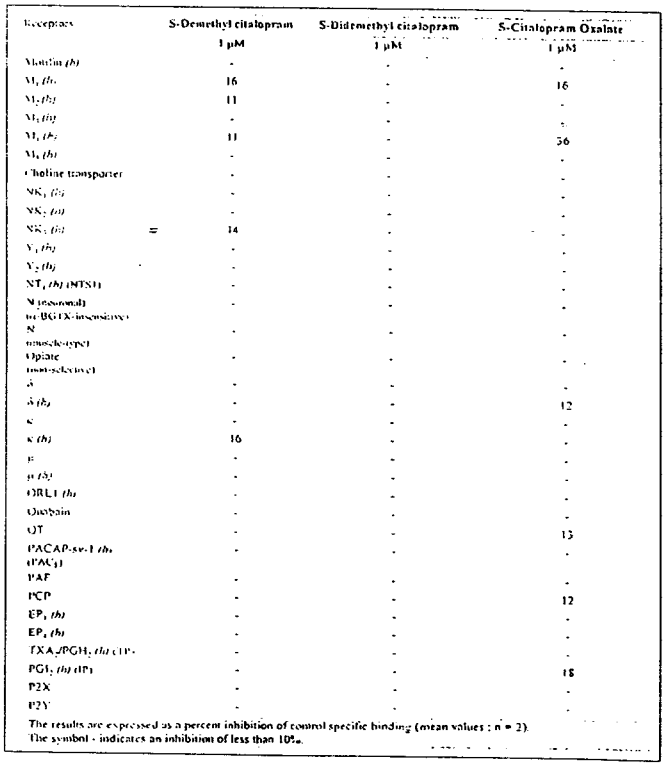
Figure 3, from page 16 of Report 4605



Receptors	S-Demethyl citalopram	S-Didemethyl citalopram	S-Citalopram Oxalate
	1 µM	1 µM	1 µM
Glycine (strychnine-sensitive)	-	-	-
Glycine (strychnine-insensitive)	-	-	-
IGF (h)	-	-	-
PDGF	-	-	-
TGF-β	-	-	-
IL-1β	-	14	-
IL-2	-	-	-
IL-6	12	15	-
IL-8 (h)	-	12	-
IL-8A (h) (CXCR1)	-	-	-
IL-8B (h) (CXCR2)	-	-	-
TNF-α (h)	-	-	-
CCR1 (h)	-	-	-
CCR3 (h)	-	-	12
CCR5 (h)	-	-	-
H_1 (central)	21	25	11
H (peripheral)	-	-	-
H_2	57	22	42
H_3	-	-	-
I_1 (central)	-	-	13
I_2 (peripheral)	-	-	-
IP_3	-	-	-
Insulin	-	-	-
LTB_4 (h) (BLT)	-	-	11
LTD_4 (h)	-	-	-
LH-RH	-	-	-
M_1CH (h)	-	11	15
MC_2 (h)	-	-	-
MC_4 (h)	-	-	-
MC_5 (h)	-	16	-
ML_1	-	-	-
$ML_2(MT_2)$	-	-	16

The results are expressed as a percent inhibition of control specific binding (mean values ; n = 2).
The symbol - indicates an inhibition of less than 10%.

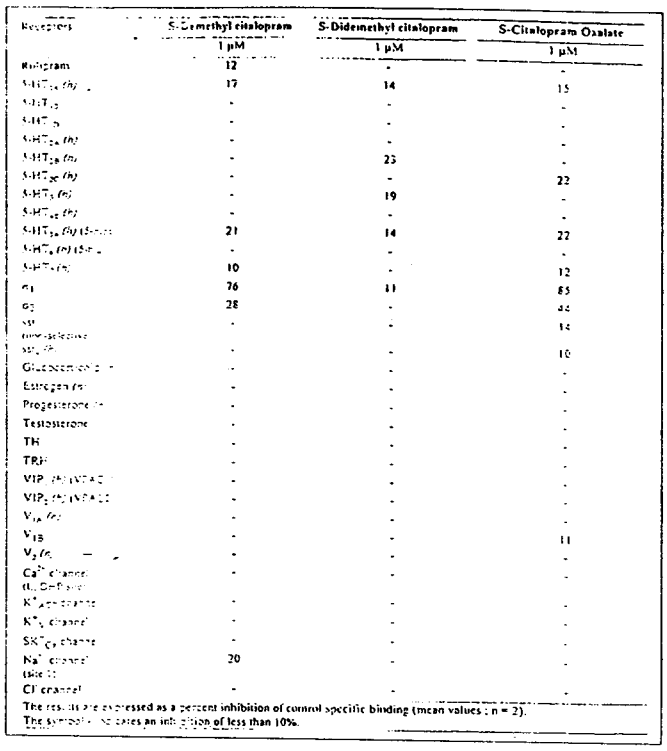
Figure 4, from page 17 of Report 4605



Receptors	S-Demethyl citalopram	S-Didemethyl citalopram	S-Citalopram Oxalate
	1 µM	1 µM	1 µM
Nicotine (h)	-	-	-
M_1 (h)	16	-	16
M_2 (h)	11	-	-
M_3 (h)	-	-	-
M_4 (h)	11	-	36
M_5 (h)	-	-	-
Choline transporter	-	-	-
NK_1 (h)	-	-	-
NK_2 (h)	-	-	-
NK_3 (h)	14	-	-
Y_1 (h)	-	-	-
Y_2 (h)	-	-	-
NT_1 (h) (NTS1)	-	-	-
N (neuronal) (α-BGTX-insensitive)	-	-	-
N (muscle-type)	-	-	-
Opiate (non-selective)	-	-	-
δ	-	-	-
δ (h)	-	-	12
κ	-	-	-
κ (h)	16	-	-
μ	-	-	-
μ (h)	-	-	-
ORL1 (h)	-	-	-
Orexin	-	-	-
OT	-	-	13
PACAP-sv-1 (h) (PAC1)	-	-	-
PAF	-	-	-
PCP	-	-	12
EP_1 (h)	-	-	-
EP_4 (h)	-	-	-
TXA_2/PGH_2 (h) (TP)	-	-	-
PGI_2 (h) (IP)	-	-	18
P2X	-	-	-
P2Y	-	-	-

The results are expressed as a percent inhibition of control specific binding (mean values ; n = 2).
The symbol - indicates an inhibition of less than 10%.

Figure 5, from page 18 of Report 4605



Receptors	S-Demethyl citalopram	S-Didemethyl citalopram	S-Citalopram Oxalate
	1 µM	1 µM	1 µM
Reboxetine	12	-	-
5-HT$_{1A}$ (h)	17	14	15
5-HT$_{1B}$	-	-	-
5-HT$_{1D}$	-	-	-
5-HT$_{2A}$ (h)	-	-	-
5-HT$_{2B}$ (h)	-	23	-
5-HT$_{2C}$ (h)	-	-	22
5-HT$_3$ (r)	-	19	-
5-HT$_{4E}$ (h)	-	-	-
5-HT$_{5A}$ (h) (SF-)	21	14	22
5-HT$_6$ (h) (SH-)	-	-	-
5-HT$_7$ (r)	10	-	12
σ_1	76	11	85
σ_2	28	-	44
NE (non-selective)	-	-	14
NE (S,S)	-	-	10
Glucocorticoid (r)	-	-	-
Estrogen (r)	-	-	-
Progesterone (r)	-	-	-
Testosterone	-	-	-
TH	-	-	-
TRH	-	-	-
VIP (h) (VPAC)	-	-	-
VIP$_2$ (h) (VPAC$_2$)	-	-	-
V$_{1A}$ (r)	-	-	-
V$_{1B}$	-	-	11
V$_2$ (r)	-	-	-
Ca^{2+} channel (L, D-H)	-	-	-
K$^+$ ATP channel	-	-	-
K^+_V channel	-	-	-
SK$^+_{Ca}$ channel	-	-	-
Na$^+$ channel (site 1)	20	-	-
Cl$^-$ channel	-	-	-

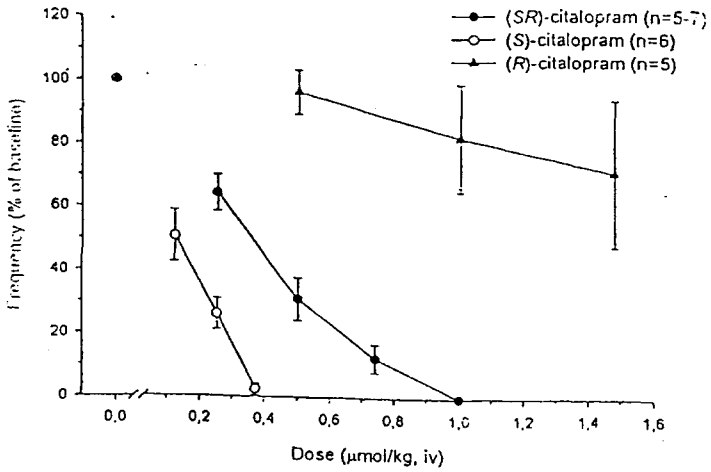
The results are expressed as a percent inhibition of control specific binding (mean values ; n = 2).
The symbol - indicates an inhibition of less than 10%.

Figure 6, from page 19 of Report 4605

	Citalopram	(+)	(-)	Demethyl-citalopram	(+)	(-)
	Lu 10-171-B	Lu 26-054-O	Lu 26-055-O	Lu 11-109-C	Lu 26-119-O	Lu 26-120-O
5-HTP potentiation, mice, 30 min, s.c.	3.3 (1.3)	1.1 (1.8)	59 (1.3)	NT	>50	>50
l-5-HTP potentiation, mice, 30 min, s.c.						
Head weaving	0.61 (1.3)	0.85 (1.3)	>48			
Tremor	0.66 (1.3)	1.5 (1.3)	>48			
Hind limb abduction	>12	3.7 (1.5)	>48			
Full syndrome	1.8 (1.5)	1.7 (1.2)	>48			
5-HT syndrome, mice, 30 min, s.c.	>49	>6.0	>190	NT	>50	>50
Potentiation of apomorphine gnawing, mice, 15 min, s.c.	>49	>24	>97	NT	*>50	*>50
Locomotor activity, mice, s.c.	>99	>97	>97	NT	NT	NT

Shown are ED50-values in µmol/kg. * preliminary results. NT = not tested.

Figure 7, from page 11 of Report 68/809



The effects of administration of cumulative doses (i.v.) of (*SR*)-, (*S*)-, or (*R*)-citalopram on the firing activity of dorsal raphe nucleus 5-HT neurones. The time between each dose was 2-3 min. All values are mean ± SEM and expressed as % of baseline. Baseline frequency of the groups were: (*SR*)-citalopram, 10.4±2.0 spikes/10 s; (*S*)-citalopram, 17.5±3.7 spikes/10 s; and (*R*)-citalopram, 14.0±2.9 spikes/10 s.

Figure 8, from page 11 of Report 98/808

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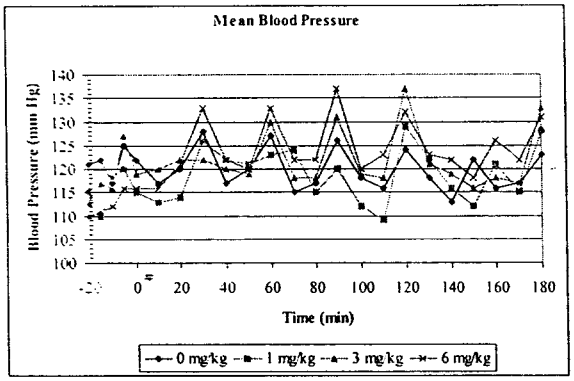
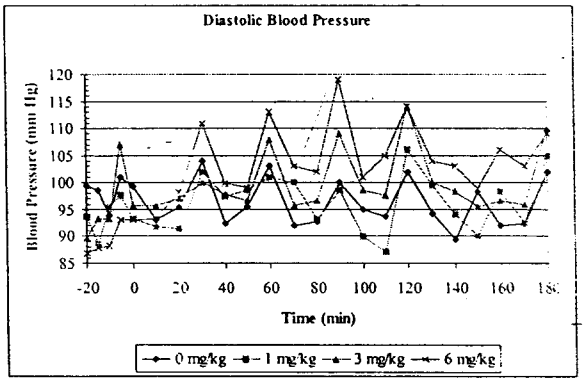
SAFETY PHARMACOLOGY-CARDIOVASCULAR/RESPIRATORY

Cardiovascular and Respiratory Study with Lu 26-054-0 after Intravenous Infusion in Conscious Beagle Dogs

Study: 99283, GLP
Species: Dog, Beagle, 3/sex, crossover design, 17-19 months old
Doses: 0, 1, 3, 6 mg/kg, Intravenous infusion over two hours
Parameters: ECG, Blood pressure, heart rate, respiratory parameters, PK; dogs monitored from 20 minutes predosing through 60 minutes post dosing
Substance: S-Citalopram, batch 002

Results:
Clinical signs- sedation in 4/6 dogs at 3 and 6 mg/kg; whimpering in 4/6 dogs at 3 and 3/6 dogs at 6 mg kg; no effects at 1 mg/kg
ECG- No significant effects on ECG parameters
Heart Rate- No significant effects
Blood Pressure- dose dependent increased mean and diastolic blood pressure at 6 mg/kg; sponsor considers 3 mg/kg to be NOEL, but there appears to be a small effect at this dose. This reviewer would consider 1 mg/kg to be the NOEL.





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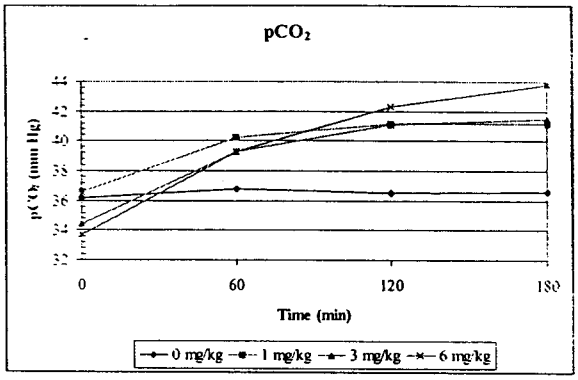
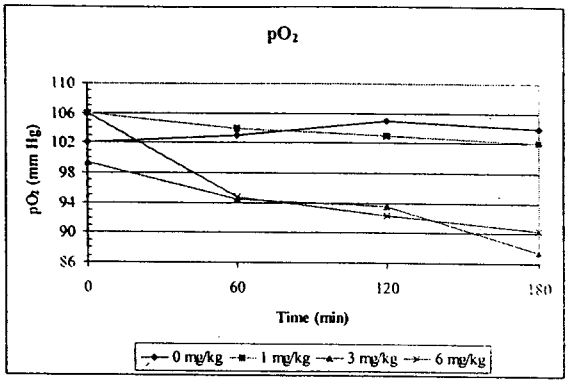
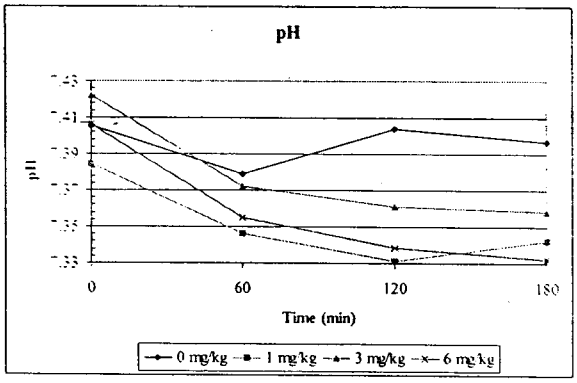
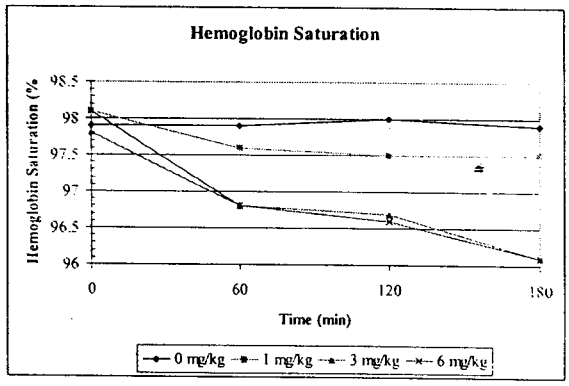
Blood gases- Increased pCO_2 and decreased pH, pO_2 and hemoglobin oxygen starting at 1 mg/kg









Respiration rate- no significant effects

Pharmacokinetics-

S-Citalopram Concentrations (nmol/L)

Dose	0.5 hours	1 hours	1.5 hours	2 hours	4 hours
1 mg kg	130	211	263	298	113
3 mg kg	290	545	689	720	438
6 mg kg	538	1017	1435	1988	1265

Demethylcitalopram Concentrations (nmol/L)

Dose	0.5 hours	1 hours	1.5 hours	2 hours	4 hours
1 mg kg	12	25	36	58	37
3 mg kg	19	69	138	209	286
6 mg kg	40	129	264	380	593

Didedemethylcitalopram Concentrations (nmol/L)

Dose	0.5 hours	1 hours	1.5 hours	2 hours	4 hours
1 mg kg	NA	NA	NA	NA	NA
3 mg kg	85	281	436	525	744
6 mg kg	71	199	294	329	512

The Effect of LU 26-054-0 on ECG and Haemodynamics in the Isolated Perfused Guinea Pig Heart

Study: 99288, GLP
Source Volume 15, Page 5-00830
Species: Guinea pig, male; 8 heart preps for vehicle and s-citalopram
Doses: 0, 0.5, 1.0, 2.5 uM
Parameters: ECG parameters, left ventricular pressure; hearts paced at 220 bpm
Substance: S-Citalopram, batch 002; no positive control

Results:

Lu 26-054-O (mean + sem, n=8)

Study parameters	Baseline	0.5 µM	1 µM	2.5 µM
PQ (ms)	59.8±1.4[a]	61.3±1.6	62.5±1.0[b]	64.8±2.0[c]
QRS (ms)	21.4±0.9	21.4±0.8	22.3±1.0	21.8±0.8
QT (ms)	162.0±2.3	163.8±2.8	167.0±2.0[d]	169.4±2.0[e]
ST (ms)	140.6±1.5	142.4±2.0	144.8±1.0[f]	147.6±2.0[g]
LVP (mmHg)	146.7±5.7	136.7±6.0[h]	127.0±6.7[i]	109.6±6.7[j]
dLVP/dT max (mmHg/sec)	2301.0±127.2	2198.5±148.4	1974.1±113.1[k]	1654.6±103.6[l]

a: P = 0.0492 compared to the time matched control group.
b: P = 0.008 compared to the time matched vehicle group and P= 0.0001 compared to the baseline value.
c: P = 0.0075 compared to the time matched vehicle group and P= 0.0001 compared to the baseline value.
d: P = 0.0106 compared to the time matched vehicle group.
e: P = 0.0414 compared to the time matched vehicle group and P= 0.0007 compared to the baseline value.
f: P = 0.030 compared to the time matched vehicle group.
g: P = 0.0357 compared to the time matched vehicle group and P= 0.0011 compared to the baseline value.
h: P = 0.0030 compared to the time matched vehicle group and P= 0.0002 compared to the baseline value.
i: P = 0.0003 compared to the time matched vehicle group and P= 0.0000 compared to the baseline value.
j: P = 0.0000 compared to the time matched vehicle group and P= 0.0000 compared to the baseline value.
k: P = 0.0062 compared to the time matched vehicle group and P= 0.0003 compared to the baseline value.
l: P = 0.0000 compared to the time matched vehicle group and P= 0.0000 compared to the baseline value.

Time matched Vehicle group (mean + sem, N=8)

Study parameters	Baseline	10 min	20 min	30 min
PQ (ms)	55.6±1.3	54.8±1.3	56.0±1.0	56.4±1.1
QRS (ms)	20.4±0.7	20.5±0.6	20.8±0.5	20.6±0.6
QT (ms)	154.1±3.1	156.3±2.6	156.5±2.7	157.3±2.6
ST (ms)	133.8±2.4	135.8±1.9	135.8±2.2	136.6±2.0
LVP (mmHg)	154.5±3.8	155.5±3.9	153.5±3.8	151.1±4.1
dLVP/dT max (mmHg/sec)	2431.5±115.6	2387.6±83.8	2385.5±115.4	2370.2±76.3

Figure 9, from page 17 of Report 154/856

Key points:
1. Effects were dose dependent.
2. 0.5 uM was negative inotropic response as indicated by decreased LVP and dLVP/dT.
3. 1 uM caused prolongation of PQ and QT intervals, but the changes are small.

The Effect of S-Citalopram (LU 26-054-0), citalopram (Lu 10-171-B), Sertraline (Lu 02-130-C), Fluoxetine (Lu 00-203-C), Paroxetine (Lu 00-217-C), Femoxetine (Lu 00-202-C) on ECG and Hemodynamics in the Isolated Perfused Guinea Pig Heart

Study: 99557, non-GLP
Source Volume 15, Page 5-00862
Species: Guinea pig, male; 8 heart preps for vehicle and s-citalopram
Doses: All substances tested at 0, 0.5, 1.0, 2.5 uM
Parameters: ECG parameters, left ventricular pressure; hearts paced at 220 bpm
Substance: S-Citalopram, batch 002;

Results:

Parameter	Drug	Baseline	0.5 uM	1 uM	2.5 uM
PQ (ms)	S-Citalopram	60.1 (2.2)	60.5 (2.3)	61.5 (2.2)	65.4 (2.1)
	RS-Citalopram	60.4 (2.0)	60.6 (2.2)	62.0 (2.1)	64.9 (2.3)
	Vehicle	71.4 (1.8)	72.0 (2.0)	72.4 (2.2)	73.0 (2.0)
QRS (ms)	S-Citalopram	25.8 (3.4)	25.9 (3.0)	25.1 (3.0)	25.1 (3.0)
	RS-Citalopram	23.9 (1.8)	24.3 (1.8)	25.9 (2.5)	25.5 (2.1)
	Vehicle	25.5 (1.8)	25.0 (1.6)	25.5 (1.9)	25.6 (1.9)
QT (ms)	S-Citalopram	170.4 (3.9)	173.6 (2.3)	174.6 (2.8)	175.0 (3.0)
	RS-Citalopram	164.0 (2.5)	166.8 (2.7)	168.1 (3.0)	**171.4 (2.5)**
	Vehicle	175.9 (2.1)	175.5 (1.9)	175.8 (1.8)	175.1 (2.3)
ST (ms)	S-Citalopram	144.6 (3.4)	147.8 (3.1)	149.5 (2.9)	149.9 (2.9)
	RS-Citalopram	140.1 (2.3)	142.5 (2.7)	142.3 (2.5)	145.9 (2.1)
	Vehicle	150.4 (3.5)	150.5 (2.9)	150.3 (3.1)	149.5 (3.3)
LVP (mm Hg)	S-Citalopram	148.6 (4.8)	145.2 (5.2)	138.3 (5.9)	**125.6 (5.8)**
	RS-Citalopram	145.1 (5.6)	144.8 (6.3)	139.7 (7.1)	**123.8 (7.0)**
	Vehicle	126.2 (4.8)	124.2 (5.3)	123.0 (5.8)	122.5 (5.9)
dLVP/dT (mm Hg/sec)	S-Citalopram	2349.9 (212.2)	2155.4 (130.3)	2023.6 (122.4)	**1840.6 (92.8)**
	RS-Citalopram	2105.7 (53.6)	2125.8 (34.9)	2184.7 (91.9)	**1842.4 (69.7)**
	Vehicle	1854.7 (90.2)	1783.1 (70.0)	1908.4 (146.5)	1760.0 (114.3)

Key points
1. Effects were dose dependent.
2. Both S-citalopram and RS-citalopram were negative inotropic agents causing similar degrees of effect.
3. Small effects on QT interval were observed.

The Effect of S-Citalopram (LU 26-054-O), Citalopram (Lu 10-171-B), Sertraline (Lu 02-130-C), Fluoxetine (Lu 00-203-C), Fluvoxamine (Lu 00-362-M), 35-138-C, and Sertindole (Lu 23-174-O) on L-type Calcium currents in Isolated Cardiac Myocytes

Study: 99499, non-GLP
Source Volume 14, Page 5-00411
Species: isolated guinea pig myocytes
Doses: S-citalopram and RS-citalopram tested at 30, 100, 300 uM
Parameters: inhibition of L-type calcium channels
Substance: S-Citalopram, batch 002;

Results:
S-citalopram IC50 was 92 uM
RS-citalopram IC50 was 75 uM

Comparative Electrophysiological Effects of Marketed and Novel Selective Serotonin Reuptake Inhibitors (SSRIs) on Cloned Human Cardiac Ion channels (HERG and SCN5A)

Study: 99558, non-GLP
Source Volume 14, Page 5-00439
Species: CHO cells
Parameters: inhibition of potassium (HERG, I_{Kr}) and sodium channel (SCN5A, I_{Na})
Substance: S-Citalopram, batch 002;

Compound	Lu number	HERG (I_{Kr}) IC_{50} µM	SCN5A (I_{Na}) IC_{50} µM	5-HT uptake IC_{50} µM
Citalopram	Lu 10-171	4.9	160	0.004
S-citalopram	Lu 26-054	3.7	150	0.002
R-citalopram	Lu 26-055	8.7	140	0.280
DCT	Lu 11-109	20	> 30	0.014
DDCT	Lu 11-161	29	>30	0.220

Figure 10, from page 13 of report 053/807

The Effect of Citalopram (Lu 10-171-B), Sertraline (Lu 02-130-C), Fluoxetine (Lu 00-203-C), Fluvoxamine (Lu 00362-M), Femoxetine (Lu 00-202-C) on ECG and Hemodynamics in the Isolated Perfused Guinea Pig Heart

Study: 99335, non-GLP
Source Volume 27, Page 5-05328
Species: Guinea pig, male; 8 heart preps for vehicle and 5 for citalopram
Doses: All substances tested at 0, 0.5, 1.0, 2.5 uM
Parameters: ECG parameters, left ventricular pressure; hearts paced at 220 bpm
Substance: Citalopram

Results:

Parameter	Drug	Base	0.5 uM	1 uM	2.5 uM	5 uM	10 uM	25 uM	100 uM
PQ (ms)	Cital	62.2 (4.3)	63.0 (4.6)	63.6 (4.8)	64.6 (4.6)	68.6 (5.1)	75.2 (6.8)	86.0 (8.7)	NM
	Cont	71.4 (1.8)	71.6 (1.9)	72.0 (2.0)	72.4 (2.1)	72.4 (2.2)	71.8 (2.0)	73.0 (2.0)	73.3 (2.2)
QRS (ms)	Cital	29.4 (2.2)	29.0 (1.8)	30.2 (2.0)	30.2 (1.7)	29.0 (1.4)	26.8 (1.7)	29.8 (1.8)	NM
	Cont	25.5 (1.8)	25.8 (1.8)	25.0 (1.6)	24.9 (1.7)	25.5 (1.9)	25.6 (1.6)	25.6 (1.9)	25.9 (1.7)
QT (ms)	Cital	171.8 (3.1)	172.8 (2.9)	175.2 (1.6)	177.6 (1.9)	177.4 (1.8)	175.4 (2.2)	162.4 (6.0)	NM
	Cont	175.9 (2.1)	174.0 (2.4)	175.5 (1.9)	175.0 (2.1)	175.8 (1.8)	175.8 (2.2)	175.1 (2.3)	175.0 (2.4)
ST (ms)	Cital	142.4 (3.9)	143.8 (3.3)	145.0 (2.5)	147.4 (1.5)	148.4 (1.7)	148.6 (2.1)	132.6 (6.9)	NM
	Cont	150.4 (3.5)	148.3 (3.6)	150.5 (2.9)	150.1 (3.0)	150.3 (3.1)	150.1 (3.2)	149.5 (3.3)	149.1 (3.1)
LVP (mm Hg)	Cital	134.2 (5.5)	134.7 (5.4)	128.7 (5.8)	117.7 (6.4)	98.8 (9.2)	77.3 (10.7)	54.7 (11.7)	28.8 (10.7)
	Cont	126.2 (4.8)	125.2 (5.2)	124.2 (5.3)	125.2 (6.2)	123.0 (5.8)	121.6 (5.7)	122.5 (5.9)	119.3 (6.0)
dLVP/dT (mm Hg/sec)	Cital	2335 (272)	2192 (243)	1975 (112)	1848 (154)	1469 (208)	1250 (197)	1100 (229)	716 (157)
	Cont	1855 (90)	1837 (90)	1783 (70)	1903 (76)	1908 (147)	1907 (79)	1760 (114)	1802 (88)

Key points
1. Citalopram had a negative inotropic effect starting at about 2.5 uM.
2. Increased QT interval was observed at 1 uM through 5 uM followed by a decline in QT interval.
3. Results are consistent in isolated perfused guinea pig heart.

PHARMACOKINETICS/TOXICOKINETICS

S-citalopram is metabolized via cytochromes (CYP) 2D6, -2C19, and –3A in human liver microsomes to S-desmethylcitalopram (S-DCT). The CYP3A isozyme accounted for 35-46% of net intrinsic clearance. S-DCT is further metabolized to S-didesmethylcitalopram via CYP2D6.

S-citalopram is a weak or negligible inhibitor of human CYP1A2, -2C9, -2C19, -2D6, -2E1, and -3A in human liver microsomes.

TOXICOLOGY

General Comments

Since S-citalopram is the active enantomer of RS-citalopram, which is already approved for use in depressive disorders, the purpose of the toxicity tests is to determine the equivalence of toxicity between the S- and RS-citalopram. Therefore, the FDA DNDP only required submission of a 4-week, 13-week and a segment II reproductive toxicity study. All studies were to be conducted in the rat.
Note: LU 26-054-0 = S-Citalopram, LU 10-171-B = RS-Citalopram

Lu 26-054-0 and Lu 10-171-B Acute Oral Toxicity Study in Rats.

Study No: 36110/854, Report 17712
Amendment #, Vol #, and page #: Vol 15, Pages 5-00953
Conducting laboratory and location: [redacted]
Date of study initiation: May 12, 1999
GLP compliance: Yes
QA- Report Yes (X) No ()
Methods:
Dosing:

- species/strain: Rat, Han Wistar (Crl: Han Wist (GLx.BR1)BR strain)
- #/sex/group or time point: see below
- age: 8 weeks
- weight: 170-180 g (females); 210-220 g (males)
- satellite groups used for toxicokinetics or recovery:
- dosage groups in administered units:

Test Material	Group	Dose Level of Lu 26-054 ($mg.kg^{-1}$)	Dose Concentration of Lu 26-054-0 ($mg.ml^{-1}$)	Animal	
				Male	Female
Lu 26-054-0	Dose Ranging				
	1	100	12.8	1,2	-
	2	250	32.0	3,4	-
	3	500	64.0	5,6	-
	4	750	96.0	7,8	-
	5	1000	128.0	9,10	-
	Main Study				
	1	500	64.0	11-15	26-30
	2	1000	128.0	16-20	31-35
	3	250	32.0	21-25	36-40
Test Material	Group	Dose Level of Lu 10-171 ($mg.kg^{-1}$)	Dose Concentration of Lu 10-171-B ($mg.ml^{-1}$)	Animal	
				Male	Female
Lu 10-171-B	Dose Ranging				
	1	100	12.5	51,52	-
	2	250	31.25	53,54	-
	3	500	62.5	55,56	-
	4	750	93.75	57,58	-
	5	1000	125.0	59,60	-
	Main Study				
	1	500	62.5	61-65	76-80
	2	650	81.25	66-70	81-85
	3	250	31.25	71-75	86-90

Figure 11, from page 13 of Report 17712

- route, form, volume, and infusion rate: Oral gavage

Drug, lot#, radiolabel, and % purity: S-Citalopram Batch 003, [redacted] ; RS-Citalopram Batch E 3061 [redacted]
Formulation/vehicle: Saline
Observations and times:

- Clinical signs: 1X/day
- Body weights: Day 1, 8, 15
- Food consumption: Not done
- Ophthalmoscopy: Not done
- EKG: Not done
- Hematology: Not done
- Clinical chemistry: Not done
- Urinalysis: Not done
- Organ weights: Not done
- Gross pathology: Day 15
- Organs weighed: Not done
- Histopathology: Not done
- Toxicokinetics: Not done
- Other:

Results:

- Clinical signs:

Mortality, dose range finding study (males only)

Drug	100 mg/kg	250 mg/kg	500 mg/kg	750 mg/kg	1000 mg/kg
S-Citalopram	0/2	0/2	0/2	0/2	1/2
RS-Citalopram	0/2	0/2	0/2	2/2	1/2

Drug	Dose (mg/kg)	Male	Female	Clinical Signs
S-Citalopram	250	0/5	0/5	Salivation
	500	1/5	2/5	Mortality on Day 2; hunched appearance, irregular breathing, prostration, staggering, tremors; recovery by Days 2 (male) and 3 (female)
	1000	4/5	3/5	Deaths on Days 1 (3 males), 2 (1 male, 2 female), and 6 (1 female); clinical signs same as 500 mg/kg; recovery on Day 4
RS-Citalopram	250	0/5	0/5	Salivation
	500	1/5	2/5	Deaths on Days 1 (1 female) and 2 (1 male and 1 female); hunched appearance, irregular breathing, prostration, salivation, tremors, convulsions, subdued behavior;recovery by day 3
	650	3/5	1/5	Deaths on Days 1 (1 male, 1 female) and 2 (2 males; clinical signs same as 500 mg/kg; recovery on Day 4

- Body weights one male at 650 mg/kg RS-citalopram lost 30 grams over the observation period.
- Food consumptionNot done

- Ophthalmoscopy No done
- Electrocardiography Not done
- Hematology Not done
- Clinical chemistry Not done
- Urinalysis Not done
- Organ Weights Not done
- Gross pathology

Necropsy Findings: Lu 26-054-O

Dose Level ($mg.kg^{-1}$ Lu 26-054)	Animal/Sex	Necropsy Finding	Day of Death
250	21-25♂	No abnormalities detected	15
	36-40♀	No abnormalities detected	15
500	11,12, 14,15♂	No abnormalities detected	15
	13♂	Skin: Brown staining at muzzle Stomach: Distended by contents	2
	26,27♀	Stomach: Distended by fluid	2
	28-30♀	No abnormalities detected	15
1000	16,18♂	Stomach: Glandular area reddened, distended by gas and mucous-like fluid	1
	17♂	Stomach: Distended by fluid	2
	19♂	Stomach: Distended by contents	15
	20♂	Stomach: Distended by clear fluid, reddened glandular mucosa Duodenum: Reddened Intestines: Clear fluid present	1
	31,33♀	Stomach: Distended by fluid	2
	32♀	No abnormalities detected	15
	34♀	Animal autolysed and cannibalised	6
	35♀	Thymus: Reddened	15

Figure 12, from page 34 of Report 17712

Necropsy Findings: Lu 10-171-B

Dose Level ($mg.kg^{-1}$ Lu 10-171)	Animal/Sex	Necropsy Finding	Day of Death
250	71-75♂	No abnormalities detected	15
	86-90♀	No abnormalities detected	15
500	61-63,65♂	No abnormalities detected	15
	64♂	Stomach: Distended by fluid	2
	76,77,80♀	No abnormalities detected	15
	79♀	Skin: Hairloss on ventral abdomen Stomach: Distended by fluid, glandular mucosa reddened Jejunum: Green/brown fluid	1
	78♀	Stomach: Distended by fluid	2
650	66♂	Stomach: Distended by gas, filled with mucus-like fluid	1
	67♂	Stomach: Distended by fluid	2
	68♂	No abnormalities detected	15
	69♂	Autolysed Stomach: Distended by fluid	2
	70♂	Stomach: Distended by contents Ileum, caecum, colon: Distended by gas	15
	81,84,85♀	No abnormalities detected	15
	82♀	Stomach: Distended by green/clear fluid Intestines: Small, reddened, dark, contain red/green fluid	1
	83♀	Colon, rectum: Distended by gas	15

Figure 13, from page 35 of Report 17712

- Histopathology Not done
- Toxicokinetics Not done

Key Study Findings:

1. The minimal lethal dose for both S and RS-citalopram was 500 mg/kg.
2. Clinical signs and gross pathology were similar for both enantiomers.

Lu 26-054-0 and Lu 10-171-B Acute Intravenous Toxicity Study in Rats.

Study No: 36109/854, Report 17751
Amendment #, Vol #, and page #: Vol 15, Pages 5-01029
Conducting laboratory and location:
Date of study initiation: May 12, 1999
GLP compliance: Yes
QA- Report Yes (X) No ()
Methods:
Dosing:

- species/strain: Rat, Han Wistar (Crl: Han Wist (GLx.BR1)BR strain)
- #/sex/group or time point: see below
- age: 8 weeks
- weight: 170-180 g (females); 210-220 g (males)
- satellite groups used for toxicokinetics or recovery:
- dosage groups in administered units:

Test Material	Group	Dose Level of Lu 26-054 ($mg.kg^{-1}$)	Dose Concentration of Lu 26-054-O ($mg.ml^{-1}$)	Animal	
				Male	Female
Lu 26-054-O	Dose Ranging				
	1	5	0.64	1,2	-
	2	10	1.28	3,4	-
	3	20	2.56	5,6	-
	4	30	3.84	7,8	-
	5	35	4.48	9,10	-
	Main Study				
	1	15	1.92	11-15	26-30
	2	22	2.82	16-20	31-35
	3	30	3.84	21-25	36-40
Test Material	Group	Dose Level of Lu 10-171 ($mg.kg^{-1}$)	Dose Concentration of Lu 10-171-B ($mg.ml^{-1}$)	Animal	
				Male	Female
Lu 10-171-B	Dose Ranging				
	1	5	0.63	51,52	-
	2	10	1.25	53,54	-
	3	20	2.50	55,56	-
	4	30	3.75	57,58	-
	5	35	4.38	59,60	-
	Main Study				
	1	15	1.88	61-65	76-80
	2	22	2.75	66-70	81-85
	3	30	3.75	71-75	86-90

Figure 14, from page 12 of Report 17751

- route, form, volume, and infusion rate: Intravenous administration

Drug, lot#, radiolabel, and % purity: S-Citalopram Batch 003 RS-Citalopram Batch E 3061

Formulation/vehicle: Saline
Observations and times:

- Clinical signs: 1X/day
- Body weights: Day 1, 8, 15
- Food consumption: Not done
- Ophthalmoscopy: Not done
- EKG: Not done
- Hematology: Not done

- Clinical chemistry: Not done
- Urinalysis: Not done
- Organ weights: Not done
- Gross pathology: Day 15
- Organs weighed: Not done
- Histopathology: Not done
- Toxicokinetics: Not done
- Other:

Results:

- Clinical signs:

Mortality, dose range finding study (males only)

Drug	5 mg/kg	10 mg/kg	20 mg/kg	30 mg/kg	35 mg/kg
S-Citalopram	0/2	0/2	0/2	1/2	2/2
RS-Citalopram	0/2	0/2	0/2	0/2	1/2

Drug	Dose (mg/kg)	Male	Female	Clinical Signs
S-Citalopram	15	0/5	0/5	No signs
	22	0/5	0/5	Increased breathing, subdued behavior
	30	3/5	2/5	All deaths occurred at dosing: labored breathing, subdued behavior, convulsions, and staggering; symptoms decreased at 30 minutes
RS-Citalopram	15	0/5	0/5	No signs
	22	0/5	0/5	No signs
	30	1/5	5/5	Deaths occurred at dosing (5 females) or within 40 minutes (1 male); irregular breathing, subdued behavior, convulsions, tremors and staggering; symptoms decreased at 40 minutes

- Body weights No effects
- Food consumption Not done
- Ophthalmoscopy No done
- Electrocardiography Not done
- Hematology Not done
- Clinical chemistry Not done
- Urinalysis Not done
- Organ Weights Not done
- Gross pathology No significant effects
- Histopathology Not done
- Toxicokinetics Not done

Key Study Findings:

1. The minimal lethal dose for both S and RS-citalopram was 30 mg/kg.
2. Clinical signs and gross pathology were similar for both enantiomers.

Lu 26-054-0/Lu 10-171-B 4 Week Toxicity Study in Rats with Administration by the Oral (Gavage) Route.

Study No: 3585/854, Report 17751
Amendment #, Vol #, and page #: Vol 16, Pages 5-01101
Conducting laboratory and location: [redacted]
Date of study initiation: March 16, 1998
GLP compliance: Yes
QA- Report Yes (X) No ()
Methods:
Dosing:

- species/strain: Rat, Han Wistar (Crl: Han Wist (GLx.BR1)BR strain)
- #/sex/group or time point: 10/sex/dose
- age: 8 weeks
- weight: 170-180 g (females); 210-220 g (males)
- satellite groups used for toxicokinetics or recovery:
- dosage groups in administered units: S-Citalopram- 5, 20, 40, 60 mg/kg; RS-Citalopram 20, 60 mg/kg
- route, form, volume, and infusion rate: Oral gavage

Drug, lot#, radiolabel, and % purity: S-Citalopram Batch 001 [redacted] RS-Citalopram Batch U 2681 [redacted]
Formulation/vehicle: Saline
Observations and times:

- Clinical signs: 2X/day
- Body weights: 2X/week
- Food consumption: 2X/week
- Ophthalmoscopy: Week 4
- EKG: Not done
- Hematology: Week 4
- Clinical chemistry: Week 4
- Urinalysis:Week 4
- Organ weights:
- Gross pathology:
- Organs weighed:
- Histopathology:
- Toxicokinetics: Days 1, 29; 0, 0.5, 1, 1.5, 3, 6, 9, 12, 24 hours post-dose
- Other:

Results:

- Clinical signs:

Observation/Finding	Group/Dose Level (mg Lu 26-054.kg^{-1}.day^{-1})					Group/Dose Level (mg Lu 10-171. kg^{-1}.day^{-1})	
	1 (0)	2 (5)	3 (20)	4 (40)	5 (60)	6 (20)	7 (60)
Males							
Staining around mouth and muzzle	0	0	4	5	9	2	6
Encrusted eyelid	0	0	1	1	0	0	0
Salivation	0	0	3	8	10	5	9
Mydriasis	0	0	1	1	0	0	4
Unkempt coat	0	0	0	3	5	0	0
Wheezing respiration	0	0	0	0	1	0	0
Staining of coat	0	0	0	0	1	0	0
Total number with no abnormality detected	10	10	2	1	0	4	1
Total number examined	10	10	10	10	10	10	10

Observation/Finding	Group/Dose Level (mg Lu 26-054.kg^{-1}.day^{-1})					Group/Dose Level (mg Lu 10-171. kg^{-1}.day^{-1})	
	1 (0)	2 (5)	3 (20)	4 (40)	5 (60)	6 (20)	7 (60)
Females							
Hair loss	1	0	0	0	0	0	0
Staining around mouth and muzzle	0	0	2	5	7	2	4
Salivation	0	0	2	7	9	4	10
Wheezing respiration	0	0	1	1	2	1	2
Unkempt coat	0	0	0	2	4	1	5
Total number with no abnormality detected	8	10	8	3	1	4	0
Total number examined	10	10	10	10	10	10	10

Figure 15, from page 29 of Report 16401

- Body weights-

Body weight gain in grams

	0 mg/kg	S-Citalopram				RS-Citalopram	
		5 mg/kg	20 mg/kg	40 mg/kg	60 mg/kg	20 mg/kg	60 mg kg
Males	72	74	68	71	64	71	**52**
Females	35	35	36	33	31	33	**25**

Values in bold significantly different at $p<0.05$

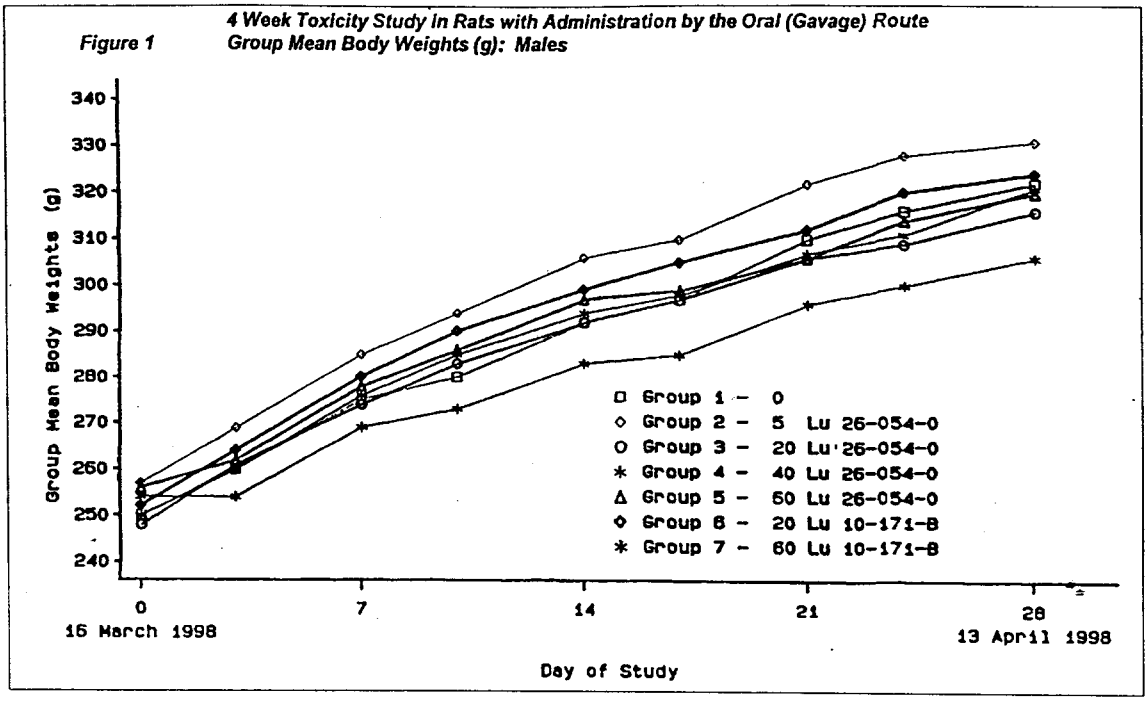


Figure 16, from page 81 of Report 16401

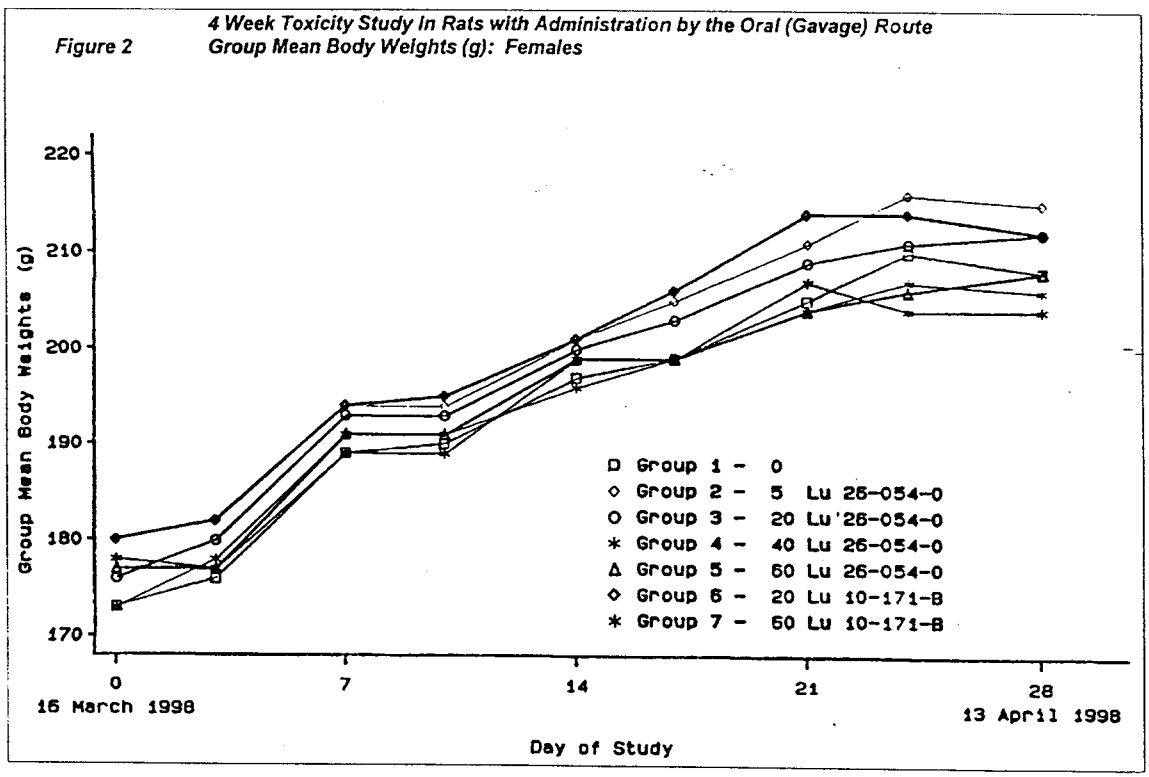


Figure 17, from page 82 of Report 16401

- Food consumption- Generally comparable between treatment groups,

60 mg/kg S-Citalopram- slight decreased food consumption on Day 3 (-9%, $p<.05$)
60 mg/kg RS-Citalopram- decreased food consumption on Day 3 (-15%) and Day 28 (-9%)

- Ophthalmoscopy No effects
- Electrocardiography Not done
- Hematology

Mean percent vacuolated lymphocytes (incidence)

	0 mg/kg	S-Citalopram				RS-Citalopram	
		5 mg/kg	20 mg/kg	40 mg/kg	60 mg/kg	20 mg/kg	60 mg/kg
Males	0 (0/10)	0.67 (3/9)	0.67 (4/10)	1.3 (7/10)	0.4 (3/10)	1.4 (6/10)	12.1 (10/10)
Females	0.3 (2/10)	0.5 (3/10)	0.2 (1/10)	1.0 (5/10)	0.9 (3/10)	1.1 (6/10)	5.4 (9/10)

Animal 49 (60 mg/kg M S citalopram) had increased platelet level (1699 vs 716 control mean)
Animal 225 (60 mg/kg F S citalopram) had decreased platelet level (190 vs 803 control mean)
60 mg/kg S-citalopram- Slight decrease in hemoglobin in females only (14.3 vs 14.6 controls, $p<.05$), in historical range and not considered significant
60 mg/kg RS-citalopram- increased prothrombin time (23 vs 20 control $p<0.01$) in males only, but within historical range
Animal 246 (60 mg/kg female RS citalopram) had decreased platelet level (276 vs 803 control mean)

- Clinical chemistry

60 mg/kg S-citalopram females- ↑ total bilirubin (1.6 vs 1.3 ($p<.05$), but within historical control range 0.5-2.4)
60 mg/kg RS-citalopram females- ↑ total bilirubin (1.7 vs 1.3 ($p<.05$), but within historical control range 0.5-2.4)

- Urinalysis

No effects

- Organ Weights- Relative organ weights as percent of control

Organ	S-Citalopram				RS-Citalopram	
	5 mg/kg	20 mg/kg	40 mg/kg	60 mg/kg	20 mg/kg	60 mg/kg
Liver, Females	100	101	104	110*	98	111*
Liver, Males	100	105	112*	107	103	110*

*=statistically significant

- Gross pathology

No effects

- Histopathology

		S-Citalopram				RS-Citalopram	
	0 mg/kg	5 mg/kg	20 mg/kg	40 mg/kg	60 mg/kg	20 mg/kg	60 mg/kg
Histological Findings, Males							
Epididymides, Vacuolated	0/10	0/10	0/10	0/10	9/10	0/10	10/10
Mild	0/10	0/10	0/10	0/10	9/10	0/10	0/10
Moderate	0/10	0/10	0/10	0/10	0/10	0/10	10/10
Kidney, Inflammatory cell infiltration	0/10				1/10		0/10
Liver, Vacuolation, Centrilobular	1/10	0/10	2/10	2/10	1/10	0/10	1/10
Minimal	1/10	0/10	1/10	2/10	0/10	0/10	1/10
Mild	0/10	0/10	1/10	0/10	1/10	0/10	0/10
Lung, Macrophage Accumulation*	1/10	3/10	0/10	1/10	6/10	1/10	5/10
Histological Findings, Females							
Liver, Inflammatory Cell Infiltration	2/10	2/10	0/10	4/10	3/10	1/10	0/10
Lung, Macrophage Accumulation*	4/10	3/10	3/10	4/10	4/10	1/10	5/10

*Lung macrophage accumulation includes increased foamy alveolar macrophages, increased pigmented macrophages and increased macrophages.

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- Toxicokinetics The 5 mg/kg dose did not yield enough drug positive to evaluate..

Summary of TK parameters: Males for S-CT and R-CT Analytes

		Lu 26 - 054			Lu 10 - 171			
	Dose	20	40	60	20		60	
		S-CT	S-CT	S-CT	S-CT	R-CT	S-CT	R-CT
Cmax(obs) (nmol/l)	D1	429.33	1031.67	1253.67	585.00	762.33	1681.00	2006.67
	D29	492.00	1330.67	1462.67	579.00	944.33	857.00	2074.33
Tmax(obs) (h)	D1	1.5	1	0.5	1	1	1.5	1.5
	D29	1	1	0.5	1.5	1	1.5	3
AUC (0-t) (nmol.h/l)	D1	2827.75	3821.17	6405.29	1761.25	2158.50	13777.60	17955.30
	D29	1850.13	7821.17	7660.46	3170.62	7198.79	9728.62	32585.00
AUC (0- ∞) (nmol.h/l)	D1	5127.34	3964.35	9475.55	1953.75	2333.23	14198.08	18569.29
	D29	1963.47	10533.34	8259.40	3415.72	7608.76	10097.19	35148.75
T½el (h)	D1	11.98	2.58	5.52	1.67	1.51	4.86	5.08
	D29	2.04	18.25	3.23	3.30	5.52	4.96	5.90

Figure 18, from page 316 of Report 16401

Summary of TK parameters: Females for S-CT and R-CT Analytes

		Lu 26 - 054			Lu 10 - 171			
	Dose	20	40	60	20		60	
		S-CT	S-CT	S-CT	S-CT	R-CT	S-CT	R-CT
Cmax(obs) (nmol/l)	D1	870.67	1124.67	1907.00	676.33	1077.67	1143.33	2354.67
	D29	875.33	2127.67	2903.33	681.67	1239.67	1615.67	3917.67
Tmax(obs) (h)	D1	0.5	1.5	0.5	1	1	3	3
	D29	0.5	0.5	0.5	1.5	1.5	1	1.5
AUC (0-t) (nmol.h/l)	D1	2093.92	4394.58	9440.17	1608.92	3175.42	9663.83	20377.50
	D29	3693.67	9838.29	15500.37	2753.12	7942.29	18046.46	59923.83
AUC (0- ∞) (nmol.h/l)	D1	2357.29	4607.59	9813.26	1691.42	3337.38	10805.88	22458.48
	D29	3879.54	10270.51	16200.52	3009.00	8338.40	20568.06	77657.58
T½el (h)	D1	3.73	1.92	5.02	1.24	1.25	7.53	6.84
	D29	3.35	2.91	3.04	3.44	5.33	7.85	11.52

Figure 19, from page 317 of Report 16401

Summary of TK parameters: Males for S-DCT and R-DCT Analytes

		Lu 26 - 054			Lu 10 - 171			
	Dose	20	40	60	20		60	
		S-DCT	S-DCT	S-DCT	S-DCT	R-DCT	S-DCT	R-DCT
Cmax(obs) (nmol/l)	D1	487.00	925.33	1253.00	384.67	724.67	899.00	1518.00
	D29	670.33	1731.67	1955.67	292.67	649.67	1016.00	2331.00
Tmax(obs) (h)	D1	1.5	1	3	1	1	1.5	1.5
	D29	1	3	3	3	9	12	12
AUC (0-t) (nmol.h/l)	D1	3298.58	6914.58	16574.10	2027.83	4657.67	11244.40	22329.90
	D29	4193.83	17903.13	26917.75	4023.83	9124.58	18989.83	44299.00
AUC (0- ∞) (nmol.h/l)	D1	6305.46	7093.33	18820.53	2195.45	4848.34	12349.52	25021.10
	D29	4427.93	18204.94	27407.98	4204.46	9248.94	26103.98	73103.37
T½el (h)	D1	11.78	4.53	7.73	3.08	4.90	6.66	6.68
	D29	5.15	3.91	3.61	4.64	3.19	12.81	17.99

Figure 20, from page 318 of Report 16401

Summary of TK parameters: Females for S-DCT and R-DCT Analytes

		Lu 26 - 054			Lu 10 - 171			
	Dose	20	40	60	20		60	
		S-DCT	S-DCT	S-DCT	S-DCT	R-DCT	S-DCT	R-DCT
Cmax(obs) (nmol/l)	D1	161.67	458.67	554.33	172.00	429.00	422.67	1058.33
	D29	322.67	879.50	1086.00	188.00	414.00	956.33	2383.67
Tmax(obs) (h)	D1	1	1.5	1.5	1.5	3	3	6
	D29	1	6	3	1.5	9	12	12
AUC (0-t) (nmol.h/l)	D1	601.37	3266.00	7509.75	806.92	3966.08	5354.25	14309.30
	D29	2158.58	10969.50	16383.50	2506.83	6367.67	19212.75	49556.17
AUC (0- ∞) (nmol.h/l)	D1	919.63	3406.09	7648.62	1379.87	4127.00	6638.06	20174.90
	D29	2351.11	11302.41	16882.07	3353.44	6655.04	ND	ND
T½el (h)	D1	6.89	5.02	3.57	6.56	4.85	10.27	11.86
	D29	6.35	4.31	4.06	12.06	4.46	ND	ND

Figure 21, from page 319 of Report 16401

Summary of TK parameters: Males for S-DDCT and R-DDCT Analytes

		Lu 26 - 054			Lu 10 - 171			
	Dose	20	40	60	20		60	
		S-DDCT	S-DDCT	S-DDCT	S-DDCT	R-DDCT	S-DDCT	R-DDCT
Cmax(obs) (nmol/l)	D1	159.00	244.67	319.00	109.67	320.67	202.00	810.33
	D29	118.00	268.67	404.00	67.00	366.67	316.00	1377.00
Tmax(obs) (h)	D1	1.5	9	12	1.5	3	9	9
	D29	3	9	12	9	9	1	1
AUC (0-t) (nmol.h/l)	D1	1136.17	3387.67	5606.08	1282.25	4373.17	3675.33	12984.00
	D29	1591.87	4081.54	7006.33	952.13	5825.17	6184.42	26527.17
AUC (0- ∞) (nmol.h/l)	D1	1412.12	3443.58	6548.23	1386.69	4427.09	5195.09	23496.26
	D29	1702.57	4210.32	7584.38	1048.64	6629.42	16409.15	90075.42
T½el (h)	D1	7.65	3.37	7.73	6.29	3.25	12.15	17.21
	D29	5.75	3.97	5.63	5.82	6.64	36.82	49.72

Figure 22, from page 320 of Report 16401

Summary of TK parameters: Females for S-DDCT and R-DDCT Analytes

		Lu 26 - 054			Lu 10 - 171			
	Dose	20	40	60	20		60	
		S-DDCT	S-DDCT	S-DDCT	S-DDCT	R-DDCT	S-DDCT	R-DDCT
Cmax(obs) (nmol/l)	D1	31.83	185.00	229.00	110.67	240.33	112.33	351.67
	D29	46.33	177.50	283.00	48.83	231.00	244.00	1264.33
Tmax(obs) (h)	D1	1.5	1.5	9	3	6	6	6
	D29	6	6	9	24	9	12	12
AUC (0-t) (nmol.h/l)	D1	194.71	1907.50	3408.75	883.67	3004.25	1595.67	6904.25
	D29	686.33	3012.33	4640.08	896.75	4249.33	4750.50	26614.83
AUC (0- ∞) (nmol.h/l)	D1	346.05	1962.94	3595.75	968.86	3156.89	2894.00	ND
	D29	770.85	3288.03	5077.45	ND	6492.45	ND	ND
T½el (h)	D1	7.77	4.71	4.83	6.22	4.70	19.28	ND
	D29	6.63	6.03	5.92	ND	13.76	ND	ND

Figure 23, from page 321 of Report 16401

Key Study Findings:

3. Toxicity of the RS-citalopram enantomer was similar to that in 1 year chronic study.
4. S-citalopram was less toxic than the RS-enantomer
5. Increased incidence of unkempt coat in male 60 mg/kg rats
6. Increased salivation and mouth staining at 20 mg/kg in both S and RS-citalopram
7. Slightly decreased body weight at 60 mg/kg, more severe with RS-citalopram than S-citalopram

8. Slight increase in vacuolated lymphocytes in treated males, but not as significant as in RS-citalopram treated animals
9. Increased liver weight at 40 mg/kg in females and 60 mg/kg in males
10. Vacuolated epidydimus in males at 60 mg/kg
11. Lung macrophage accumulation at 60 mg/kg in males only (females had high background rate).

Lu 26-054-0/Lu 10-171-B 13 Week Toxicity Study in Rats with Administration by the Oral (Gavage) Route and 5 Week Recovery Period

Study No: 3610/854
Amendment #, Vol #, and page #: Vol 18, Pages 5-01774
Conducting laboratory and location: —
Date of study initiation: July 2, 1998
GLP compliance: Yes
QA- Report Yes (X) No ()
Methods:
Dosing:

- species/strain: Rats, Han Wistar (Crl: Han Wist (Glx.BRI)Br Strain)
- #/sex/group or time point: 10/sex/dose
- age: 8-9 weeks
- weight:
- satellite groups used for toxicokinetics or recovery:
  Toxicokinetics- 18/sex/dose (treated groups);
  Recovery- 10/sex/dose (0, 120 mg/kg S-citalopram, 60 mg/kg RS-citalopram)
- dosage groups in administered units: S-Citalopram: 0, 10, 40, 120 (decreased to 100 on Day 12, decreased to 80 during Week 5 for males and Week 6 for females, study terminated at Week 10); RS-Citalopram 5, 60 mg/kg
- route, form, volume, and infusion rate: Oral Gavage

Drug, lot#, radiolabel, and % purity: 001 —
Formulation/vehicle: Saline
Observations and times:

- Clinical signs: 2X/day
- Body weights: 1X/day
- Food consumption: 1X/week
- Ophthalmoscopy: 6 weeks and termination
- EKG:Not done
- Hematology: termination
- Clinical chemistry: termination
- Urinalysis: Week 13 (10 for high dose)
- Organ weights: See addendum
- Gross pathology: yes
- Organs weighed: yes
- Histopathology: see addendum
- Toxicokinetics: 0, 0.5, 1, 1.5, 3, 6, 9, 12, 24 hours, Days 1, 41, and 90
- Other:

Results:

- Clinical signs: Mortality was observed at the high dose of s-citalopram only

	Males	Females
120 mg/kg (weeks 0-1 Males, 0-5 Females)	11/38	7/38
100 mg/kg (weeks 2-6 Males only)	5/27	---
80 mg/kg (weeks 7-10 Males, 6-10 Females)	4/22	0/31
Total	20/38	7/38

Pathological findings in early decedents suggested cardiac failure, clinical signs included piloerection, hunched appearance, salivation and coat staining

		S-Citalopram			RS-Citalopram	
Clinical Signs	0 mg/kg	10 mg/kg	40 mg/kg	80-120 mg/kg	5 mg/kg	60 mg/kg
Males						
Number Examined	20	10	9	17	9	20
Coat Staining	0	0	8	17	0	20
Salivation	0	0	7	10	0	20
Irregular Respiration	1	0	0	0	0	0
Piloerection	0	0	0	11	0	0
Hunched Appearance	0	0	0	3	0	0
Females						
Number Examined	20	10	10	28	10	19
Coat Staining	1	1	9	23	0	15
Salivation	0	0	6	15	0	19
Irregular Respiration	0	0	0	10	0	0
Piloerection	0	0	0	1	0	0
Hunched Appearance	0	0	0	1	0	0

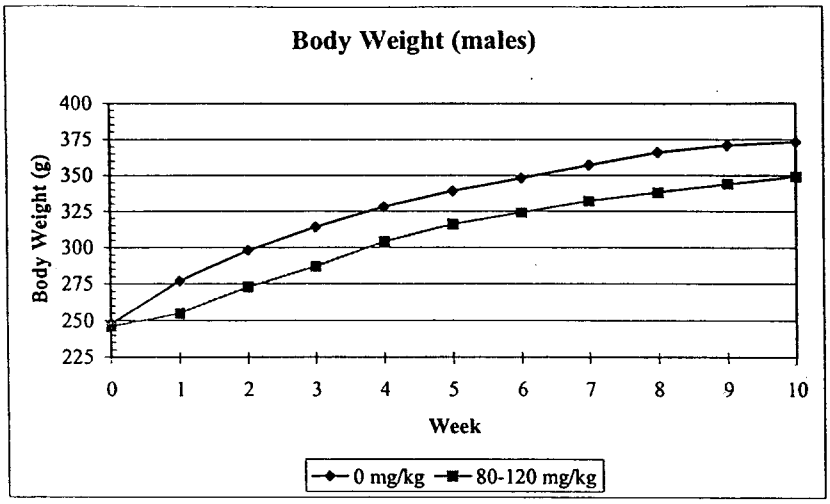
Piloerection was observed primarily at 120 mg/kg

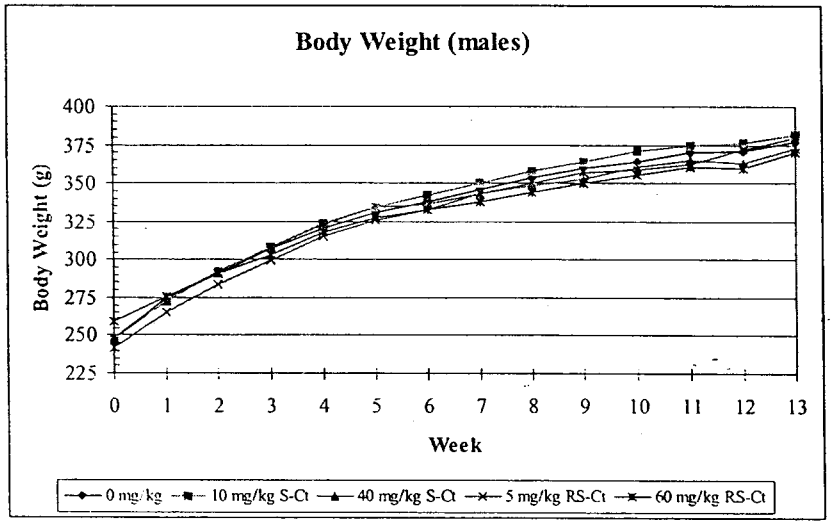
- Body weights

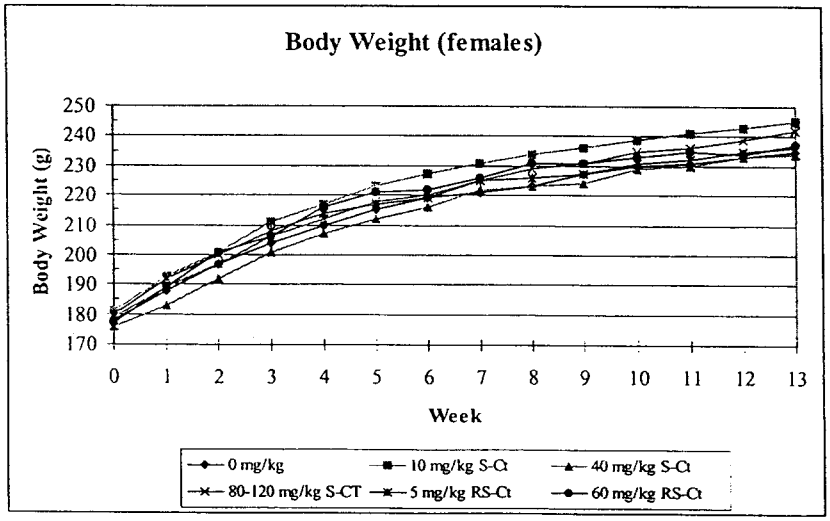
80-120 mg/kg males- Body weight 7% lower then controls, body weight gain decreased 18%; recovery during recovery period
60 mg/kg RS citalopram males- 14% decrease in body weight gain; body weight was only 2% lower due to difference in baseline bodyweights.
No effects at other dose levels or in females

- Food consumption

120 mg/kg males had 25% decrease in food consumption, food consumption returned to normal when dose lowered to 100 mg/kg; slight decrease at 120 mg/kg in females, returned to normal when dose lowered to 80 mg/kg, but no effects at other doses.


Body Weight (males)
Body Weight (g)
400
375
350
325
300
275
250
225
0 1 2 3 4 5 6 7 8 9 10
Week
0 mg/kg
80-120 mg/kg


Body Weight (males)
Body Weight (g)
400
375
350
325
300
275
250
225
0 1 2 3 4 5 6 7 8 9 10 11 12 13
Week
0 mg/kg
10 mg/kg S-Ct
40 mg/kg S-Ct
5 mg/kg RS-Ct
60 mg/kg RS-Ct


Body Weight (females)
Body Weight (g)
250
240
230
220
210
200
190
180
170
0 1 2 3 4 5 6 7 8 9 10 11 12 13
Week
0 mg/kg
10 mg/kg S-Ct
40 mg/kg S-Ct
80-120 mg/kg S-CT
5 mg/kg RS-Ct
60 mg/kg RS-Ct

- Ophthalmoscopy No effects
- Electrocardiography Not done
- Hematology

80 mg/kg males- decreased APTT time (27%), the sponsor states that the difference was exaggerated by an unusually high value in the controls (33 sec vs 23-25) and an unusually low value in the treated animals (11 sec vs 19-21); the effect may be exaggerated, but there still appears to be some decrease in APTT time;

APTT Times

	0 mg/kg	S-Citalopram			RS-Citalopram	
		10 mg/kg	40 mg/kg	80 mg/kg	5 mg/kg	60 mg/kg
Males	26, 23	23	23	19	23	21
Females	35	26	29	21	27	22

White blood cell counts

	0 mg/kg	S-Citalopram			RS-Citalopram	
		10 mg/kg	40 mg/kg	80 mg/kg	5 mg/kg	60 mg/kg
Males	6.60, 7.02	7.02	7.60	6.63	7.84	7.82
Females	5.82	5.73	5.30	4.78	5.67	4.33

- Clinical chemistry

Males

	0 mg/kg	S-Citalopram			RS-Citalopram	
		10 mg/kg	40 mg/kg	80 mg/kg	5 mg/kg	60 mg/kg
Calcium	2.66, 2.87	2.91 (101%)	2.95 (103%)	**2.86 (108%)**	2.88 (100%)	2.91 (101%)
Phosphorous	1.42, 1.80	1.68 (93%)	1.88 (104%)	**1.75 (123%)**	1.64 (91%)	1.85 (103%)
Chloride	106, 106	106 (100%)	**104 (98%)**	**103 (97%)**	107 (101%)	107 (101%)
Total Protein	68, 71	71 (100%)	71 (100%)	68 (100%)	71 (97%)	71 (97%)
Glucose	9.64, 8.78	8.65 (99%)	9.59 (109%)	9.73 (101%)	**10.37 (118%)**	**9.79 (112%)**

Females

	0 mg/kg	S-Citalopram			RS-Citalopram	
		10 mg/kg	40 mg/kg	80 mg/kg	5 mg/kg	60 mg/kg
Calcium	2.75	2.87 (104%)	2.86 (104%)	2.90 (105%)	2.86 (104%)	2.89 (105%)
Phosphorous	2.30	1.69 (73%)	1.66 (72%)	2.11 (92%)	1.64 (71%)	1.68 (73%)
Chloride	104	105 (101%)	103 (99%)	**103 (99%)**	105 (101%)	**107 (103%)**
Total Protein	75	72 (96%)	**70 (93%)**	**70 (93%)**	73 (97%)	**69 (92%)**
Glucose	7.65	8.32 (109%)	7.48 (98%)	**9.15 (120%)**	8.32 (109%)	7.98 (104%)

- Urinalysis

80 mg/kg females- decreased urine pH

- Organ Weights

Males

	0 mg/kg	S-Citalopram			RS-Citalopram	
		10 mg/kg	40 mg/kg	80 mg/kg	5 mg/kg	60 mg/kg
Liver	11.54, 12.83	12.55 (98%)	**14.02 (109%)**	**14.10 (122%)**	13.17 (103%)	**14.39 (112%)**
Heart	1.22, 1.17	1.17 (100%)	1.15 (98%)	1.16 (95%)	1.18 (101%)	1.10 (94%)
Thyroid	0.0196, 0.0209	0.0279 (133%)	0.0268 (128%)	0.0207 (106%)	0.0259 (124%)	0.0251 (120%)
Kidney	2.25, 2.17	2.20 (101%)	2.17 (100%)	2.32 (103%)	2.20 (101%)	**2.35 (108%)**

Females

	0 mg/kg	S-Citalopram			RS-Citalopram	
		10 mg/kg	40 mg/kg	80 mg/kg	5 mg/kg	60 mg/kg
Liver	7.36	7.70 (105%)	**8.62 (117%)**	**9.31 (126%)**	7.74 (105%)	**8.64 (117%)**
Heart	0.84	0.84 (100%)	0.83 (99%)	**1.00 (119%)**	0.84 (100%)	0.80 (95%)
Thyroid	0.0316	**0.0225 (71%)**	**0.0226 (72%)**	**0.0226 (72%)**	**0.0210 (66%)**	**0.0191 (60%)**
Kidney	1.57	1.52 (97%)	1.55 (99%)	1.62 (103%)	1.57 (100%)	**1.71 (109%)**

- Gross pathology

No effects

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- Histopathology

		S-Citalopram			RS-Citalopram	
	0 mg/kg	10 mg/kg	40 mg/kg	80 mg/kg	5 mg/kg	60 mg/kg
Histological Findings, Males						
Epididymides, Vacuolated	0/10	0/10	6/9	9/10	0/10	10/10
Minimal	0/10	0/10	3/9	0/10	0/10	0/10
Mild	0/10	0/10	3/10	3/10	0/10	0/10
Moderate	0/10	0/10	0/10	6/10	0/10	10/10
Liver, Vacuolation, Centrilobular	1/10	1/10 (scattered)	0/10	0/10	0/10	2/10
Lung, Macrophage Accumulation*	0/10	0/10	1/9	3/10	0/9	8/10
Histological Findings, Females						
Progressive cardiomyopathy, myocardial hypertrophy, pappilary muscle ossification	0/10	0/10	0/10	1/18	0/10	0/10
Liver, Inflammatory Cell Infiltration	2/10	2/10	0/10	4/10	1/10	0/10
Lung, Macrophage Accumulation*	0/10	0/10	2/10	6/18	0/10	6/10

*Lung macrophage accumulation includes increased foamy alveolar macrophages, increased pigmented macrophages and increased macrophages.

80 mg/kg males- 3/6 rats had vacuolated epididymides after 5 week recovery, in addition. 4/7 rats had heart abnormalities including papillary muscle ossification (2/7), myocardial hypertrophy (3/7), and progressive cardiomyopathy (2/7). In addition, there was difficulty in obtaining peripheral blood samples which is suggestive of decreased peripheral blood circulation.

Toxicokinetics It was noted that it was difficult to obtain blood samples; The sponsor attributed the difficulties to drug-induced toxicity that caused decreased peripheral blood circulation and resulting difficulty in obtaining blood from the tail vein bleeding site (IND Amendment 004, Volume 1, Page 4 of cover letter)

Summary of TK parameters: Males for S-CT and R-CT Analytes

		Lu 26 - 054						Lu 10 - 171			
	Dose	10		40		120		5		60	
		S-CT	R-CT	S-CT	R-CT	S-CT	R-CT	S-CT	R-CT	S-CT	R-CT
Cmax(obs) (nmol/l)	D1	62.00	ND	903.33	23.50	1649.50	36.75	17.33	20.33	891.67	1062.00
	D41	165.50	ND	859.67	30.67	ND	ND	55.00	69.00	1053.00	2085.00
	D90	181.00	ND	1076.00	43.00	ND	ND	84.67	108.67	976.00	2259.33
Tmax(obs) (h)	D1	1.0	ND	1.0	1.0	3.0	3.0	1.0	1.0	1.5	1.5
	D41	1.0	ND	1.0	1.0	ND	ND	1.0	0.5	0.5	0.5
	D90	1.0	ND	0.5	0.5	ND	ND	0.5	0.5	0.5	6.0
AUC (0-t) (nmol.h/l)	D1	96.50	ND	3347.50	59.50	14180.71	372.81	24.79	53.46	9029.42	12126.75
	D41	435.00	ND	4906.29	114.17	ND	ND	233.25	296.08	10765.08	32338.00
	D90	643.33	ND	6551.54	146.50	ND	ND	335.83	466.38	13100.92	39162.88
AUC (0- ∞) (nmol.h/l)	D1	108.45	ND	3436.11	76.62	14796.32	417.83	34.59	75.81	9278.17	12484.33
	D41	448.36	ND	4928.47	144.16	ND	ND	251.21	312.50	11323.83	35808.67
	D90	660.37	ND	6603.62	174.83	ND	ND	353.13	483.71	16361.31	57072.39
T½el (h)	D1	0.78	ND	2.17	2.37	5.08	6.24	1.23	3.10	4.97	4.25 ±
	D41	1.74	ND	3.07	3.90	ND	ND	2.49	2.28	5.48	6.70
	D90	2.36	ND	3.44	3.93	ND	ND	2.18	2.40	10.20	13.53

1. ND = Not Determined
2. The 120 mg/kg dose group was reduced to 100 mg/kg on day 12 (males) and to 80 mg/kg on day 41 (males and females).

Summary of TK parameters: Females for S-CT and R-CT Analytes

		Lu 26 - 054						Lu 10 - 171			
	Dose	10		40		120		5		60	
		S-CT	R-CT	S-CT	R-CT	S-CT	R-CT	S-CT	R-CT	S-CT	R-CT
Cmax(obs) (nmol/l)	D1	194.67	ND	1392.33	50.00	2658.00	105.00	57.33	76.00	1166.67	2026.67
	D41	345.33	14.17	1609.33	69.00	ND	ND	88.33	140.33	1294.33	2678.67
	D90	774.67	30.33	1382.67	71.00	2066.00	120.00	119.00	180.33	1511.50	3558.50
Tmax(obs) (h)	D1	0.5	ND	1.0	1.0	1.5	1.5	1.0	1.0	1.5	1.5
	D41	1.0	1.0	1.0	1.0	ND	ND	1.0	1.0	3.0	3.0
	D90	1.0	1.0	1.5	1.5	0.5	3.0	0.5	0.5	1.5	1.5
AUC (0-t) (nmol.h/l)	D1	407.00	ND	5010.17	157.25	18418.17	765.54	95.75	131.67	9278.42	28009.63
	D41	943.79	17.63	8599.79	436.50	ND	ND	364.46	668.21	12026.00	41145.92
	D90	1198.58	39.46	9165.25	589.00	19609.00	1514.63	442.08	811.42	11713.33	44647.50
AUC (0- ∞) (nmol.h/l)	D1	436.43	ND	5032.68	173.78	21392.70	833.79	109.60	151.35	9672.91	20774.74
	D41	960.13	22.66	8627.81	491.66	ND	ND	379.90	683.13	13113.69	50696.40
	D90	1212.61	46.16	9184.72	630.42	19939.20	1540.09	455.62	827.78	12344.77	55163.05
T½el (h)	D1	1.49	ND	3.12	1.64	9.20	6.10	0.87	0.89	5.66	4.71
	D41	1.48	0.70	2.77	3.28	ND	ND	1.95	2.07	6.59	9.66
	D90	1.94	0.84	2.70	5.74	4.09	3.53	1.88	2.13	5.58	9.79

1. ND = Not Determined
2. The 120 mg/kg dose group was reduced to 100 mg/kg on day 12 (males) and to 80 mg/kg on day 41 (males and females).

Summary of TK parameters: Males for S-DCT and R-DCT Analytes

		Lu 26 - 054						Lu 10 - 171			
	Dose	10		40		120		5		60	
		S-DCT	R-DCT	S-DCT	R-DCT	S-DCT	R-DCT	S-DCT	R-DCT	S-DCT	R-DCT
Cmax(obs) (nmol/l)	D1	91.67	ND	1007.33	44.67	1575.00	65.00	26.33	51.67	697.00	1323.67
	D41	227.50	10.00	1218.67	46.83	ND	ND	44.33	90.33	1091.00	2269.00
	D90	305.33	16.25	1382.50	60.50	ND	ND	75.00	153.33	1193.67	2652.67
Tmax(obs) (h)	D1	1.0	ND	1.5	1.5	3.0	3.0	1.0	1.0	6.0	6.0
	D41	1.0	1.0	1.0	1.0	ND	ND	0.5	1.0	6.0	6.0
	D90	0.5	3.0	3.0	3.0	ND	ND	0.5	1.5	6.0	0.5
AUC (0-t) (nmol.h/l)	D1	154.92	ND	6417.67	239.42	24197.92	897.92	34.54	133.33	10184.33	20468.67
	D41	721.29	12.08	13578.08	576.75	ND	ND	238.13	645.79	20248.08	44896.67
	D90	1094.29	31.35	17843.04	791.37	ND	ND	470.37	1021.83	23618.08	53889.58
AUC (0- ∞) (nmol.h/l)	D1	174.42	ND	6441.23	265.33	28169.27	934.79	48.25	155.39	11325.03	23419.01
	D41	739.77	ND	13707.44	626.91	ND	ND	262.56	751.80	30241.64	71899.95
	D90	1121.53	ND	18268.36	885.04	ND	ND	535.69	1079.54	74230.03	172617.7
T½el (h)	D1	0.80	ND	2.97	3.27	9.16	4.65	1.21	1.99	7.04	7.55
	D41	2.33	ND	3.13	6.32	ND	ND	3.08	13.36	14.40	16.21
	D90	2.36	ND	4.25	7.21	ND	ND	7.76	6.86	42.89	43.34

1. ND = Not Determined
2. The 120 mg/kg dose group was reduced to 100 mg/kg on day 12 (males) and to 80 mg/kg on day 41 (males and females).

Summary of TK parameters: Females for S-DCT and R-DCT Analytes

		Lu 26 - 054						Lu 10 - 171			
	Dose	10		40		120		5		60	
		S-DCT	R-DCT	S-DCT	R-DCT	S-DCT	R-DCT	S-DCT	R-DCT	S-DCT	R-DCT
Cmax(obs) (nmol/l)	D1	95.33	ND	571.33	37.00	787.50	51.50	33.67	88.00	426.00	977.67
	D41	160.67	12.67	647.00	43.50	ND	ND	35.33	102.00	899.00	2001.00
	D90	302.00	16.50	734.00	46.00	1585.00	88.50	53.67	118.33	1003.00	2728.50
Tmax(obs) (h)	D1	0.5	ND	1.5	1.5	1.5	9.0	0.5	1.0	3.0	12.0
	D41	1.0	0.5	6.0	6.0	ND	ND	3.0	3.0	6.0	0.5
	D90	1.0	1.5	6.0	6.0	6.0	12.0	1.5	1.5	1.5	1.5
AUC (0-t) (nmol.h/l)	D1	230.17	ND	3282.50	223.08	11314.21	732.38	59.13	237.83	6923.42	17794.83
	D41	564.04	16.00	9265.25	652.17	ND	ND	237.54	719.62	16111.00	42479.08
	D90	738.54	32.71	10231.75	677.88	28667.88	1589.38	331.63	1113.79	17283.17	46681.92
AUC (0- ∞) (nmol.h/l)	D1	270.81	ND	3309.53	252.19	13077.48	849.06	65.27	263.45	7862.26	21948.01
	D41	623.47	22.59	9463.81	691.64	ND	ND	262.17	771.27	24699.32	92367.89
	D90	764.27	ND	10483.00	716.12	34482.23	ND	355.68	1197.42	27764.11	112609.0
T½el (h)	D1	1.97	ND	3.41	3.67	7.15	6.88	0.77	1.69	7.07	8.85
	D41	3.05	0.83	3.75	4.97	ND	ND	3.10	2.59	15.28	25.85
	D90	2.43	ND	3.90	4.82	8.50	ND	2.86	6.96	16.84	30.31

1. ND = Not Determined
2. The 120 mg/kg dose group was reduced to 100 mg/kg on day 12 (males) and to 80 mg/kg on day 41 (males and females).

Summary of TK parameters: Males for S-DDCT and R-DDCT Analytes

		Lu 26 - 054						Lu 10 - 171			
	Dose	10		40		120		5		60	
		S-DDCT	R-DDCT	S-DDCT	R-DDCT	S-DDCT	R-DDCT	S-DDCT	R-DDCT	S-DDCT	R-DDCT
Cmax(obs) (nmol/l)	D1	51.00	ND	240.33	30.00	365.50	53.50	11.83	60.00	147.67	619.67
	D41	39.50	ND	234.00	29.67	ND	ND	15.17	72.00	253.00	1412.00
	D90	47.50	16.75	315.50	36.00	ND	ND	16.00	92.00	297.50	1829.00
Tmax(obs) (h)	D1	1.5	ND	3.0	3.0	12.0	12.0	1.0	1.0	6.0	12.0
	D41	1.0	ND	12.0	12.0	ND	ND	1.0	6.0	1.5	1.5
	D90	1.5	3.0	12.0	12.0	ND	ND	6.0	6.0	1.0	1.0
AUC (0-t) (nmol.h/l)	D1	176.25	ND	3196.17	401.00	6918.96	833.75	19.21	336.08	2501.58	12331.83
	D41	307.13	ND	3850.42	500.04	ND	ND	83.75	890.75	4752.92	29310.25
	D90	366.75	212.60	5122.88	577.87	ND	ND	112.42	1040.71	5606.79	33827.17
AUC (0- ∞) (nmol.h/l)	D1	204.08	ND	3219.51	464.15	ND	2012.28	39.56	357.97	4607.23	ND
	D41	325.65	ND	ND	546.58	ND	ND	173.24	930.65	31772.95	192014.1
	D90	395.49	356.74	ND	ND	ND	ND	ND	1080.68	ND	ND
T½el (h)	D1	3.51	ND	2.94	7.96	ND	25.80	2.29	2.76	19.99	ND
	D41	2.33	ND	ND	5.86	ND	ND	11.28	5.03	99.45	100.01
	D90	2.60	18.17	ND	ND	ND	ND	ND	4.75	ND	ND

1. ND = Not Determined
2. The 120 mg/kg dose group was reduced to 100 mg/kg on day 12 (males) and to 80 mg/kg on day 41 (males and females).

Summary of TK parameters: Females for S-DDCT and R-DDCT Analytes

		Lu 26 - 054						Lu 10 - 171			
	Dose	10		40		120		5		60	
		S-DDCT	R-DDCT	S-DDCT	R-DDCT	S-DDCT	R-DDCT	S-DDCT	R-DDCT	S-DDCT	R-DDCT
Cmax(obs) (nmol/l)	D1	28.33	ND	97.50	17.33	147.33	30.33	8.33	55.33	61.33	453.67
	D41	23.00	ND	141.67	29.67	ND	ND	ND	59.00	187.00	1202.33
	D90	37.67	14.83	149.00	28.67	394.50	66.50	10.50	74.33	192.50	1303.00
Tmax(obs) (h)	D1	1.5	ND	6.0	3.0	12.0	12.0	0.5	1.5	12.0	12.0
	D41	3.0	ND	12.0	12.0	ND	ND	ND	6.0	0.0	3.0
	D90	1.0	1.5	9.0	9.0	9.0	9.0	6.0	6.0	1.5	3.0
AUC (0-t) (nmol.h/l)	D1	102.50	ND	1216.00	140.58	2596.04	404.50	9.54	299.83	1189.96	8271.21
	D41	184.04	ND	2439.42	511.75	ND	ND	ND	784.79	3314.58	24385.75
	D90	314.71	12.50	2510.08	479.13	8534.88	1416.75	64.92	947.12	3586.08	23593.25
AUC (0- ∞) (nmol.h/l)	D1	220.34	ND	1248.66	206.82	ND	933.25	22.78	325.01	ND	ND
	D41	395.26	ND	ND	693.78	ND	ND	ND	822.29	8524.44	85245.07
	D90	386.19	ND	3602.75	596.81	23692.64	6345.17	ND	1018.12	9973.52	84618.57
T½el (h)	D1	5.51	ND	4.12	6.26	ND	21.56	1.67	3.17	ND	ND
	D41	10.71	ND	ND	12.41	ND	ND	ND	4.73	32.05	47.38
	D90	9.01	ND	11.90	8.74	35.55	61.00	ND	5.65	36.00	50.54

1. ND = Not Determined
2. The 120 mg/kg dose group was reduced to 100 mg/kg on day 12 (males) and to 80 mg/kg on day 41 (males and females).

Key Study Findings:

1. Increased mortality in males at 80-120 mg/kg and in females at 120 mg/kg only. Pathological examination of decedents suggested cardiac failure contributed to death.

2. 1/18 females at 80-120 mg/kg had progressive cardiomyopathy, myocardial hypertrophy, and papilary muscle ossification; no substantial heart abnormalities in males. Decreased peripheral blood circulation was observed, as indicated by difficulty in obtaining peripheral blood samples for TK analysis.
3. Irregular respiration observed in females, but not males, at 120 mg/kg.
4. Decreased body weight gain in males at 80-120 mg/kg.
5. Decreased hemoglobin and APTT values in 80-120 mg/kg treated animals.
6. Vacuolated epididymides starting at 40 mg/kg
7. Macrophage accumulation in lungs starting at 40 mg/kg in both sexes

60-Day Oral Toxicity Study with Citalopram in the Rat

Study No: 6F/854
Amendment #, Vol #, and page #: Vol 18 / Page 5-01718
Conducting laboratory and location: ———
Date of study initiation: 1996
GLP compliance: No
QA- Report Yes () No ()
Methods:
Dosing:

- species/strain: Rat, Wistar
- #/sex/group or time point: 10 Γ/dose
- age:5 weeks
- weight: 178-186 g
- satellite groups used for toxicokinetics or recovery: 5 animals for TK
- dosage groups in administered units:

Drug	Dose	Main Study Group	TK Study Group
Control	0 mg/kg	1	---
RS-Citalopram	7.5 mg/kg	2	9
RS-Citalopram	15 mg/kg	3	10
RS-Citalopram	30 mg/kg	4	11
RS-Citalopram	60 mg/kg	5	12
R-Citalopram	30 mg/kg	6	13
S-Citalopram	30 mg/kg	7	14

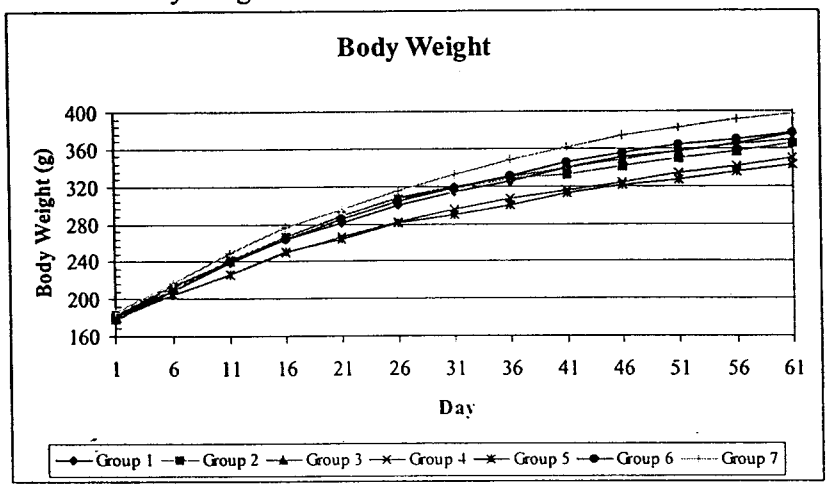
- route, form, volume, and infusion rate: Oral gavage

Drug, lot#, radiolabel, and % purity: ———
Formulation/vehicle: saline
Observations and times:

- Clinical signs: 2X/day
- Body weights: 1X/day
- Food consumption: Not done
- Ophthalmoscopy: Not done
- EKG: Not done
- Hematology: Not done
- Clinical chemistry: Not done
- Urinalysis: Not done
- Organ weights:
- Gross pathology: liver, testes and epididymides only
- Organs weighed:
- Histopathology: liver, testes and epididymides only
- Toxicokinetics: Day 17 (S-citalopram), Day 45 (RS-citalopram), 0.5, 1, 1.5, 3, 6, 9, 12, 24 hours
- Other:

Results:

- Clinical signs: salivation, tail rigidity, sedation (no data)
- Body weights



- Food consumption not done
- Ophthalmoscopy not done
- Electrocardiography not done
- Hematology not done
- Clinical chemistry

Serum serotonin levels

Drug	Dose (mg/kg)	5-HT Concentration ± SD (ng/ml)	Percent of Control
Control	0	1,391 ± 359	---
RS-Citalopram	7.5	416 ± 136	30%
RS-Citalopram	15	190 ± 39	14%
RS-Citalopram	30	96 ± 29	7%
RS-Citalopram	60	37 ± 9	3%
R-Citalopram	30	412 ± 134	30%
S-Citalopram	30	214 ± 111	15%

- Urinalysis not done
- Organ Weights no effects
- Gross pathology
- Histopathology- one rat at 60 mg/kg RS-citalopram had degenerative changes in the seminiferous epithelium with decreased spermatogenesis.

Drug	Dose (mg/kg)	Epididymides vacuolation	Mean severity (0-6)
Control	0	0/10	0
RS-Citalopram	7.5	5/10	1.6
RS-Citalopram	15	6/10	2.2
RS-Citalopram	30	10/10	4.2
RS-Citalopram	60	10/10	4.8
R-Citalopram	30	10/10	3.0
S-Citalopram	30	10/10	1.7

- Toxicokinetics:

Group No.	Mean AUC[1] (Range)			Mean C_{max}[2] (Range)		
	CT	DCT	DDCT	CT	DCT	DDCT
9	421 (328-501)	618 (469-756)	444 (298-674)	106 (83-129)	84 (62-104)	47 (29-71)
10	1763 (1215-2157)	1780 (1309-2183)	1095 (869-1360)	322 (255-363)	201 (151-262)	83 (67-100)
11	5467 (4089-6684)	6822 (5460-7879)	3602 (3218-4222)	755 (682-925)	509 (451-555)	216 (168-255)
12	14138 (12402-15027)	25857 (22446-30609)	10081 (8573-11977)	1650 (1371-1854)	1413 (1191-1661)	575 (503-625)
13	6503 (2619-8337)	7281 (4498-11857)	5697 (5460-9566)	737 (476-947)	515 (351-636)	288 (271-325)
14	899 (752-1284)	2154 (1788-2728)	579 (398-882)	224 (199-312)	358 (256-418)	47 (43-75)

[1] AUC expressed as ng•h/ml
[2] C_{max} expressed as ng/ml

CT = Citalopram
DCT = Demethylcitalopram
DDCT = Didemethylcitalopram

Key Study Findings:

1. S-citalopram caused vacuolation of the epididymides at the only dose tested (30 mg/kg).
2. No effects were observed on testicular histology
3. S-citalopram decreased blood serotonin levels to 15% of control.

APPEARS THIS WAY
ON ORIGINAL