Table 4
The Effects of LY139603, Amitriptyline and Saline on P-R Interval of Lead II ECG in Anesthetized Dogs

Time (min)	Dose (mg/kg, i.v.)	Saline P-R Interval (msec ± S.E.)	LY139603 P-R Interval (msec ± S.E.)	Amitriptyline P-R Interval (msec ± S.E.)
0	Pre-drug	108 ± 4	90 ± 1	106 ± 3
10	2	108 ± 4	92 ± 2	105 ± 2
20	4	108 ± 4	97 ± 2	110 ± 5
30	6	108 ± 4	100 ± 2	112 ± 6
40	8	110 ± 4	103 ± 2[c]	120 ± 7
50	10	112 ± 5	106 ± 4[c]	120 ± 6
80		108 ± 4	99 ± 2[c]	114 ± 3
110		109 ± 4	98 ± 2	110 ± 4

LY139603 or amitriptyline was infused at 0.2 mg/kg min for 50 min. Doses given are cumulative. Saline was given at a volume rate equal to that administered to the drug groups (0.02 ml/kg min). Values for LY139603 and amitriptyline are the means (± S.E.) from 4 dogs. Significant differences in mean changes from pre-drug values compared to saline group (a) or between LY139603 group and amitriptyline group (b) were determined by Duncan's multiple range test ($P = 0.05$). Due to a relatively large variance (among the differences from pre-drug values) in the amitriptyline treated group, an analysis of variance was performed on the differences coded by rank. Significant ($P < 0.05$) differences between saline group and either the LY139603 group or amitriptyline group are indicated (c).

Table 5

The Effects of LY139603, Amitriptyline and Saline on Corrected Q-T Interval (QTc) of Lead II ECG in Anesthetized Dogs

Time (min)	Dose (mg/kg, i.v.)	Saline QTc (msec/ sec ± S.E.)	LY139603 QTc (msec/ sec ± S.E.)	Amitriptyline QTc (msec/ sec ± S.E.)
0	Pre-drug	361 ± 13	324 ± 25	363 ± 26
10	2	355 ± 17	355 ± 24	353 ± 4
20	4	358 ± 11	372 ± 30	356 ± 12
30	6	352 ± 14	387 ± 18[a]	346 ± 9[b]
40	8	345 ± 20	392 ± 15[a]	357 ± 9[b]
50	10	336 ± 11	396 ± 14[a]	358 ± 6[b]
80		319 ± 29	392 ± 17[a]	374 ± 21
110		327 ± 26	352 ± 20	371 ± 8

LY139603 or amitriptyline was infused at 0.2 mg/kg min for 50 min. Doses given are cumulative. Saline was given at a volume rate equal to that administered to the drug groups (0.02 ml/kg min). Values for LY139603 and amitriptyline are the means (± S.E.) from 4 dogs. Significant differences in mean changes from pre-drug values compared to saline group (a) or between LY139603 group and amitriptyline group (b) were determined by Duncan's multiple range test ($P = 0.05$).

Table 6

The Effects of LY139603, Amitriptyline and Saline on Stroke Work Index in Anesthetized Dogs

Time (min)	Dose (mg/kg, i.v.)	Saline Stroke Work Index (gm-m/beat/m^2 ± S.E.)	LY139603 Stroke Work Index (gm-m/beat/m^2 ± S.E.)	Amitriptyline Stroke Work Index (gm-m/beat/m^2 ± S.E.)
0	Pre-drug	55.8 ± 5.2	51.6 ± 3.6	54.0 ± 3.8
10	2	60.8 ± 9.3	47.1 ± 2.8	39.6 ± 4.0
20	4	59.8 ± 5.9	47.3 ± 5.0	28.7 ± 3.1[ab]
30	6	63.3 ± 7.3	45.3 ± 3.9	27.8 ± 1.7[ab]
40	8	68.5 ± 10.7	47.8 ± 4.6	25.2 ± 1.2[ab]
50	10	67.6 ± 8.6	48.9 ± 4.3	24.8 ± 1.3[ab]
80		62.5 ± 8.1	46.4 ± 6.6	28.6 ± 0.9[ab]
110		64.4 ± 12.8	54.3 ± 6.0	29.6 ± 1.8[ab]

LY139603 or amitriptyline was infused at 0.2 mg/kg min for 50 min. Doses given are cumulative. Saline was given at a volume rate equal to that administered to the drug groups (0.02 ml/kg min). Values for LY139603 and amitriptyline are the means (± S.E.) from 4 dogs. Significant differences in mean changes from pre-drug values compared to saline group (a) or between LY139603 group and amitriptyline group (b) were determined by Duncan's multiple range test (P = 0.05).

Study title: THE EFFECTS OF TOMOXETINE (LY139603) ON HEART RATE AND BLOOD PRESSURE IN THE CONSCIOUS MONGREL DOG

Key study findings:

- No effects on electrocardiographic parameters, heart rate, and blood pressure in conscious mongrel dogs at oral doses of 4-16 mg/kg.

Study no:
Volume # 29, and page #: (not paginated)
Conducting laboratory and location: Department LG796, Lilly Research Laboratories, Division of Eli Lilly and Company, Greenfield, IN 46140
Date of study initiation: March 26, 1984
GLP compliance: yes (x) no ( )
QA report: yes (x) no ()
Drug Tomoxetine HCl (LY139603), **lot #** 866-83f-248, **radiolabel** not applicable, **and % purity:** 98.3%
Formulation/Vehicle: LY139603 in gelatin capsules

Dosing:

Species/strain: Mongrel dog
#/sex: 4/sex
Satellite groups used for toxicokinetics or recovery: Not applicable
Age: Adult
Weight: 18.1-23.3 kg males and 16.6-19.3 kg females
Doses in administered units: 0 (empty capsules), 2, 4, 6, 8, 10 mg/kg
Route, form, volume, and infusion rate: Oral, once daily

Methods: The dogs were housed in individual pens in a room maintained at 20±3°C and 45% humidity with a 12-hour light-dark cycle, and were fed 600 g/d standard canine diet with water provided *ad libitum*. The dogs were surgically implanted (femoral artery) with indwelling electrodes connected to a telemetry system for recording of electrocardiograms, and intra-arterial cannulas connected to a pressure transducer for measurement of blood pressure.

The dogs were dosed as follows:

Treatment Schedule for LY139603

Animal Number	Treatment Date				
	3/26/84	3/27/84	3/28/84	3/29/84	3/30/84
18330 18281	0 mg/kg	0 mg/kg	16 mg/kg	4 mg/kg	8 mg/kg
19334 18277	0 mg/kg	4 mg/kg	0 mg/kg	8 mg/kg	16 mg/kg
18332 18283	0 mg/kg	8 mg/kg	4 mg/kg	16 mg/kg	0 mg/kg
18335	0 mg/kg	16 mg/kg	8 mg/kg	0 mg/kg	4 mg/kg

18280					

The following parameters were studied: survival (daily for 6 days), clinical signs of toxicity (daily for 6 days), body weights (pretreatment and Day 6), food consumption (daily for 6 days), electrocardiograms (every 30 minutes from 0-7.5 hours after dosing and every hour from 8-23 hours after dosing), heart rate (from number of QRS complexes within 10-second ECG samples), and arterial blood pressure (as for electrocardiograms).

Results: There were no deaths during the study, and no treatment-related effects on body weights and food consumption. One dog (18280) vomited at the high dose on day 2. There were no treatment-related effects on the electrocardiogram parameters, heart rate, and blood pressure.

Summary of individual study findings: LY139603 had no effects on electrocardiographic parameters, heart rate, and blood pressure in conscious mongrel dogs at oral doses of 4-16 mg/kg.

__Pulmonary effects__:

Study title: EFFECT OF ACUTE ORAL ADMINISTRATION OF TOMOXETINE HYDROCHLORIDE (LY139603) ON BREATHING FREQUENCY AND DEPTH IN FISCHER 344 RATS

Key study findings:
- Slight increase (9%-21%) in respiratory rate in LY139603-treated (10-100 mg/kg PO) rats compared to controls, not statistically significant and not dose-related
- No treatment-related effects on breathing depth

Study no: ———
Volume # 29, and page #: (not paginated)
Conducting laboratory and location: Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285
Date of study initiation: April 24, 2000
GLP compliance: yes (x) no ( )
QA report: yes (x) no ()
Drug Tomoxetine hydrochloride (LY139603), **lot #** 399SB7, **radiolabel** not applicable, **and % purity:** 98.5% (stable in solution for 8 days at room temperature or refrigerated at 5°C)
Formulation/Vehicle: LY139603 dissolved in purified water

__Dosing:__

Species/strain: Fischer 344 rats ———
#/sex/group: 10 males/dose group
Satellite groups used for toxicokinetics or recovery: Not applicable

Age: 11 weeks
Weight: 208-242 g
Doses in administered units: 0, 10, 50, and 100 mg/kg
Route, form, volume, and infusion rate: oral gavage at 10 ml/kg

Methods: The rats were individually housed in stainless steel cages in temperature- (72±8°F) and humidity-maintained (50%±30%) animal room, with 12 hour light/dark cycle, and food and water provided *ad libitum*. The rats were administered a single dose of LY139603 or vehicle. Pulmonary function evaluations were made for breathing frequency (for 1 minute at 60-70 minutes after dosing) and depth (at 5 minutes after the frequency observation), using a pressure transducer attached to plethysmograph.

Results: Breathing frequencies were 19%, 9%, and 21% higher than the control group frequency at 10, 50, and 100 mg/kg, respectively, although the differences did not reach statistical significance. There were no treatment-related effects on breathing depth.

Summary of individual study findings: LY139603 had no statistically significant effect on breathing frequency and depth at doses of 10-100 mg/kg PO in male rats.

<u>**Renal effects**</u>:

Study title: EFFECTS OF LY139603 ON RAT URINE AND ELECTROLYTE EXCRETIONS

Key study findings:
- Mild, dose-related diuresis (+68% and +152% at 10 and 50 mg/kg, respectively compared to controls) for 5 hours after dosing
- No changes in sodium, potassium and chloride concentrations
- Osmolality decreased at 10 (16%) and 50 (23%) mg/kg compared to control values
- Creatinine excretion increased and the concentration decreased at 50 mg/kg (43%)
- Total sodium, potassium, chloride, and total electrolyte excretion increased proportionally to the increase in urine volume
- Similar results reported after administration of imipramine and desipramine

Study no: [redacted]
Volume # 29, and page #: (not paginated)
Conducting laboratory and location: Department GL796, Lilly Research Laboratories, Division of Eli Lilly and Company, Greenfield, IN 46140
Date of study initiation: March 31, 1981
GLP compliance: yes (x) no ( )
QA report: yes (x) no ()
Drug LY139603, **lot #** 525-U332-072-D, **radiolabel** not applicable, **and % purity:** Not provided in this submission
Formulation/Vehicle: LY139603 dissolved in 0.9% saline

Dosing:

Species/strain: Sprague-Dawley rat
#/sex/group: 8 females/dose
Satellite groups used for toxicokinetics or recovery: Not applicable
Age: Not provided in this submission
Weight: 200 g
Doses in administered units: 0, 2, 10, and 50 mg/kg
Route, form, volume, and infusion rate: Oral, at 25 ml/kg

Methods: Housing conditions were not described in this submission. Fasted (overnight), 0.9% saline-hydrated (25 ml/kg PO) female rats were administered oral LY139603 in 0.9% saline hydrating medium and placed in metabolism cages. Urine was collected for 5 hours after dosing. The following measurements were made: urine volume (over 5 hours post-dose), sodium and potassium chloride (osmolality (freezing point depression using an Advanced Osmometer), and creatinine (alkaline picrate method). The study was performed in triplicate, and the data was pooled.

Results: The results of the measurements of urine volume, electrolyte concentrations, and electrolyte, osmolal and creatinine excretions are presented in the following table:

Results of the Study on LY139603 Effects on Rat Urine and Electrolyte Excretions (mean± S.E.)

Parameter	**0 mg/kg**	**2 mg/kg**	**10 mg/kg**	**50 mg/kg**
Urine Volume	5.0±0.6	5.6±0.4	8.4±0.5*** (+68%)	12.6±0.5*** (+152%)
Na Concentration(mcEq/ml)	118.3±9.7	146.5±10.5	122.5±5.4	112.8±3.2
K Concentration(mcEq/ml)	38.0±3.6	43.2±2.3	34.2±2.5	33.6±2.6
Cl Concentration(mcEq/ml)	129.8±11.2	147.7±12.0	121.9±5.1	107±2.6
Osmolality (mcOsm/g)	62.0±41	72.1±56	52.2±20* (-16%)	47.7±13*** (-23%)
Creatinine Concentration (mg/ml)	0.28±0.05	0.30±0.03	0.19±0.01 (_32%)	0.16±0.01* (-43%)
Total Sodium Excretion (mcEq)	619.3±95.4	812.4±70.7	1024±68.0*** (+65%)	1420.9±64.6*** (+129%)
Total Potassium Excretion (mcEq)	202.5±33.3	240.2±18.7	287.6±26.8 (+42%)	424.2±36.0*** (+109%)
Total Cloride Excretion (mcEq)	668.0±96.0	814.7±71.8	1018.0±64.6*** (+52%)	1355.5±61.8*** (+103%)
Osmolal Excretion	3172±456	4072±389	4351±242*	6010±276***

(mcOsmoles)			(+37%)	(+89%)
Total Creatinine Excretion (mg)	1.4±1.2	1.6±0.2	1.6±0.1 (+14%)	2.0±0.1** (+43%)

***0.05>p>0.02; **0.02>p>0.01; ***p<0.01**

Summary of individual study findings: LY139603 induced a mild, but dose-related diuresis (+68% and +152% at 10 and 50 mg/kg, respectively, compared to controls), without changes in the concentrations of sodium, potassium and chloride during the 5-hour period after dosing. Osmolality was decreased at 10 (16%) and 50 (23%) mg/kg compared to the control values. Creatinine excretion increased and the concentration decreased at 50 mg/kg (43%) compared to controls. Total sodium, potassium, chloride, and total electrolyte excretion were increased proportionally to the increase in urine volume. Similar results were reported by the sponsor after administration of the antidepressant drugs imipramine and desipramine.

Gastrointestinal effects:

Study title: THE ACUTE EFFECTS OF ORALLY ADMINISTERED TOMOXETINE HYDROCHLORIDE (LY139603) ON GASTROINTESTINAL MOTILITY IN MALE CD-1 MICE

Key study findings:
- No treatment-related effects on gastrointestinal motility in mice, measured by charcoal meal transit distance

Study no: [redacted]
Volume # 29, and page #: (not paginated)
Conducting laboratory and location: Eli Lilly and Company, 2001 West Main Street, Greenfield, IN 46140
Date of study initiation: November 9, 1999
GLP compliance: yes (x) no ( )
QA report: yes (x) no ()
Drug Tomoxetine hydrochloride (LY139603, Compound 404363 hydrochloride), **lot #** 399SB7, **radiolabel** not applicable, **and % purity:** 98.5% (Stable at room temperature [25°C] and refrigerated [5°C] for 8 days)
Formulation/Vehicle: LY139603 dissolved in purified water

Dosing:

Species/strain: CD-1 [Crl:CD-1®(ICR)] mice
#/sex/group or time point (main study): 10 males/dose
Satellite groups used for toxicokinetics or recovery: not applicable
Age: 6-7 weeks
Weight: 23.5-28.5 g
Doses in administered units: 0, 10, 30, and 100 mg/kg
Route, form, volume, and infusion rate: Oral at 0.01 mL/g body weight

Methods: The mice were housed in plastic cages at 10/cage in a temperature (22±4°C) controlled room, at 20%-80% humidity, with a 12 hour light-dark cycle. The mice were fasted (12 hours), and administered oral LY139603 followed by a charcoal meal (0.3 ml 10% charcoal powder) 60 minutes after dosing. The mice were sacrificed by cervical dislocation and the intestinal tracts were excised from the pyloric sphincter to the cecum, 20 minutes after the charcoal meal. The length of intestine and distance traveled by the charcoal meal were measured.

Summary of individual study findings: The results showed a 17% decrease in mean charcoal transit distance at the low dose (mean distance 60.4% ± 3.6% compared to 73.0% ± 2.2% in the control mice). This observation is probably unrelated to treatment because no effects were observed at the mid- and high doses. The results of this study suggest a low potential for tomoxetine-induced diarrhea or constipation.

Immune System:

Study title: TESTS OF COMPOUND LY139603 FOR EFFECTS ON THE IMMUNE RESPONSE OF MICE

Key study findings:
- No treatment-related effect on immune response in mice, measured by sheep red blood cell antigen-induced serum hemagglutinin, at oral daily doses of 1.6-25 mg/kg for 10 days

Study no: —
Volume # 29, and page #: (not paginated)
Conducting laboratory and location: Department GL796, Immunology and Connective Tissue Research (MC905), Lilly Research Laboratories, Division of Eli Lilly and Company, Indianapolis, IN 46206
Date of study initiation: August 11, 1980
GLP compliance: yes (x) no ( )
QA report: yes (x) no ( )
Drug LY139603, **lot #** 525-U332-072D, **radiolabel** not applicable, **and % purity:** Not provided in this submission
Formulation/Vehicle: LY139603 dissolved in 0.85% saline

Dosing:

Species/strain: Cox (Swiss) mice (—
#/sex/group: 10 males/dose
Satellite groups used for toxicokinetics or recovery: Not applicable
Age: Not provided in this submission
Weight: 19-21 g
Doses in administered units: 0, 1.6, 3.1, 6.2, 12.5, 25 mg/kg
Route, form, volume, and infusion rate: Oral gavage at 0.2 ml

Methods: The mice were housed in stainless steel cages (10/cage) in a temperature (72±2°F), humidity (50±10%), and ventillation (12-15 air changes/hour) controlled animal room with a 12-hour light-dark cycle. Food (standard rodent chow) and water were provided *ad libitum*. The mice were administered LY139603 once daily for 10 days beginning 3 days before a single antigen injection with sheep red blood cells. One day after the last LY139603 dose (7 days after the antigen injection), the mice were bled by cardiac puncture and serra assayed for antibody content (hemagglutinin).

Results: The results of the hemagglutinin measurements, with comparative values for known immunosuppressive drugs, are presented in the following table:

Results of the Study on LY139603 Effects on Immune Response in Mice

Treatment	Dose (mg/kg x 10)	Survivors/10-mouse Group	Log_2 Hemagglutinin (mean ± S.E.)
LY139603	25.1	10	8.00 ± 0.26
	12.5	10	8.70 ± 0.33*
	6.2	10	7.90 ± 0.38
	3.1	10	8.10 ± 0.35
	1.6	10	7.60 ± 0.22
	0 (control)	10	7.80 ± 0.25
Cyclophosphamide	25	6	0.17 ± 0.17**
	0 (control)	10	6.30 ± 0.26
Frentizole	25	10	3.30 ± 0.70**
	0 (control)	10	6.80 ± 0.29
Methotrexate	3.1	4	0.50 ± 0.50**
	0 (control)	10	7.10 ± 0.35

*p<0.05; **p<0.001

Summary of individual study findings: No depression of immune response was observed as a result of LY139603 administration at oral daily doses of 1.6-25 mg/kg for 10 days in male mice, under the conditions of this study. A slight, but statistically significant increase in serum hemagglutinin concentration at the next to highest dose, is deemed to be inconsequential.

<u>**Safety pharmacology summary**</u>:

The primary pharmacodynamic studies demonstrated that atomoxetine HCl (LY139603) is a selective norepinephrine reuptake inhibitor. Potential adverse effects associated with norepinephrine reuptake inhibition and subsequent indirect enhancement of dopaminergic activity, observed in other drugs in this therapeutic class, can include agitation, seizures, sedation, hypotention, anticholinergic effects, weight gain, sexual effects and cardiac effects. A core battery of GLP Safety Pharmacology studies on vital functions were performed, including studies on the effects of LY139603 on central nervous system (CNS), cardiovascular system (CV) and respiratory system (RS) parameters.

Central Nervous System:

LY139603 CNS effects were studied in male albino mice, and included evaluation of motor activity, behavioral changes, coordination, sensory/motor reflex responses and body temperature as recommended in the ICH Guidance for Industry S7A (Safety Pharmacology Studies for Human Pharmaceuticals). The sponsor evaluated LY139603 effects on pentylenetetrazol-induced convulsions and electroconvulsive shock, acetic acid induced writhing, sleeping time, and weight gain. The effects of LY139603 on locomotor activity, a measure of psychomotor stimulation, were compared with those of methylphenidate and d-amphetamine in male CF-I®BR mice. Acute behavioral effects of LY139603 were studied in male and female Fischer 344 rats. Additionally, neurological examinations were performed in a 4-Week oral capsule toxicity and toxicokinetic study in young beagle dogs.

The results of the study on neurological effects of oral LY139603 in male mice administered doses of 25-400 mg/kg PO showed deaths associated with clonic convulsions in 2/3 animals at the 400 mg/kg dose (18X the MRHD of 1.8 mg/kg on a BSA basis). The treatment-related effects of LY139603 on motor activity, behavior, and sensory motor reflex were decreased motor activity, irritability, leg weakness, jerky gait, exophthalmos, and piloerection, observed at doses of 50 mg/kg and above, tremors (particularly when walking), grasping loss, pinna reflex, mydriasis, and lacrimation at doses of 100 mg/kg and above, and increased respiration, vibrissal response, analgesia, placing loss, decreased abdominal tone, corneal loss, and righting loss at 200 or 400 mg/kg. Reduced weight gain was observed at all doses from 6.25-59 mg/kg, and decreased apomorphine-induced hypothermia was observed at 3.125-12.5 mg/kg. Although there were no effects on pentylenetetrazole-induced tonic extensor convulsions, LY139603 increased the ECS50 and decreased the tonic extensor convulsions induced by electroconvulsive shock at 50 mg/kg. LY139603 attenuated writhing in response to acetic acid injection at 25 mg/kg but not at 50 mg/kg PO, suggesting analgesia at the low dose, probably without pharmacological relevance. A dose-related increase in hexobarbital sleeping time was observed from 6.26-50 mg/kg LY139603. Decreased weight and rectal temperature, and antagonism of hypothermia by apomorphine are expected effects of norepinephrine uptake inhibition.

The effects of LY139603 on locomotor activity, a measure of psychomotor stimulation, were compared with those of methylphenidate and d-amphetamine in male CF-I®BR mice LY139603 had no effects on locomotion at doses of 0.1-30 mg/kg PO (up to 1.35X the MRHD of 1.8 mg/kg on a BSA basis). In comparison, methylphenidate (10-56 mg/kg PO) and d-amphetamine (1-10 mg/kg PO) induced a dose-related increase in locomotor activity, suggesting a potential for producing psychomotor stimulation in clinical use.

Acute behavioral effects of LY139603 were studied in male and female Fischer 344 rats The rats were administered oral doses of 0, 10, 50 and 100 mg/kg in purified water (1X-9X the MRHD of 1.8 mg/kg on a BSA basis, n=8/sex/dose), and spontaneous activity, rectal body temperature, auditory startle habituation (measure of sensorimotor reactivity), and passive avoidance (measure of learning and memory) were measured. An additional dose group received 1 mg/kg for the passive avoidance test. The results showed decreased body temperature in the female rats given doses of 50 (-0.9°C to –1.5°C compared to control) and 100 (-0.3°C to –1.5°C compared to control) mg/kg, at 30-360 minutes after dosing. Body temperature was 1.0°C lower than the control value in the female rats given 10 mg/kg at the 120-minute timepoint only. Lethargy was observed in 1-3 male rats at 50 mg/kg at 30-120 minutes, and in 3-4 rats at 100 mg/kg at 60-360 minutes after dosing. There were no effects of LY139603 on ambulatory activity levels, auditory startle responding, and passive avoidance (latency to enter shock compartment).

In another study on behavioral effects of LY139603 male and female Fischer 344 rats were administered oral doses of 100-300 mg/kg (9X-27X the MRHD of 1.8 mg/kg on a BSA basis, n=10/sex/dose) or vehicle control (purified water). The rats were observed for clinical signs of central nervous system effects and changes in body temperature (autonomic function). There was one death in a female given 300 mg/kg LY139603, 24 hours after dosing. The death was preceded by repetitive myoclonic jerking. There was a treatment-related increase in incidence of decreased activity and lethargy at doses of 200 mg/kg (18X the MRHD of 1.8 mg/kg on a BSA basis) and higher in the male and female rats. Myoclonic jerking was observed at doses of 225 mg/kg and higher in the males and at 275 mg/kg and higher in the females. Additionally, the males showed treatment-related soiling and distended penis at the highest doses. Body temperature was decreased approximately 1°C in the male rats at 300 mg/kg, 30 minutes after dosing, and 1.2-2.6°C in the female rats at 175-300 mg/kg, at varying timepoints from 30 minutes to 24 hours after dosing.

Neurological examinations were performed in a 4-Week oral capsule toxicity and toxicokinetic study in young beagle dogs (Toxicology Report 44, Vol. 45). Male and female dogs of approximately 8-9 weeks of age, were administered LY139603 at doses of 4, 8, and 16 mg/kg PO (0.8X-2.6X the MRHD in poor metabolizers and 2.4X-7.6X the MRHD in extensive metabolizers on an AUC basis) in gelatin capsules, or empty capsules (negative control), once daily for 4 weeks (n=4/sex/group). The dogs were evaluated for gait (paraplegia, paresis, hemiparesis, hypermetria, hypometria, ataxia, wide-based gait), head posture (tilt, bobbing, tremors, dysphagia, dysphonia, tongue atrophy, dropped lip, jaw, ear, and eyelid, prolapsed nictitating membrane, strabismus, nystagmus), coordination, cranial nerve reflexes, pupillary light reflex, mydriasis, oculocephalogyric reflex, palpebral reflex, pain perception, gag reflex, and neck, forelimb and hindlimb evaluations (including placing, triceps reflex, flexor reflex, patellar reflex, spinal reflexes, flexor reflex), before initiation of treatment and during Week 4. Additional evaluations of pupillary light reflex and mydriasis were conducted at 1.5 and 24 hours after dosing during Weeks 1, 2, and 4. The pupillary light reflex (left and right) was decreased in 1 high-dose male dog and in a dose-related manner (1-4 animals) in the female dogs (Weeks 1, 2, 4). The results showed a dose-related increase in incidence of mydriasis in the male and female dogs at pre-dose, and at 1.5 hours and 24 hours after dosing during Weeks 1, 2, and 4. There were no other treatment-related effects in the neurological examination.

Compound 30,761 was evaluated as a potential cocaine treatment medication in male Sprague-Dawley rats — and male rhesus monkeys (Study — trained to discriminate cocaine. The test article increased cocaine-like responding rates in the rats at doses of 5-50 mg/kg IP, with maximal effect at 50 mg/kg IP, although seizures were observed in 2 of the 6 animals at that dose. Compound 30,761 showed variable cocaine discriminative stimulus effects among the monkeys, without producing behavioral effects or seizures at doses up to 10 mg/kg IM.

Cardiovascular System:

In isolated canine purkinje fibers, the racemic mixture (Compound 93627) decreased the maximum rate of rise of the action potential (Vmax), but was 1/3 less potent than amitriptyline in this effect. The racemic mixture also decreased the resting membrane potential and action potential duration at 95% full repolarization, to a lesser extent than did amitriptyline. To determine if there is a difference in potency by the isomers of 93627, the (-) and (+) isomers LY139603 and 139602, respectively, were tested. LY139603 was 2X more potent in decreasing the Vmax, and decreased amplitude, membrane resting potential, and APD_{95} to a similar extent compared to the (+) isomer. Therefore, although the racemic mixture showed a smaller effect on Vmax compared to amitriptyline, suggesting a lower potential to alter conduction velocity than the approved drug, the (-) isomer LY139603 is responsible for most of the effect observed.

The HERG ion channel blocking profile of LY139603 was studied in human embryonic kidney 293 cells transfected with the HERG clone, using the whole-cell variant of the patch clamp method. HERG blockade was significantly increased (10%-94%) at all LY139603 concentrations tested, from 10 nM-10mcM LY139603, in a dose dependent manner. The IC50 for blockade of HERG by LY139603 at 0.1 HZ was 0.869mcM. Evaluation of rate-dependence showed no effect of pacing rate at 1 - 3 Hz. The mean % HERG block also increased 19%-98% in a dose dependent manner by the metabolites N-desmethyltomoxetine (0.88-88 mcM), and 10%-100% by 4-hydroxytomoxetine (0.88-264 mcM). The IC50 values for blockade of HERG by Compounds 137876 and 424478 were 5.71 and 20.0 mcM, respectively, at 0.1 HZ. There was no effect of pacing rate on HERG blockade by the metabolites. The expected maximum unbound plasma concentration at the highest clinical dose (1.8 mg/kg/d) is 0.016-0.082 mcM in extensive metabolizers and 0.108-0.219 mcM in poor metabolizers. The results of this study indicate a risk of HERG blockade, and increased potential for QT prolongation, at clinically relevant doses. At these concentrations, the predicted HERG blockade is 21% in extensive and 31% in poor metabolizers. Although the concentrations tested spanned a broad range producing a concentration-response curve, and exceeded the anticipated maximal therapeutic plasma concentration, appropriate positive control articles were not used. However, the positive, dose-related effects observed in this study validate the responsiveness of the test system, confirming the presence of the I_{Kr} channels. A comparison of HERG blockade by LY139603 and the metabolites in this study with the unbound plasma concentrations of LY139603 in poor metabolizers and extensive metabolizers, the plasma concentration in the 4-week toxicology study in juvenile dogs, and the concentration tested in the study in canine Purkinje fibers is presented in the following graph.

The estimated plasma concentrations of LY139603 and the metabolites N-desmethyltomoxetine and 4-hydroxytomoxetine, corresponding to the concentrations producing HERG blockade in the *in vitro* study are presented in the following table:

Table 1: Total and Unbound Plasma Concentration Data for LY139603 and Its Two Metabolites, Compound 137876 and Compound 424478, Corresponding to 20%, 30%, and 40% HERG Blockade In Vitro; Studies LLY_10, LLY_11, and LLY_12

	LY139603; Tomoxetine (Mol. Wt. = 255.36 g/mole) Protein Binding = 98.7 ± 0.3%			137876; N-Desmethyltomoxetine (Mol. Wt. = 241.33 g/mole) Protein Binding = 99.2 ± 0.3%			424478; 4-Hydroxytomoxetine (Mol. Wt. = 271.36 g/mole) Protein Binding = 65.5 ± 2.9%		
	Unbound Plasma C_{max} (µM)	Unbound Plasma C_{max} (ng/mL)	Total Plasma C_{max} (ng/mL)	Unbound Plasma C_{max} (µM)	Unbound Plasma C_{max} (ng/mL)	Total Plasma C_{max} (ng/mL)	Unbound Plasma C_{max} (µM)	Unbound Plasma C_{max} (ng/mL)	Total Plasma C_{max} (ng/mL)
Highest human exposures*									
HERG Blockade									
20%	0.067	17.12	1317	1.009	243.4	30423	3.659	993	2878
30%	0.194	49.58	3814	2.011	485.2	60653	7.255	1968	5706
40%	0.438	111.9	8608	3.494	843.2	105,395	12.468	3383	9807

Based upon human plasma protein binding data and the HERG blockade results provided in this study, the above table can be used for guidance in evaluating total tomoxetine, N-desmethyltomoxetine, and 4-hydroxytomoxetine plasma concentrations in human subjects.
*For reference, the highest predicted human tomoxetine concentrations at the maximum dose of 0.9 mg/kg BID (1.8 mg/kg/day) in Phase III studies, and the highest observed metabolite concentrations in Study B4Z-LC-LYAE are provided.

LY139603 had no effects on electrocardiographic parameters, heart rate, and blood pressure in conscious mongrel dogs at single oral doses of 4-16 mg/kg (1X-5X the MRHD of 1.8 mg/kg on a BSA basis).

In anesthetized beagle dogs, single intravenous doses of LY139603 increased heart rate (28%-38% at 4-10 mg/kg) but had no effect on blood pressure. LY139603 increased the respiration rate (43%-76% at 4-10 mg/kg IV), P-R interval (14%-18% at 8-10 mg/kg IV and 30 post-infusion), and the corrected Q-T interval (corrected for heart rate increases, QT_C = QT/square root of R-R interval, 19%-22% at 6-10 mg/kg IV), slightly increased PCO_2 (at 2 mg/kg and 30 minutes after infusion), and decreased arterial blood pH (<1%-1%) at 2-6 mg/kg IV in the non-pretreated (atropine and propranolol) dogs. In the pretreated dogs, LY139603 increased the PCO_2 (4%-7% at 4-10 mg/kg IV and 11%-13% post-infusion), and increased the corrected Q-T interval (7-32% at all doses from 2-10 mg/kg IV).

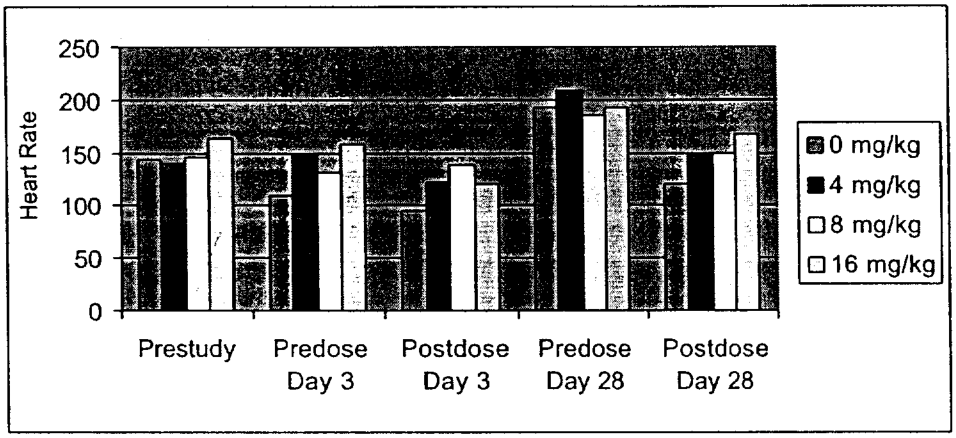
In comparison, the approved antidepressant drug amitriptyline increased heart rate to a much greater extent than did LY139603 (62%-116% at 2-10mg/kg IV, without pretreatment with atropine and propranolol) in the anesthetized dogs. Amitriptyline increased the respiration rate (37%-76% at 2-10 mg/kg IV and post-infusion without pretreatment and 14%-23% at 8-10 mg/kg IV and 30 in post-infusion with pretreatment), decreased the Stroke Work Index (45%-54% at 4-10 mg/kg IV and post-infusion without pretreatment and 16%-24% at 4 mg/kg IV and 60 minutes post-infusion with pretreatment), decreased Pulmonary Capillary Wedge Pressure (11%-56% at 4-10 mg/kg IV, and post-infusion without pretreatment and 29%-71% at 2-10 mg/kg IV and post-infusion with pretreatment), increased Minute Volume (7%-27% at all doses and post-infusion without pretreatment), decreased arterial blood pH (1% at 2-8 mg/kg IV without pretreatment), increased the P-R interval (up to 13% at 8-10 mg/kg IV without pretreatment and 36% at 10 mg/kg with pretreatment), increased the QRS duration (8%-16% at 4-10 mg/kg IV and post-infusion with dose relationship without pretreatment and 14%-72% at all doses and post-infusion with dose relationship with pretreatment), decreased the Q-T interval (8%-11% at 6-10 mg/kg IV, without pretreatment), and increased the Q-T interval (8%-24% at all doses and post-infusion with pretreatment).

At comparable doses, amitriptyline had considerably more extensive effects on the cardiovascular parameters than did LY139603 in anesthetized dogs. Amitriptyline decreased blood pressure 6%-8% and peripheral vascular resistance 11%-23%, while LY139603 slightly increased blood pressure and increased peripheral vascular resistance 0.4%-18% (significant difference at 30 minutes post-dose only) in the absence of pretreatment. Amitriptyline increased heart rate and minute volume (nonpretreated dogs), and decreased stroke work index and pulmonary capillary wedge pressure to a greater extent than did LY139603. On the other hand, LY139603 induced a similar increase in respiration rate and greater increase in minute volume (pretreated dogs) than did amitriptyline. In the ECG evaluation, there was a significant increase in the P-R interval by LY139603 but not by amitriptyline in the absence of pretreatment, and increased P-R interval by amitriptyline only in the pretreated animals. The QRS duration was increased by amitriptyline only in non-pretreated and pretreated dogs. The Q-T interval was increased by LY139603 and decreased by amitriptyline without pretreatment, and moderately increased by both drugs, to similar extent with pretreatment.

These results of the study on cardiovascular effects of LY139603 in anesthetized dogs were predicted by the results of the *in vitro* studies conducted in canine cardiac purkinje fibers and human embryonic kidney cells transfected with the HERG clone to express I_{Kr} channels. In the purkinje fibers, LY139603 decreased the maximum rate of rise of the action potential and increased the action potential duration, although with less potency than amitriptyline, indicating a potential to alter conduction velocity. LY139603, and the metabolites N-desmethyltomoxetine and 4-hydroxytomoxetine increased HERG block at clinically relevant concentrations, suggesting increased potential for QT prolongation, particularly in poor metabolizers. Although LY139603 was less potent than amitriptyline in actions on cardiovascular function, the results of these studies indicate a need for appropriate monitoring of cardiovascular effects in clinical use.

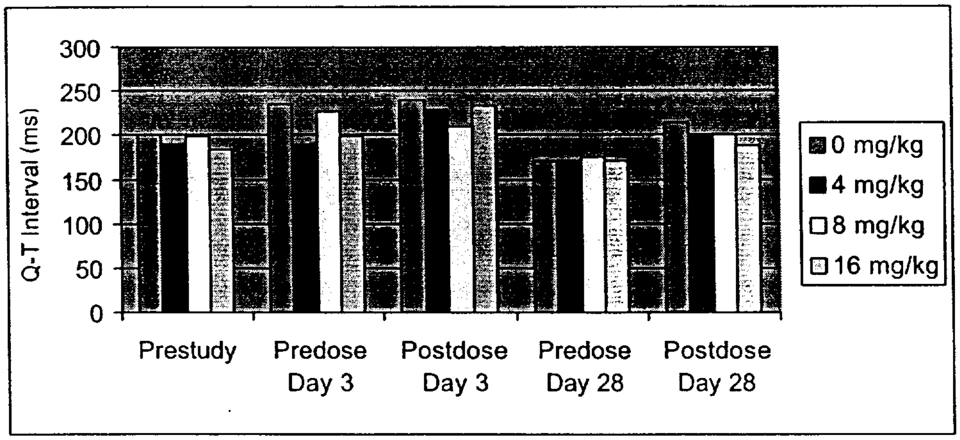
Electrocardiographic measurements were conducted in a 4-Week oral capsule toxicity and toxicokinetic study in young beagle dogs (Toxicology Report 44, Vol. 45). Male and female dogs of approximately 8-9 weeks of age and weighing 1.7-3.8 kg, were administered LY139603 at doses of 4, 8, and 16 mg/kg PO (0.8X-2.6X the MRHD in poor metabolizers and 2.4X-7.6X the MRHD in extensive metabolizers on an AUC basis) in gelatin capsules, or empty capsules (negative control), once daily for 4 weeks (n=4/sex/group). The dogs were evaluated before initiation of treatment, and 1 hour after dosing on Days 3 and 28. The results showed a slight increase in heart rate in the high-dose male dogs at the pre-dose measurement on Day 3 (mean of 150 beats/minute) and post-dose on Day 28 (mean of 162 beats/minute) compared to the controls at the same timepoints (means 104 and 118 beats/minute, respectively). However, heart rate in the high-dose males was unchanged from the pre-study value (mean of 166 beats/minute) and was within the range observed throughout the study (means 120-192 beats/minute) in this group. The results of the heart rate measurements in the male dogs are presented in the following figure:

Heart Rate (beats/minute) in Male Dogs



The QTC interval was also slightly increased by LY139603 in the female dogs on Day 3 pre-dose (mean of 0.265 seconds compared to 0.249 seconds in the controls) and Day 28 post-dose (mean of 0.252 seconds compared to 0.232 seconds in the controls), although the changes from baseline value of 0.255 seconds (+4% and -2% on Day 3 pre-dose and Day 28 post-dose respectively) were similar to the changes from baseline observed in the control dogs at these timepoints (+2% and -5%, respectively). The R-R interval was decreased in the male dogs post dose on Day 28 (mean of 373 ms) compared to the controls at the same timepoint (mean of 519 ms) and showed a reduction in mean change from pre-study baseline (+2%) compared to the mean change in the controls (+27%), but was within the ranges in the control male dogs (266-731 ms) and the high-dose male dogs (283-576 ms) observed throughout the study. The Q-T interval was slightly decreased in the high dose males post-dose on Day 28 (mean of 188 ms, range 180-195) compared to the controls at the same timepoint (mean of 214 ms, range 200-250), but was within the ranges in the control male dogs (160-260 ms) and the high-dose male dogs (170-234 ms) observed throughout the study. The results of the Q-T interval measurements are presented in the following figure:

Q-T Interval in Male Dogs



An increased incidence of 2nd degree atrioventricular block was observed in the post-dose recordings, with greatest increase in the control dogs. The incidence per 24 post-dose recordings were 8, 5, 6, and 2 at 0, 4, 8, and 16 mg/kg/day, respectively. Overall, there were no effects on the electrocardiographic measurements in young (8-13 weeks of age) beagle dogs that are considered to be attributed with certainly to LY139603 administered daily at doses of 4-16 mg/kg/day PO (0.8X-2.6X the MRHD in poor metabolizers and 2.4X-7.6X the MRHD in extensive metabolizers on an AUC basis) for 4 weeks, under the conditions of this study. Historical data are not available for beagle dogs in the age group tested.

Respiratory System: Pulmonary function was studied in Fischer 344 rats, using a pressure transducer attached to a plethysmograph. The LY139603-treated rats showed a slight increase in respiratory rate compared to the control rats, but there were no statistically significant effects on breathing frequency and depth at doses of 10-100 mg/kg PO (.9X-9X the MRHD of 1.8 mg/kg on a BSA basis).

Supplemental Safety Pharmacology Studies:

Renal/Urinary System:

The effects of LY139603 on renal parameters were assessed in Sprague-Dawley rats administered oral doses of 2-50 mg/kg (.2X-4.5X the MRHD of 1.8 mg/kg on a BSA basis). LY139603 induced a mild, but dose-related diuresis (+68% and +152% at 10 and 50 mg/kg, respectively, compared to controls), without changes in the concentrations of sodium, potassium and chloride during the 5-hour period after dosing. Osmolality was decreased at 10 (16%) and 50 (23%) mg/kg compared to the control values. Creatinine excretion increased and the concentration decreased at 50 mg/kg (43%) compared to controls. Total sodium, potassium, chloride, and total electrolyte excretion were increased proportionally to the increase in urine volume. Similar results were reported by the sponsor after administration of the antidepressant drugs imipramine and desipramine.

Autonomic Nervous System:

The potential for interaction of LY139603 and the metabolites 424478 (p-hydroxy) and 137877 (N-desmethyl) with receptor-mediated autonomic nervous system activity was evaluated in a GLP radiolabeled receptor binding assay using rat brain tissues (Study . The results showed poor affinity by LY139603, 424478, and 137877 for muscarinic (Ki >100 mcM), and alpha1-adrenergic (Ki = 11.4, 20.0, and 19.6 mcM, respectively), alpha2-adrenergic (Ki = 29.8, >30, and >10 mcM, respectively), and beta-adrenergic receptors (Ki = 18, 56.1, and 32.1 mcM respectively). Additionally, the affinity for the neurotransmitter receptors for serotonin (5-HT$_2$), histamine (H$_1$), the GABA receptor-mediated ionophores GABA$_A$ and benzodiazepine, and dopamine (D$_1$ and D$_2$) were assessed in this study. The affinity constants for the parent drug LY139603 and the metabolites 424478 and 137877 demonstrated poor affinity for serotonin receptors (Ki = 2.0, 1.0, and 1.7 mcM, respectively), histaminergic receptors (Ki = 12.1, >100, and >100 mcM, respectively), GABA$_A$ receptors (Ki = 0.2, >30, and >10 mcM, respectively), and benzodiazepine receptors (Ki = >100 mcM). The affinity constants of LY139603 and the metabolites were >10 mcM for both dopamine (D$_1$ and D$_2$) receptor subtypes. These results suggest little potential for interaction with the sympathetic and parasympathetic control of peripheral organ function and provide additional confirmation of receptor selectivity of tomoxetine and its metabolites.

No effects were observed at LY139603 concentrations up to 1 mcM in isolated guinea pig smooth (ileum) and cardiac muscle tissue bath preparations (Furthermore, the results of this study showed no inhibition of acetylcholine-induced (ileum) and isoproterenol-induced (atria) contractions, and therefore interaction of the proposed drug substance with peripheral adrenergic and muscarinic receptor mediated effects is unlikely.

LY139603 was 16x less potent than desmethylimipramine (DMI) in anticholinergic activity in isolated guinea pig tracheal tissues The (+) enantiomer 139602 showed 6 times greater anticholinergic activity compared to LY139603 in that study, demonstrating that the (+) isomer is responsible for most of the anticholinergic activity of the racemate (135252).

Gastrointestinal System:

There was no agonist activity by LY139603 at concentrations up to 10^{-5}M in isolated guinea pig ileum and rabbit jejunum However, in that study LY139603 depressed the concentration-response curve to carbamylcholine and KCl in guinea pig ileum and inhibited spontaneously contracting rabbit jejunum at the highest concentration, probably by direct depression of the tissues.

In a GLP study on gastrointestinal motility in male CD-1 mice, there was a 17% decrease in mean charcoal transit distance at the low dose of 10 mg/kg PO (.5X the MRHD of 1.8 mg/kg on a BSA basis, mean distance 60.4% ± 3.6% compared to 73.0% ± 2.2% in the control mice), but not at 30 and 100 mg/kg (1.35X and 4.5X the MRHD of 1.8 mg/kg on a BSA basis). These results suggest little potential for LY139603-induced diarrhea or constipation.

Immune System:

No depression of immune response was observed as a result of LY139603 administration at daily oral doses of 1.6-25 mg/kg (.01X-1X the MRHD of 1.8 mg/kg on a BSA basis) for 10 days in male mice. A slight, but statistically significant increase in serum hemagglutinin concentration at the next to highest dose, was deemed to be inconsequential.

Safety pharmacology conclusions:

The potential undesirable pharmacodynamic effects of LY139603 with relevance to human safety are primarily observed in the central nervous and cardiovascular systems in the preclinical safety pharmacology studies. In rodents, the neurological effects of LY139603 at very high doses in mice were deaths associated with clonic convulsions (300 and 400 mg/kg dose, 13.5X and 18X the MRHD of 1.8 mg/kg on a BSA basis), myoclonic jerking, decreased body temperature, decreased motor activity, lethargy, irritability, leg weakness, jerky gait, exophthalmos, and piloerection, tremors (particularly when walking), grasping loss, pinna reflex, mydriasis, lacrimation, vibrissal response, analgesia, placing loss, decreased abdominal tone, corneal loss, and righting loss. LY139603 had no effects on locomotion at doses of 0.1-30 mg/kg PO, suggesting a low potential for producing psychomotor stimulation in clinical use. A dose-related increase in hexobarbital sleeping time was observed from 6.26-50 mg/kg LY139603. Decreased weight and rectal temperature, and antagonism of hypothermia by apomorphine are expected effects of norepinephrine uptake inhibition. In young beagle dogs administered 4-16 mg/kg PO LY139603 for 4 weeks (0.8X-2.6X the MRHD in poor metabolizers and 2.4X-7.6X the MRHD in extensive metabolizers on an AUC basis), pupillary light reflex was decreased, and the incidence of mydriasis increased with dose, but no other treatment-related effects were observed in the neurological examination. LY139603 increased cocaine-like responding rates at IP doses of 5-50 mg/kg, and produced seizures at 50 mg/kg IP in rats, but was without cocaine discriminative stimulus effects, behavioral effects or seizures at up to 10 mg/kg IM in monkeys.

Based on the known pharmacology of norepinephrine, the potential cardiovascular effects of norepinephrine reuptake inhibition may include increased cardiac stroke volume, arrhythmias and coronary blood flow, increased systolic, mean arterial, diastolic and mean pulmonary blood pressure, increased total peripheral resistance, and increased respiration. Appropriate *in vitro* and *in vivo* assessments were made to address the potential by LY139603 to induce repolarization and conductance abnormalities, and to evaluate effects on blood pressure, heart rate, and the electrocardiographic parameters. The Safety pharmacology studies on cardiovascular toxicity were conducted in isolated canine purkinje fibers, human embryonic kidney cells transfected with the HERG clone to express I_{Kr} channels, anesthetized beagle dogs, and conscious mongrel dogs.

Additionally, potential cardiovascular toxicity was evaluated in a 4-week oral capsule toxicity and toxicokinetic study in beagle dogs.

LY139603 decreased the maximum rate of rise of the action potential (Vmax) in isolated canine cardiac purkinje fibers at a concentration of 10^{-5} M, suggesting a potential for interference with cardiac conduction, although LY139603 was half as potent as the approved antidepressant drug amitriptyline in this effect. Blockade of the I_{Kr} (HERG) by LY139603 and the metabolites N-desmethyltomoxetine and 4-hydroxytomoxetine in transfected human embryonic kidney cells at clinically relevant concentrations also suggest a potential for QT prolongation and predisposition to the occurrence of ventricular arrhythmias, and signaled the need for further assessment in an *in vivo* model. In anesthetized dogs, intravenous LY139603 increased heart rate to a lesser extent and increased respiratory rate to a similar extent compared to intravenous amitriptyline. There was no effect by LY139603 on the QRS duration, but a negative dromotropic effect, with prolongation of the P-R interval, was observed after both intravenous LY139603 and intravenous amitriptyline. LY139603 increased the Q-T interval as much as 22%-32% at 10 mg/kg IV with and without pretreatment with atropine and propranolol, although the changes were not statistically significant. Oral LY139603 had no effects on heart rate, respiratory rate, and ECG parameters at single doses up to 16 mg/kg (5X the MRHD of 1.8 mg/kg on a BSA basis) in conscious dogs, and after daily oral administration at up to 16 mg/kg for 4 weeks in young beagle dogs. However, the results of *in vitro* and anesthetized dog studies indicate that careful ECG monitoring should be conducted in the clinical setting.

LY139603 had no effects on respiratory function at 10-100 mg/kg PO (.9X-9X the MRHD of 1.8 mg/kg on a BSA basis) in rats. The renal effects in rats were similar to those observed by the antidepressant drugs imipramine and desipramine, and included mild, dose-related diuresis and decreased osmolality, without changes in the concentrations of sodium, potassium and chloride at 10 and 50 mg/kg PO in the rats. Creatinine excretion was increased and concentration decreased at 50 mg/kg PO (4,5X the MRHD on a BSA basis). No agonist effects were observed in isolated guinea pig ileum and rabbit jejunum at concentrations up to 10^{-5}M, and there were no effects on gastrointestinal mobility in mice. Also, LY139603 had no effects on immune response, measured by alteration of hemagglutinin concentration in response to sheep red blood cell antigen injection, at oral daily doses of 1.6-25 mg/kg (.01X-1X the MRHD of 1.8 mg/kg on a BSA basis) for 10 days in male mice. Evaluation of receptor-binding showed poor affinity by LY139604 and the p-hydroxy and N-desmethyl metabolites for muscarinic, alpha1-adrenergic, alpha2-adrenergic, beta-adrenergic, serotonin (5-HT_2), histamine (H_1), $GABA_A$ and benzodiazepine receptors, and dopamine (D_1 and D_2) receptors, suggesting a low potential for interaction with the sympathetic and parasympathetic control of peripheral organ function. Further evaluation of the potential for autonomic nervous system toxicity showed no effects at concentrations up to 1 mcM in isolated guinea pig smooth (ileum) and cardiac muscle tissue bath preparations, and no inhibition of acetylcholine-induced (ileum) and isoproterenol-induced (atria) contractions.

III. PHARMCOKINETICS/TOXICOKINETICS:

PK parameters: some of the toxicity studies that are reviewed later included toxicokinetic studies (see details in these reviews, 3-month rat toxicity study, rabbit teratology study). Most of the following information was obtained from the sponsor's summary of the pharmacokinetic section.

The following summary table was provided by the sponsor for pharmacokinetic parameters after <u>a single dose</u> of treatment in mouse, adult rat, and adult dog.

Table 1: Mean Pharmacokinetic Parameters After Oral and Intravenous Administration of Atomoxetine

Pharmacokinetic Parameter	Mouse	Rat	Dog	Human CYP2D6 EM	Human CYP2D6 PM
N	3	3	4	20	8
Sex	M	M	F	M/F	M/F
Oral Administration					
Dose (mg/kg)	25	50	2	0.54[a]	0.50[a]
C_{max} (ng/mL)	173	165	729	326	564
T_{max} (hr)	0.167	2.0	1.3	1.0	6.0
$AUC_{0-\infty}$ (ng•hr/mL)	171	906	4,300	1,800	14,470
$T_{1/2}$ (hr)	0.62	2.8	3.7	3.7	20
Bioavailability (% of Dose)	5	4	74	63	94
Intravenous Administration					
Dose (mg/kg)	5	5	2	0.27[a]	0.25[a]
C_0 (ng/mL)[b]	937	2,890	2,176	663	555
$AUC_{0-\infty}$ (ng•hr/mL)	764	2,291	5,671	1,370	7,570
$T_{1/2}$ (hr)	1.2	1.4	3.4	3.6	21
CL (mL/min/kg)	8.9	36	7.4	3.7	0.57
Vd (L/kg)	109	4.3	1.4	1.1	1.0
Report Number	ADME Report 11	ADME Report 6	ADME Report 32	B4Z-LC-LYAM	B4Z-LC-LYAK

Abbreviations: CYP2D6 EM = subject with CYP2D6 extensive metabolizer genotype; CYP2D6 PM = subject with CYP2D6 poor metabolizer genotype; N = number of animals/timepoint for the rat and mouse, total number of animals or subjects for the dog and human, respectively; M = males, F = females; C_{max} and C_0 = maximal observed plasma concentration; T_{max} = time to reach maximal plasma concentration; $AUC_{0-\infty}$ = total systemic exposure (area under the plasma concentration-time curve from 0 to infinity); $T_{1/2}$ = defined as the $\beta T_{1/2}$ or elimination half-life; CL = systemic clearance; Vd = volume of distribution.

[a] The mg/kg dose was based upon the mean weight of 81.3 kg (Clinical Pharmacology Study B4Z-LC-LYAK) and 74.6 kg (Clinical Pharmacology Study B4Z-LC-LYAM) and a total dose of 20-mg (intravenous administration) and 40-mg (oral administration) of atomoxetine (base weight).

[b] After intravenous administration, the values reported for C_0 were extrapolated to zero, except for human data which was administered as a 20-minute infusion.

In Rhesus monkeys (study 6180-443, ADME rpt 66), following a single oral or intravenous dose of [^{14}C]atomoxetine, there were no differences between sexes. The oral bioavailability of atomoxetine was ~45% (moderate first pass effect) while the oral bioavailability of the [^{14}C]equivalents was ~75%. The AUC value for atomoxetine represented ~ 10% of the AUC for total radioactivity. The N-desmethyl metabolite was the major metabolite and the exposure to this metabolite was even higher than that of atomoxetine. The AUC value for this metabolite represented ~13% of the AUC of the total radioactivity and a very low fraction of the radioactivity was due to the 4-hydroxymetabolite. This indicates that other metabolites comprise the majority of the radioactivity observed in the plasma. Tmax was 2 h for atomoxetine and 3 for the metabolites. The elimination half-life was 1.3 h for atomoxetine and 45.9 for the [^{14}C]equivalents. The main elimination route is in the urine.

In single dose studies in young rats (PND 11) higher levels of the drug were reported in comparison to mature rats (PND 69). Cmax was 11-fold higher while AUC values were 6-fold higher in young animals compared to mature animals. The clearance of atomoxetine was much lower in younger rats compared to matured ones (CL/F [ml/min/kg] was 95 at PND 11 and 551 at PND 69).

Opposite findings were reported for dogs, with young dogs (8 weeks old) having lower plasma levels compared to adult animals (2.5-4 years). Cmax was 2.3-fold higher and AUC values were 4.4-fold higher in adult animals in comparison to young animals.

In repeated treatment studies in mice the exposure to atomoxetine was not linear with respect to dose and differences between sexes were observed. In mice treated with the drug in diet for three months plasma levels of the N-desmethyl metabolite were higher than the hydroxy-metabolite. Repeated treatment in rats (study R03498, ADME rpt 21) indicated a decline in plasma levels with treatment. Later studies (ADME rpt 43) indicated that there was no decrease in levels with continued treatment but instead remained relatively constant or increased slightly (at higher doses, see tox rpt 46). No differences were observed between sexes.

In dogs there was no drug accumulation with time and the increase in plasma levels was dose dependent. There were no differences between sexes.

In repeat dose studies in young rats, similar findings to those observed with single dose studies were reported.

In repeat dose studies in dogs higher exposures were observed with repeated treatment. The sponsor stated that an increase in oral bioavailability is seen by 12 weeks of age.

Absorption: it appears to be well absorbed from the gastrointestinal tract in rats since following oral administration of radiolabeled atomoxetine, 89% of the dose was recovered with 58% in urine, 30% in feces (which appears to be from bile), and 0.9% in caracass. In another study in rats the total recovery of radioactivity was even higher (97%). However, low oral bioavailability was reported in mice (4.5%) and rat (5%) mostly due to first pass hepatic and/or intestinal metabolism. Oral bioavailability in dogs was 75% and in monkeys 45% (moderate first pass effect).

Distribution: in rats following a single oral dose, peak tissue concentrations were observed one hour after dosing in all tissues except the prostate (3h), the liver (0.25 h), and the stomach wall (0.25 h). Milk excretion and placental transfer of radioactivity associated with atomoxetine treatment was seen in pregnant Fischer 344 rats.

Metabolism: atomoxetine is extensively metabolized. The following table summarizes the metabolites of atomoxetine in plasma of animals and humans. The most abundant phase I metabolite of atomoxetine was 4-hydroxyatomoxetine in mouse, rat, dog, and humans extensive metabolizers followed by the N-desmethylatomoxetine metabolite. The N-desmethylatomoxetine metabolite was the major phase I metabolite in New Zealand white rabbits, rhesus monkeys, and human poor metabolizers followed by the N-hydroxy metabolite. Two metabolites that were detected in humans but not in mouse, rat or dog were hydroxy-carboxyatomoxetine-O-glucuronide and 2,4-dihydroxyatomoxetine.

Table 17: Metabolites of Atomoxetine Identified by — In Plasma from the B6C3F$_1$ Mouse, Fischer 344 Rat, Adult Beagle Dog, and CYP2D6 EM and PM Human Following Oral Administration of ^{14}C-Atomoxetine

Proposed Metabolite Identification	ID Number	B6C3F$_1$ Mouse	Fischer 344 Rat	Beagle Dog	Human[a] CYP2D6 PM	Human[a] CYP2D6 EM
Dose (mg/kg)		25	50	2		
4-Hydroxy-*N*-desmethylatomoxetine (*LY440035*)	M-1	ND	Detected	ND		
4-Hydroxyatomoxetine (*LY424478*)	M-2	Detected	Detected	Detected		
2-Hydroxymethylatomoxetine	M-3	Detected	ND	ND		
***N*-Desmethylatomoxetine (*LY137877*)**	M-4	ND	ND	Detected		
4-Hydroxy-*N*-desmethyatomoxetine-*O*-glucuronide (*LY440035-O-glucuronide*)	M-5	ND	Detected	Detected		
4-Hydroxyatomoxetine-*O*-glucuronide (*LY424478-O-glucuronide*)	**M-6**	**Major**	**Major**	**Major**		
4-Hydroxy-2-carboxyatomoxetine-*O*-glucuronide (*LY492181-O-glucuronide*)	M-7	ND	Detected	ND		
Dihydroxyatomoxetine-*O*-glucuronide	M-8	ND	Detected	ND		
2-Carboxyatomoxetine (*LY466247*)	M-9	ND	Detected	Detected		
2-Hydroxymethylatomoxetine-*O*-glucuronide (*LY415973-O-glucuronide*)	M-11	ND	Detected	ND		
Hydroxy-carboxyatomoxetine-*O*-glucuronide	M-17	ND	ND	ND		
2,4-Dihydroxyatomoxetine (*LY504727*)	M-20	ND	ND	ND		
Atomoxetine (*LY404363*)	P	Detected	Detected	Detected		
Report Number		ADME Report 25	ADME Report 53	ADME Report 54	B4Z-LC-HFBH	B4Z-LC-HFBH

Abbreviations: CYP2D6 EM = subject with CYP2D6 extensive metabolizer genotype; CYP2D6 PM = subject with CYP2D6 poor metabolizer genotype; Detected = metabolite detected; ND = metabolite not detected; Major = primary metabolite detected.

[a] The mg/kg dose was based upon the mean weight of 72.8 kg and total dose of 19.66 mg of atomoxetine (base weight). In study B4Z-LC-HFBH, following 5 days of 20-mg atomoxetine doses BID, a single 19.66 mg of ^{14}C-atomoxetine was administered.

Based on the structures of its identified metabolites, three phase I metabolic pathways predominate the biotransformation of atomoxetine in vivo: aromatic ring hydroxylation, benzylic/aliphatic hydroxylation, and N-demethylation. In human liver microsomes, aromatic hydoxylation was substantially reduced in microsomes partially deficient of cytochrome CYP2D6 and completely absent in microsomes totally deficient of CYP2D6. Therefore, it appears that CYP2D6 plays a central role in aromatic hydoxylation of atomoxetine. Subsequent glucuronidation of the hydroxylated metabolites was the only phase II metabolic pathway to result in the conjugation of these metabolites in mouse, rat, and human. In dog, O-glucurodination and O-sulfation of the hydroxylated metabolites were observed. According to the sponsor, no metabolites were observed that indicated the formation of reactive intermediates or electrophilic species. See the following figure for the proposed metabolic pathway.

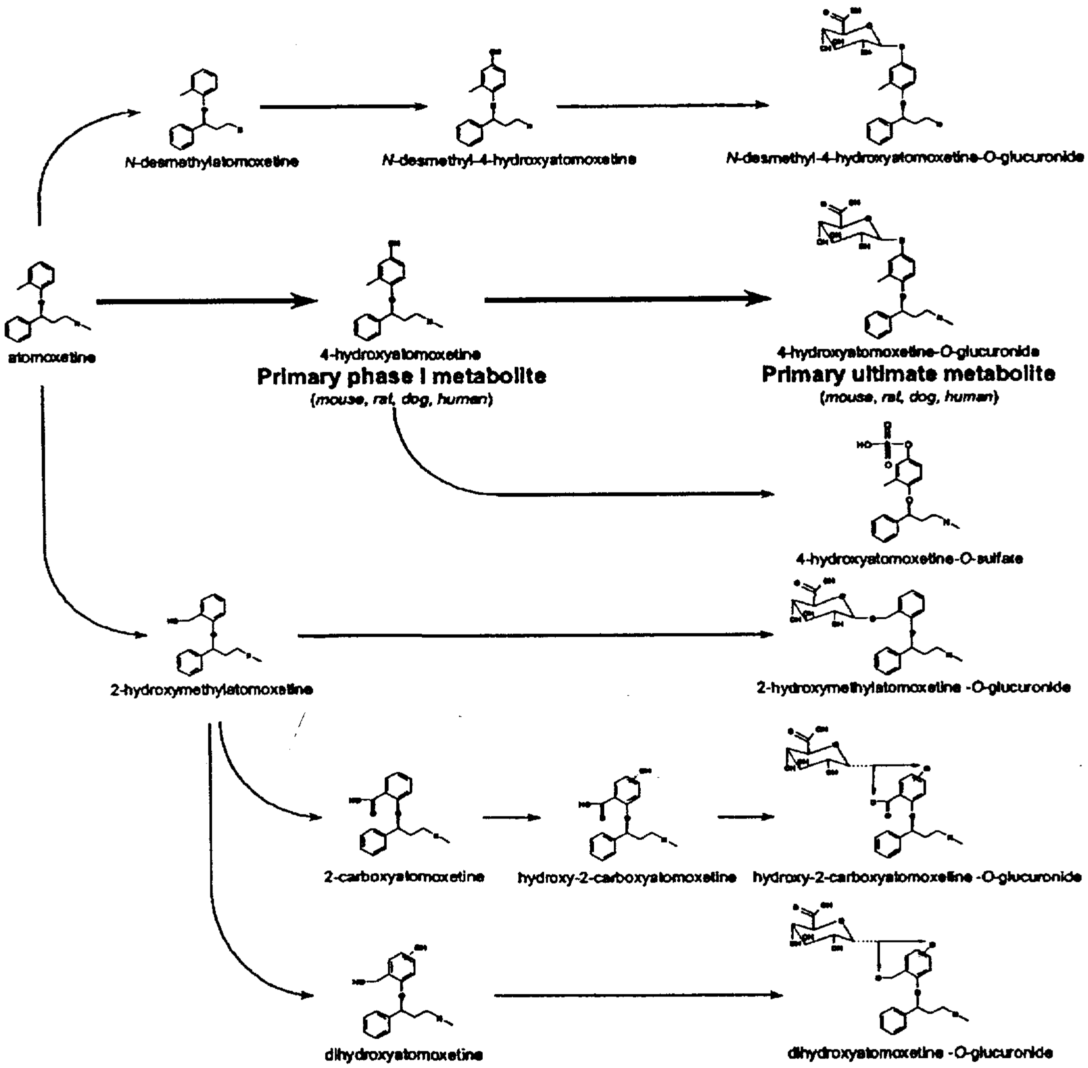


Figure 5: **Proposed biotransformation of atomoxetine in vivo.**

Excretion: the primary rout of elimination for all species tested (mice, rats, dogs, and monkeys) was via the urine (ranging from 50-80% of dose). Some radioactivity was seen in the feces (ranging from 6-42% of dose) after [^{14}C]atomoxetine treatment, which appeared to be due to biliary elimination of radiolabeled metabolites (as seen in bile cannulated rats, study 076R98, ADME rpt 28). The majority of the dose was eliminated within the first 24 h after treatment.

Other studies:

Protein binding: % plasma protein binding of atomoxetine was: 98.7, 98.5, 96.7, 96.2, 87.9, and 82 in adult human, pediatric human, beagle dog, New Zealand white rabbit, Fischer 344 rat, and B6C3F1 mouse.
Enzyme induction: in mouse (B6C3F1) and during a 3-month dietary study, atomoxetine was a strong inducer of CYP2B and a weak inducer of CYP1A and CYP3A. In Fischer rats there was an increase in hepatic CYTP450 content with a 50 mg/kg dose in both males and females. Later studies in rats treated with atomoxetine in diet for 3 months (Toxicology rpt 32, ADME rept 18) indicated that CYP1A and CYP2B in both males and females were induced. In male beagle dogs treated with 16 mg/kg orally for 3 months there was an increase in the total CYP 450 content, however, there was no increase in females. In *in vitro* studies with cultured human hepatocytes treated with atomoxetine up to 100 μM for 48 h, there was no significant induction of either CYP1A2 or CYP3A. In vivo studies in humans (with CYP3A probe substrate midazolam in CYP2D6 poor metabolizers) indicated that atomoxetine is not an inducer of CYP3A.

PK/TK summary: the drug plasma levels were increasing with dose and there were no differences between sexes in treated animals (except mice). Some decline was seen in rats with repeated treatment but this was not confirmed in later studies. Young rats had higher plasma levels compared to mature animals while the opposite was observed in dogs. Oral bioavailability was low in mouse (5%) and rats (4%) and moderate in dogs (74%) and rhesus monkeys (45%). In rats the drug was rapidly distributed to tissues and it was excreted in milk and radioactivity transferred through the placenta after treatment with radioactive atomoxetine in pregnant rats. Atomoxetine is extensively metabolized and the two major metabolites were 4-hydroxyatomoxetine and N-desmethylatomoxetine. In humans aromatic hydroxylation appears to be mainly mediated by CYP2D6. Two metabolites that were detected in humans but not in animals were hydroxy-carboxyatomoxetine-O-glucuronide and 2,4-dihydroxyatomoxetine. The major phase I metabolic pathways were aromatic ring hydroxylation, benzylic/aliphatic hydroxylation, and N-demethylation. Subsequent glucurodination of the hydroxylated metabolites was the only phase II metabolic pathway to result in conjugation in mouse, rat, and human. In addition to glucurodination, dogs also expressed O-sulfation as phase II metabolism. The major route of elimination was through urine even though some radioactivity was seen in feces of animals treated with radioactive atomoxetine which appeared to be due to biliary elimination of radioactive metabolites. The drug is highly bound to proteins (98.7%) in humans and animals (82% in mice, 96.7% in beagle dogs). The drug strongly induces CYP2B and weakly CYP1A and CYP3A in mice. Slight increases in CYP450 levels were seen in rats treated with 50 mg/kg with induction in CYP1A and 2B observed and an increase in total CYP450 levels was seen in male beagle dogs.

PK/TK conclusions: the drug has a variable oral bioavailability between species. The drug appears to distribute quickly to tissues and it is excreted in milk and passes through the placenta. It is extensively metabolized and the two major phase I metabolites are 4-hydroxyatomoxetine and N-desmethylatomoxetine which were detected in rats, dogs, mice, rabbits, rhesus monkeys and humans. In humans aromatic hydroxylation appears to be mainly mediated by CYP2D6. The major route of elimination was in the urine and some was seen in the feces mostly due to biliary elimination of metabolites. The drug is highly protein bound. Major induction of CYP450 enzymes in mice (CYP2B) and moderate induction in rats (1A and 2B).

IV. GENERAL TOXICOLGY:

Study title: a subchronic study in Fischer rats given tomoxetine hydrochloride (LY139603) in the diet daily for three months

Key study findings: decreases in body wt and food consumption. Changes in urinalysis parameters. Some changes in serum chemistry. Changes in the wt/body wt ratio of several organs. Grossly small prostate and seminal vesicles in treated animals only. Histopathological changes in the liver (vacuolation) ranging from minimal to marked with severity increasing with dose.

Study no: R06499
Volume #, and page #: vol 37-38, toxrpt 46, page 1
Conducting laboratory and location: —

Date of study initiation: May 14 – August 13, 1999
GLP compliance: yes
QA report: yes (X) no ()
Drug, lot #, radiolabel, and % purity: lot #039JD9, 100.1 on an as is basis/87.6 as free base form on an as is basis. Test article was fairly stable throughout the study duration (the purity at the end of dosing was 99.6%)
Formulation/Vehicle: diet/ — Rodent Diet —

Methods (unique aspects): drug was administered to rats at targeted daily doses of 0, 5, 40, 80, or 160 mg/kg (compared to a 3-month and a 1-year study where the drug was administered as constant % value in the diet without adjustment for the decrease in food consumption). Food consumption for animals in the satellite toxicokinetic study was not measured and the levels of the drug in the feed were changed according to the changes in food consumption in animals of the main study.
Dosing:

Species/strain: rat/Fischer 344
#/sex/group or time point (main study): 15/sex/group.
Satellite groups used for toxicokinetics or recovery: 6/sex/group
Age: 6-7 weeks
Weight: M 140-188 g
F 103-136 g

Doses in administered units: 0, 5, 40, 80, and 160 mg/kg/day. Homogeneity and stability (up to 31 days) of the compound in the feed was performed prior to this study and the compound (Lot #DPD 12336) was found to be stable and homogenous (the mean assayed concentrations of tomoxetine hydrochloride in the treated diets ranged between

81-107% of the theoretical value). According to the sponsor, the average daily mg/kg doses delivered to the animals were within 5% of the nominal doses for all treatment groups.

Route: dietary/ad libitum

Observations and times:

Clinical signs: rats were examined daily for survival, general physical condition, and behavior. A detailed examination for animals in the main study was performed weekly where muscle tone, condition of pelage, color and appearance of eyes, respiration, posture, excreta, locomotion, and presence of external lesions or growths were evaluated.

Body weights: animals in the main study were weighed prestudy and then on a weekly basis. For rats in the satellite toxicokinetic study, body weights were determined prestudy only and they were not weighed thereafter and the drug concentration in the food was corrected on a weekly basis according to the wts of animals in the main study.

Food consumption: determined on a weekly basis for the main study only.

Ophthalmoscopy: for rats in the main study, the adnexa, conjunctiva, cornea, sclera, anterior chamber, iris, and lens were examined with focal illumination and examination lens following dilation of the pupil. The fondus of the eye was evaluated by binocular indirect ophthalmoscopy. These examinations were performed prior to treatment and near the end of the live phase.

EKG: not performed

Hematology: blood samples were obtained from all surviving animals in the main study prior to necropsy via the orbital plexus with rats fasted overnight. The following parameters were evaluated: erythrocyte count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin/concentration, blood cell morphology, total leukocyte count and differential, platelet count, activated partial thromboplastin time, and prothrombin time.

Clinical Chemistry: blood collection methods similar to the hematology section. The following parameters were measured: glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate transaminase, gamma glutamyltransferase, creatinine phosphokinase, calcium, inorganic phosphorus, sodium, potassium, chloride, cholesterol, triglycerides, total protein, albumin, globulin, and albumin/globulin ratio.

Urinalysis: samples were collected overnight from the first 5 surviving rats/sex in the main study near the end of the live phase for the determination of the following parameters: color, clarity, specific gravity, pH, protein, glucose, occult blood, ketones, bilirubin, urobilinogen, volume, sodium, potassium, chloride, creatinine and total excretion of urine sodium, potassium, chloride, and creatinine (computation).

Gross pathology: necropsy was performed for rats in the main study and it included examinations of all external body surfaces and orifices; the thoracic, abdominal, pelvic, and cranial cavities and their viscera; cervical tissues and organs; and external surfaces of muscle, nerve, and spinal cord.

Organs weighed: the following organs from each rat in the main study were weighed: kidneys, liver, heart, spleen, ovaries, uterus, testes, epididymides, prostate, adrenals, thyroids with parathyroids, pituitary, and brain.

Histopathology: sections of all collected tissues (kidney, duodenum, mammary gland, urinary bladder, jejunum, harderian gland, liver, ileum, skeletal muscle, heart, cecum, bone, aorta, colon, bone marrow, trachea, rectum, adrenal, lung, ovary, thyroid, spleen, uterus, parathyroid, lymph node, cervix, pituitary, thymus, vagina, cerebrum, salivary gland, testis, cerebellum, pancreas, epididymis, brain stem, tongue, prostate, spinal cord, esophagus, seminal vesicle, sciatic nerve, stomach, skin, and eye) were examined microscopically from each control and 160-mg/kg group rats. Livers from the 5-, 40, 80-mg/kg group rats were examined microscopically. Sections of testis from each of the 5 control and five 160-mg/kg group males were stained with hematoxylin, eosin, and phloxine as counterstains (PAS-HEP).

An independent peer view evaluation was performed. The pathologic evaluation represents the consensus of the study and peer review pathologists.

Toxicokinetics: the plasma levels of tomoxetine free base, N-desmethyltomoxetine, and 4-hydroxytomoxetine were evaluated at 0 and 12 hours on study days 5, 35, and 90. Samples were collected from 6 animals/sex/group (3/sex/group at each collection time). Rats were anesthetized with isoflurane and blood samples were collected from the orbital plexus.

Results:

Mortality: no deaths observed.

Clinical signs: thinness was observed in two males at the 160 mg/kg dose. "Eye discharge red" was described for 1/15 M in the 40 mg/kg group and in 3/15 M in the 160 mg/kg group and none in the control. However, these eye discharges did not show a drug-related occurrence in F.

Body weights: drug treatment resulted in decreases, relative to control, in mean body wt and body wt gain especially in rats treated with $\geq$ 40 mg/kg (see the following table provided by sponsor). Rats (both M and F) treated with 160 mg/kg showed these decreases from the first week while those treated with 40 and 80 mg/kg experienced them around week 2-3.

		Targeted Dose (mg/kg/day)							
Parameter (% Change[a])		5		40		80		160	
	Sex	M	F	M	F	M	F	M	F
Body weight				↓8%	↓8%	↓13%	↓14%	↓23%	↓19%
Body weight gain				↓14%	↓20%	↓24%	↓33%	↓42%	↓48%
Daily food consumption			↓5%	↓11%	↓12%	↓16%	↓19%	↓23%	↓26%
Relative food consumption			↓3%	↓5%	↓7%	↓6%	↓9%	↓7%	↓12%
Efficiency of food utilization					↓9%	↓10%	↓18%	↓24%	↓30%

Abbreviations: M = male; F = female; ↓ = decrease.

[a] % change values ($p \leq .05$) are relative to the control group at the end of the live phase.

The decreases in mean body wt gain was slightly larger in females, however, the mean absolute wt did not show a gender difference (see figure 1).

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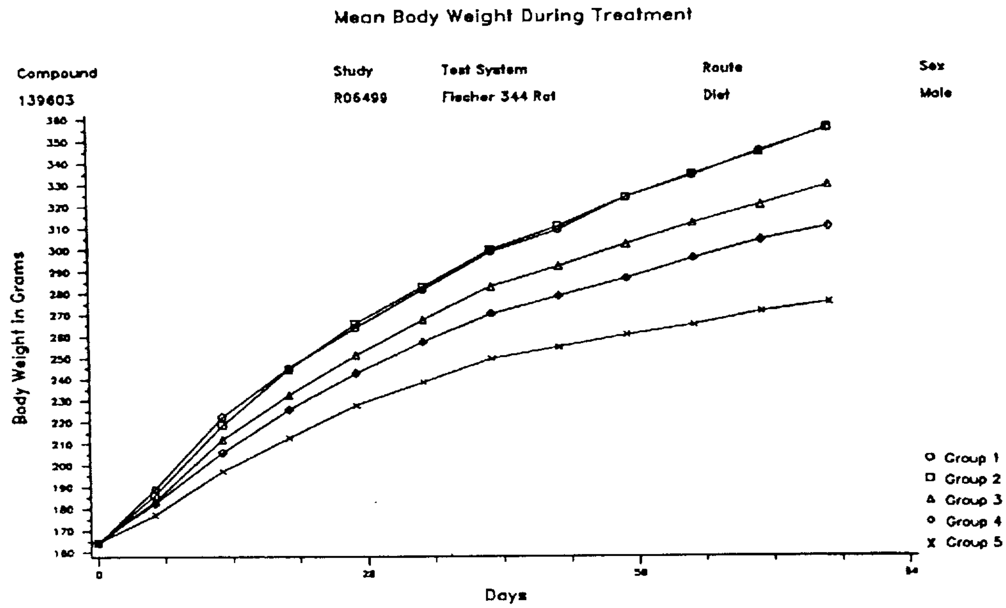

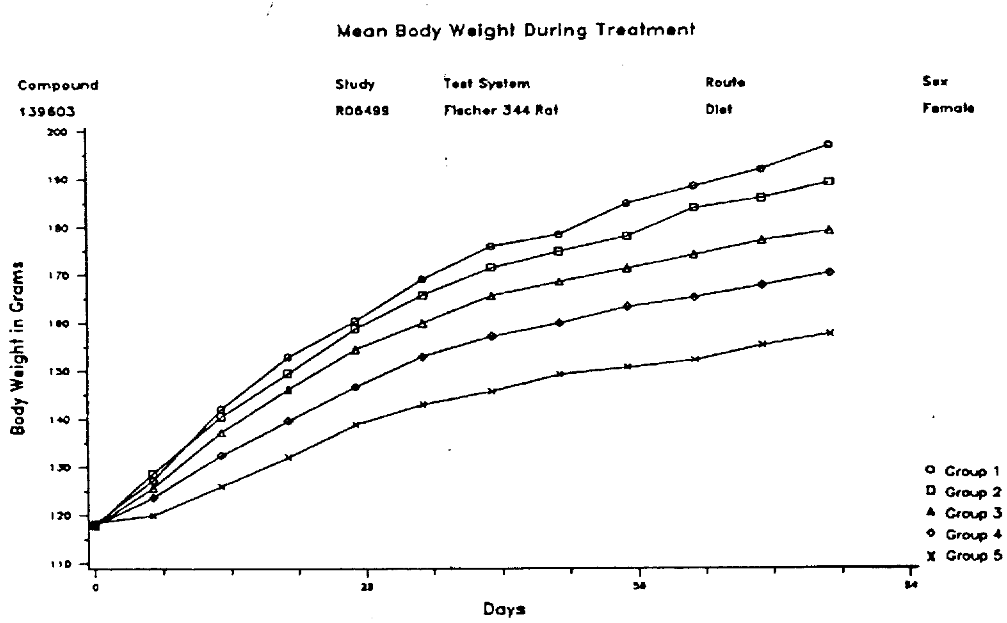

Figure 1: **Mean body weight during treatment.**

Food consumption: drug treatment also resulted in decreases in food consumption in both M and F (see table in the previous section). Decreases in food consumption were seen in F and M treated with $\geq$ 40 mg/kg from the first week of treatment. However, only F treated with 5 mg/kg experienced a decrease in food consumption (~4% compared to control) that was statistically significant starting from day 20.

Ophthalmoscopy: no treatment related findings.

Electrocardiography: not performed.

Hematology: some increase (ranging from 20-26%, not dose dependent) in WBC in females treated with 40, 80, and 160 mg/kg with comparable increases in absolute lymphocyte count. Slight decreases in prothrombin time (ranging from 6-10%, dose dependent) and activated partial thrombin time (ranging from 6-13%, dose dependent) in males treated with 40, 80, and 160 mg/kg. A slight decrease (~10%) in platelets in both males and females at the HD.

Clinical chemistry: some changes were observed and they are consistent with the following summary table provided by the sponsor.

Parameter (% Change[a])		Targeted Dose (mg/kg/day)							
		5		40		80		160	
	Sex	M	F	M	F	M	F	M	F
Glucose								↓15	
Triglycerides								↓58	↓30
Total protein									↓7
Potassium					↑5		↑6		↑11
Alkaline phosphatase						↑17	↑10	↑15	↑29

Abbreviations: M = male; F = female; ↓ = decrease; ↑ = increase

[a] % change (p≤.05) values are relative to the control group.

Urinalysis: several changes were observed (decreased volume, increased pH, and increased specific gravity). Other changes in urine chemistry were observed and these included increases in creatinine and electrolyte levels, however, since a decrease in urine volume was observed with treatment, the total excretion of these electrolytes with treatment was decreased. See the following summary table provided by the sponsor.

Parameter (% Change[a])		Targeted Dose (mg/kg/day)							
		5		40		80		160	
	Sex	M	F	M	F	M	F	M	F
Urine volume						↓37		↓51	↓50
Urine pH									↑14
Urine sodium excretion						↓23		↓33	
Urine potassium excretion				↓18		↓28	↓28	↓41	↓29
Urine chloride excretion				↓15		↓30	↓26	↓37	↓20
Urine creatinine excretion				↓18		↓30	↓36	↓45	↓40

Abbreviations: M = male; F = female; ↓ = decrease; ↑ = increase

[a] % change (p≤.05) values are relative to the control group.

Organ weights: absolute organ wt was decreased in almost all organs tested at the HD, which is probably reflective of the decrease in body wt. However, few organs showed either a decrease or an increase in the relative wt to body wt ratio. The spleen showed a slight decrease in the weight/body wt ratio in both M and F (6, 9, 13, and 10% decreases at 5, 40, 80, and 160 mg/kg in M and 7, 7, 11, and 13% at 5, 40, 80, and 160 mg/kg in F, respectively). Testes showed a decrease in a dose dependent manner in the wt/body wt ratio (7, 12, and 22% at 40, 80, and 160 mg/kg). Prostate showed a dose dependent decrease also in the wt/body wt ratio (10, 23, and 25% at the 40, 80, and 160 mg/kg, respectively). A 10% increase in the liver wt/body wt ratio in comparison to control was seen at the HD in M. An increase (8, 16, and 16% in comparison to control) in the wt/body wt ratio of the thyroid was seen in M at 40, 80, and 160 mg/kg, respectively. A decrease (26%) in the wt/body wt ratio of the uterus of F at the HD. A decrease (8 and 11%) in the wt/body wt ratio of the adrenals was seen in F at 80 and 160 mg/kg, respectively.

Gross pathology: the incidence of whole tissue alteration in the liver was increased in males with treatment (1/15 in control, 4/15 at 40 mg/kg, 3/15 at 80 mg/kg and 13/15 at 160 mg/kg). The incidence of these alterations was less in females (1/15 in control, 1/115 at 40 mg/kg, 1/15 at 80 mg/kg, and 5/15 at 160 mg/kg). The observation of small prostate was seen only in treated groups (1/15 at 40 mg/kg, 4/15 at 80 mg/kg, and 12/15 at 160 mg/kg). Small seminal vesicle was also seen only in the treatment group (1/15 at 40 mg/kg, 4/15 at 80 mg/kg, and 11/15 at 160 mg/kg).

Histopathology: slight calculus in the urinary bladder was seen in 1/15 controls and 3/15 at the 160 mg/kg. Different changes were observed in the liver as summarized in the following table from sponsor.

Parameter (n[a])	Targeted Dose (mg/kg/day)									
	0[b]		5		40		80		160	
Sex	M	F	M	F	M	F	M	F	M	F
Number	15	15	15	15	15	15	15	15	15	15
Minimal midzonal liver vacuolation					9				3	
Slight midzonal liver vacuolation					4		11		3	
Moderate midzonal liver vacuolation							4		7	
Marked midzonal liver vacuolation									2	

Abbreviations: M = male; F = female
[a] Incidence.
[b] Vehicle.

In the spleen slight focal capsular fibrosis was seen at 160 mg/kg and none in any of the other groups. In the testes slight multifocal tubular regression was seen in 2/15 in controls and 5/15 in the 160 mg/kg group.

Toxicokinetics: data were presented in ADME report 43 (study R06499). A minor dose dependent accumulation of tomoxetine and its metabolites was observed with continued dietary exposure in the higher dose groups.

	Administered Dose of LY139603 (mg/kg)							
	5		40		80		160	
Time (hour)	0	12	0	12	0	12	0	12
Tomoxetine (ng/mL)								
Study Day 5	4.92	2.79	22.0	18.6	32.4	38.9	52.7	88.2
Study Day 35	1.20	2.76[a]	9.27	25.2	30.6	53.8	66.1	112
Study Day 90	2.26	3.05	16.0	32.1	34.1	62.1	73.5	171
4-hydroxytomoxetine (424478, ng/mL)								
Study Day 5	BQL	BQL	BQL	BQL	4.62	5.12	11.8	25.1
Study Day 35	BQL	BQL	2.59[b]	BQL	9.23[c]	9.66	49.3	36.6
Study Day 90	BQL	BQL	4.47	3.37	11.6	14.9	49.0	73.4
***N*-desmethyltomoxetine (137877, ng/mL)**								
Study Day 5	BQL	BQL	BQL	BQL	BQL	BQL	BQL	3.45
Study Day 35	BQL	BQL	BQL	BQL	BQL	2.16[b]	BQL	4.80
Study Day 90	BQL	BQL	BQL	BQL	1.71[b]	2.57	3.55	8.22

Data are expressed as mean combined gender plasma concentration (n = 6; ng/mL); BQL = Below the Limit of Quantitation; NC = Not Calculated.

[a]n = 4.

[b]n = 5.

[c]n = 3.

Summary of individual study findings: targeted daily doses of 0, 5, 40, 80, and 160 mg/kg atomoxetine were administered orally in diet for three months to Fischer 344 rats (15/sex/group). A satellite group was used to measure plasma drug levels, however, adjustments of drug levels were calculated according to wt changes in animals from the main study. Animals were observed daily for survival and clinical signs. Body wt and food consumption were determined weekly. Ophthalmoscopy, hematology, clinical chemistry, and urinalysis were performed. Gross pathology was done on all animals while histopathology was performed only on control and HD animals. No deaths were reported. Decreases in body wt, wt gain and food consumption were observed. Some changes in hematology and clinical chemistry were observed (increases in WBC, decreases in prothrombin time, decreases in platelets, decreases in glucose, triglycerided, and total protein, and increases in potassium and alkaline phosphatase). Decreases in urine volume, sodium, potassium, chloride, and creatinine urine excretion. Decreases in wt/body wt ratio of spleen (M & F), testes, and prostate. Decreases in wt/body wt ratio of the uterus at HD. A slight decrease in wt/body wt ratio of the adrenals in F at HD. Slight increases in wt/body wt ratio of the liver at HD and thyroid at all doses in M. Gross pathology was associated with whole tissue alteration in the liver in M with less effect in F. Small prostate and seminal vesicles were seen in treated groups only. Vacuolation in the liver ranging from minimal to marked was in M and severity was increased with dose. Slightly higher levels of multifocal tubular regression in the testes were seen at HD compared to the control.

Study title: a repeat dose toxicity study in Fischer 344 rats given atomoxetine hydrochloride (LY139603) daily by gavage for 1 month

Key study findings: a decrease in food consumption and body wt was observed when the drug was administered orally by gavage for 1 month

Study no: # R10901
Volume #, and page #: part of IND
Conducting laboratory and location: Eli Lilly and Company
Date of study initiation: 13 November 2001-19 December 2001
GLP compliance: yes
QA report: yes (X) no ()
Drug, lot #, radiolabel, and % purity: Lot #007JD1, purity 100.4%
Formulation/Vehicle: solution/water

Methods (unique aspects): in this study, the drug was administered orally by gavage for 1 month. The study was conducted to compare the effect of giving the drug by gavage to previous studies where the drug was given in diet. In those studies where the drug was administered in food a decrease in food consumption was observed. To rule out that the decrease in food consumption with treatment was not due to poor palatability of the drug, the drug was administered by gavage in the current study.

Dosing:

Species/strain: Rat/Fischer 344
#/sex/group or time point (main study): 10/sex/group
Satellite groups used for toxicokinetics or recovery: none
Age: 6-7 weeks
Weight: M 126-152
F 105.1-120.5
Doses in administered units: 40, 80, 160 mg/kg/day
Route, form: oral/gavage

Observations and times:

Clinical signs: rats were examined daily for survival, general physical condition, and behavior. A detailed examination was performed twice weekly to evaluate muscle tone, condition of pelage, color and appearance of eyes, respiration, posture, excreta, locomotion and presence of external lesions or growths.

Body weights: weighed pretreatment, twice weekly, and near the end of the live phase.

Food consumption: pretreatment, twice weekly, and near the end of the live phase.

Ophthalmoscopy: not performed
EKG: not performed
Hematology: not performed
Clinical Chemistry: not performed

Urinalysis: not performed
Gross pathology: not performed
Organs weighed: not performed
Histopathology: not performed
Toxicokinetics: not performed
Other:

Results:

Mortality: no mortality was reported

Clinical signs: The following observations were seen only at the HD: salivation (8/10 M and 9/10 F), soiling (5/10 M and 4/10 F), rough coat (4/10 M), and respiratory effects (rales 1/10 M, audible 1/10 M).

Body weights: decreases in body wt were seen at all doses but they were more pronounced at the HD. At the LD the decreases were not statistically significant at any time point in both M and F. At the MD the decreases were seen starting day 3 but were not statistically significant until day 9 in both M (7% decrease compared to control) and F (5% decrease compared to control). At the HD the decreases were seen from day 3 but started to be statistically significant on day 6 in M (5% decrease from control) and day 9 in F (6% decrease from control) (see table provided by the sponsor at the end of next section).

Food consumption: a decrease in food consumption was seen early in the treatment at LD in M (9% decrease from control on day 3). A similar decrease was seen in F (7% compared to control) on day 3, however, this was not statistically significant (a statistically significant decrease of 5% was reached on day 9). At MD a statistically significant decrease was seen on day 3 in M (16% decrease compared to control) while in F the decrease (10%) was not statistically different until day 9. At HD the decrease in both M and F was seen at day 3 (15% decrease compared to control in both M and F). See the following table.

	% Change from Control					
Daily Dose (mg/kg):	40		80		160	
Parameter Sex:	M	F	M	F	M	F
Cumulative Body Weight Gain (g)						
Day 13	↓13	↓11	↓24*	↓37*	↓36*	↓41*
Day 27	↓16*	↓10*	↓27*	↓28*	↓39*	↓43*
Body weight (g)						
Day 13	↓4	↓2	↓8*	↓7*	↓11*	↓7*
Day 27	↓7*	↓3	↓12*	↓8*	↓17*	↓12*
Cumulative Food Consumption (g/day)						
Day 13	↓10*	↓5*	↓15*	↓12*	↓21*	↓16*
Day 27	↓9*	↓5*	↓16*	↓13*	↓23*	↓17*
EFU(g)						
Day 13	↓4	↓7	↓11	↓28*	↓21*	↓29*
Day 27	↓8	↓5	↓14*	↓18*	↓22*	↓32*

Abbreviations: M = male, F = female, ↓ = decrease.
*p≤.05.

Ophthalmoscopy: no data
Electrocardiography: no data
Hematology: no data
Clinical chemistry: no data
Urinalysis: no data
Organ weights: no data
Gross pathology: no data
Histopathology: no data
Toxicokinetics: no data

Summary of individual study findings: since atomoxetine resulted in a decrease in food consumption in other studies when it was administered orally in the diet, this study was conducted to see if the same effect would be seen when the drug is administered by gavage, thus ruling out a possibility that this decrease was due to poor palatability of the drug. Fischer 344 rats (10/sex/group) were treated with 0, 40, 80, and 160 mg/kg orally by gavage for 1-month. Animals were observed daily for survival and clinical signs and body wts were measure weekly while food consumption was measured twice weekly. No deaths were reported. Some clinical signs were seen at HD (salivation, soiling, and rough coat). Decreases in body wt were seen at all doses but more pronounced at HD. Decreases in food consumption were observed in all treatment groups and it was seen early in the study. This effect on food consumption indicates that the decrease was probably a drug effect rather than a result of poor palatability of the drug.

A 1-year toxicity study in rats was reviewed in the division and a copy of the review is included here.

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