MD), decreased absolute (11%) and relative (11%) heart (MD), and increased relative kidney (13%, MD), adrenal (17%, MD), testes (19%, MD), and lung (11%, MD) weights
SD (albino) rats: LD and MD only were evaluated: significant findings in the MD only: increased absolute (10%) and relative (27%) kidney, relative brain (14%), liver (8%), adrenal (36%), testes (20%), and lung (17%) weights and decreased absolute spleen (19%) weights
Gross pathology: LE (pigmented) rats: Treatment-related effects observed in the high dose (160 mg/kg/day) rats found dead only: Dry subcutaneous tissue, decreased adipose tissue, enlarged adrenals, small thymus, mesenteric lymph nodes, testes, prostate, and seminal vesicles, and dark lung at end of treatment; at the end of recovery enlarged spleen, and small testes, epididymides, prostate, and seminal vesicles observed in ¾ surviving high-dose rats
SD (albino) rats: Treatment-related effects observed in the high dose (160 mg/kg/day) rats found dead only: Dry subcutaneous tissue, decreased adipose tissue, enlarged adrenals, small thymus, spleen, mesenteric lymph nodes, testes, prostate, and seminal vesicles, and dark lung at end of treatment; at the end of recovery small spleen, thymus, testes, and epididymides observed in high-dose rats
Histopathology: LE (pigmented) rats: No treatment-related effects at LD and MD (HD rats not evaluated)
SD (albino) rats: No treatment-related effects at LD and MD (HD rats not evaluated)
Toxicokinetics: Not done

Study title: Subacute Oral Toxicity Study on D 145 in the Rat

Key study findings:

- Dose-related reduction in body weight gain over the dose range of 3-30 mg/kg/day memantine HCl, daily for 8 weeks by oral intubation, statistically significant at 30 mg/kg/day in the male rats (19% over week 1-8), and at 15 (11%, weeks 1-8) and 30 (17%, weeks 1-8) mg/kg/day in the female rats
- NOAEL 3 mg/kg/day (1.5X the MRHD of 20 mg/d in a 60 kg patient on a BSA basis)
- MTD 15 mg/kg/day in the male rats (7X the MRHD) and <15 mg/kg/day in the female rats based on significantly reduced body weight gain

Study no: — Project No. 3-4-170-72
Volume # 25, and page # 241
Conducting laboratory and location: Not provided. Report address:

Date of study initiation: Report Date May, 1973
GLP compliance: yes ( ) no (x)
QA report: yes ( ) no (x)
Drug D 145 (Merz and Co.), **lot #** Not provided, **radiolabel** Not applicable, **and % purity** Not provided
Formulation/vehicle: Aqueous solution

Methods (unique aspects): —
Dosing:

Species/strain: SPF-Wistar rats
#/sex/group or time point (main study): 25/sex/dose
Satellite groups used for toxicokinetics or recovery: None
Age: Not provided
Weight: Means of 65.5 g in the males and 66.2 g in the females
Doses in administered units: 0, 3, 15, and 30 mg/kg/day
Route, form, volume, and infusion rate: Oral by esophageal intubation, once daily for 2 months

Observations and times:

Clinical signs: Daily
Body weights: Weekly
Food consumption: Weekly
Water consumption: Weekly
Ophthalmoscopy: Not done
EKG: Not done
Hematology: Baseline and after 2 months (5/sex/dose)
Clinical chemistry: Baseline and after 2 months ((5/sex/dose)
Urinalysis: Baseline and after 2 months
Gross pathology: At the end of the study (after 2 months)
Organs weighed: At the end of the study (heart, liver, kidneys, adrenals, uterus, testicles, ovaries, brain, and spleen)
Histopathology: At the end of the study, 5/sex/dose (cerebrum, cerebellum, thyroid, lung, heart, colon, liver, kidneys, adrenal, spleen, testicles, epididymides, ovaries, uterus)
Toxicokinetics: Not done
Other: Irwin's activity test: at the end of the study (Included effects on consciousness [e.g., orientation, stereotypy], emotional behavior [e.g., grooming, aggression], reactivity [e.g., reaction to touch], excitation [e.g., tremor], coordination [e.g., posture, gait], muscle tone [e.g., gripping strength], reflexes [e.g., auditory and corneal reflex], and autonomic function [e.g., diuresis, pupil size, salivation, piloerection])

Results:

Mortality: No deaths
Clinical signs: No treatment-related effects, including effects on corneas, irises, lenses, and hearing tests
Body weights: Dose-related reduction in body weight gain compared to controls, statistically significant at the high dose (30 mg/kg/day) in the male rats in weeks 1-4 (10%), 5-8 (37%) and 1-8 (19%), and at 15 (20% in weeks 5-8, 11% in weeks 1-8) and 30 (15% in weeks 1-4, 21% in weeks 5-8, and 17% in weeks 1-8) mg/kg/day in the female rats
Food consumption: No treatment-related effects
Water consumption: No treatment-related effects
Ophthalmoscopy: Not done
Electrocardiography: Not done
Hematology: No treatment-related effects
Clinical chemistry: No treatment-related effects
Urinalysis: No treatment-related effects

Organ weights: Statistically significant increase in adrenal (30%-31%), testicle (16%) and brain (10%) weights in the males, and increase in adrenal (46%-57%), ovary (46%) and brain (8%) weights in the females, at the high dose.

Gross pathology: No treatment-related effects

Histopathology: No treatment-related effects in the bone marrow smears, no treatment-related effects in the microscopic examination of the organ tissues

Toxicokinetics: Not done

Other: No treatment-related effects in the Irwin's activity test

Study title: MEMANTINE hydrochloride 13-week oral (dietary administration) toxicity study in the rat, followed by a 4-week treatment-free period.

Key study findings:

- Deaths in 4 males at 135 mg/kg/day, 10 males at 200 mg/kg/day, 7 females at 180 mg/kg/day
- Treatment-related clinical signs: hyperexcitability, aggressiveness, dirty fur, ataxia, and dark scabs on the snout at 135-200 mg/kg/day in males and 120-180 mg/kg/day in females
- Dose-related reduction in body weight (8%, 20%, 33%, and 25% in the males, Groups 2, 3, 4, and 5, respectively, and 7%, 17%, 34%, and 18% in the females, Groups 2, 3, 4, 5, respectively), body weight gain, and food consumption at all doses from 40-200 mg/kg/day in the males and 30-180 mg/kg/day in the females
- Hematology findings (statistically significant but within historical control range): increased neutrophils, prothrombin time, color index, mean hemoglobin concentration, corpuscular volume, and decreased lymphocytes, platelets, hemoglobin, mean corpuscular hemoglobin, and red blood cell count
- Clinical chemistry findings (statistically significant, outside range of historical control): decreased proteins, albumin, and globulins, and increased blood urea nitrogen, albumin globulin ratio, aspartate aminotransferase (102%-144% in 5/9 females at 120 mg/kg/day and 3/6 males at 135 mg/kg/day), alkaline phosphatase (33%-46%, ≥ 30 mg/kg/day in females), and alanine aminotransferase (40% in 6/10 females at 120 mg/kg/day)
- Urinalysis findings: treatment-related increased ketones, blood in the urine, epithelial cells and casts, decreased pH
- Alopecia was observed in the gross examination and lymphoid lesions, testicular and epididymal lesions, and pulmonary macrophages were observed at the high dose in the histopathology
- NOAEL not determined in this study, due to reductions in body weights at the lowest doses tested
- Doses studied represent approximately 15X-19X (at the low dose) and 88X-97X (at the high dose) the MRHD of 20 mg/d in a 60 kg patient on a BSA basis, and approximately 3X-20X those at human therapeutic levels based on plasma memantine measurement
- MTD 40 mg/kg/day in males and 30 mg/kg/day in females, in agreement with the sponsor's conclusions

Study no: 442/003
Volume # 28, and page # 1 .
Conducting laboratory and location: .

Date of study initiation: November 4, 1987
GLP compliance: yes (x) no ( )
QA report: yes (x) no ( )
Drug Memantine Hydrochloride, **lot #** R 8825, **radiolabel** Not applicable, **and % purity** 99.8%
Formulation/vehicle: Test article mixed in standard powdered rodent diet —

Methods (unique aspects):
Dosing:

Species/strain: ICO:OFA.SD rats —
#/sex/group or time point (main study): 20/sex/dose
Satellite groups used for toxicokinetics or recovery: 10/sex/dose (Groups 1 and 5, 4 week recovery groups)
Age: 6 weeks
Weight: 158-200 g males, 140-163 g females
Doses in administered units: Males: 0 (diet alone, Group 1), 40 (Group 2), 90 (Group 3), 135 (Group 4), and 200 (Group 5) mg/kg/day; Females: 0 (diet alone, Group 1), 30 (Group 2), 75 (Group 3), 120 (Group 4), and 180 (Group 5) mg/kg/day;
Route, form, volume, and infusion rate: Oral by admixture in the diet for 13 weeks (Groups 1 [10/sex], 2, 3, 4), 10 weeks (Groups 1 [10/sex] and 5, followed by 4-week recovery period)

Observations and times:

Clinical signs: 2X daily
Body weights: Weekly
Food consumption: Weekly
Water consumption: Weekly
Test article intake: Weekly (test article concentration X daily food consumption /mean weekly body weight
Ophthalmoscopy: Baseline and Week 7 (all animals), 10 (Groups 1, 4, 5), 13 (Groups 1, 2, 3, 4, 5), and 14 (Groups 1 and 5)
EKG: Not done
Hematology: End of treatment (Week 13) and recovery period (week 14)
Clinical chemistry: End of treatment (Week 13) and recovery period (week 14)
Urinalysis: End of treatment (Week 13) and recovery period (week 14)
Gross pathology: End of treatment (Week 13) and recovery period (week 14)
Organs weighed: End of treatment (Week 13) and recovery period (week 14); see under Histopathology Inventory, below
Histopathology: End of treatment (Week 13) and recovery period (week 14); see under Histopathology Inventory, below
Toxicokinetics: Plasma and eye tissue samples (eyes with lesions only) measured in Weeks 10 and 13
Other: Electron microscopy of liver and bile duct (5/sex/group at 13 weeks or after recovery at 14 weeks)

Results:

Mortality:
Group 4: 4 deaths in the males at 135 mg/kg/day (3 sacrificed *in extremis* on days 53, 60, and 80, and one found dead on day 89)

Group 5: 10 deaths in the males (at 200 mg/kg/day, 6 sacrificed *in extremis* on days 38, 41, 49, 56, 59, 70, 4 found dead on days 27, 43, 43, and 67), and 7 deaths in the females (at 180 mg/kg/day, 5 sacrificed *in extremis* on days 33, 53, 56, 56, and 64, and 2 found dead on days 19, 67), the deaths and moribundity were associated with small testes and epididymides, mottled lungs, weight loss, foci on kidneys, enlarged urinary bladder, enlarged kidneys, unsteady gait, tremors, aggression, dirty fur, hyperexcitability or subdued behavior, labored breathing, or hypothermia in one or more animals

Clinical signs: Treatment-related signs in Groups 4 and 5: hyperexcitability, aggressivity, yellow dirty fur, ataxia, dark scabs on snout, with dose-related increase in duration

Body weights: Dose-related reduction in body weight gain in the males in Groups 2, 3, 4, and 5, and in the females in Groups 2, 3, 4, and 5, compared to controls; the final body weights in week 13 are presented in the following table:

Mean Final Body Weights Following Administration of Memantine HCl in the Diet for 13 weeks in Rats (percent difference from control body weight in parentheses)

Group[a]	Male Rats	Female Rats
1	497.5 ± 42.92 (reference)	280.0 ± 20.03 (reference)
2	456.3 ± 38.00 (-8%)*	258.9 ± 21.42 (-7%)**
3	399.9 ± 32.98 (-20%)***	231.2 ± 12.71 (-17%)***
4	333.0 ± 64.03 (-33%)***	183.8 ± 23.04 (-34%)***
5	376.8 ± 38.25 (-25%)***	228.5 ± 15.15 (-18%)***

*p<0.05; **p<0.01; ***p<0.001

[a]The doses administered in the males were 0 (diet alone, Group 1), 40 (Group 2), 90 (Group 3), 135 (Group 4), and 200 (Group 5) mg/kg/day; The doses administered to the females were 0 (diet alone, Group 1), 30 (Group 2), 75 (Group 3), 120 (Group 4), and 180 (Group 5) mg/kg/day

The percentages of body weight gain, when compared to baseline body weights, are presented in the following table:

Percent Body Weight Gain (Cumulative) in Rats Administered Memantine HCl in the Diet for 13 Weeks

Sex	Dose (mg/kg/day)	Week 1	Week 6	Week 10	Week 13	Week 14 (Recovery)
Males	0	+31%	+119%	+150%	+162%	+9%
	40	+26%	+109%	+137%	+142%	-
	90	+18%	+92%	+117%	+117%	-
	135	+8%	+58%	+69%	+74%	-
	200	-7%	+20%	+43%	-	+55%
Females	0	+18%	+64%	+78%	+86%	+10%
	30	+12%	+53%	+67%	+73%	-
	75	+5%	+39%	+47%	+55%	-
	120	0	+25%	+29%	+23%	-
	180	-12%	-2%	-5%	-	+67%

Food consumption: Dose-related reduction in the males and females; the percent differences from control food consumption are presented in the following table:

Variation in Food Consumption (Percent Change from Control Values) in Rats Administered Memantine HCl in the Diet for 13 Weeks

Group	Weeks	Males	Females
2	1 – 13	-5% to -15%	0 to -5%
3	1 – 13	-10% to -30%	-5% to -15%
4	1 – 13	-25% to -35%	-15% to -30%
5	1 – 6	-40%	-35%
	7 – 8	-35%	-40%
	9 - 10	-25%	-35%

Water consumption: Generally decreased in the first 1-6 weeks of treatment compared to controls, thereafter (weeks 7-13) similar or increased compared to water consumption in the control animals

Test article intake: The results of the test article intake measurements are presented in the following table:

Test Article Intake in Rats Administered Memantine HCl in the Diet for 13 Weeks

Group	Weeks	Males			Females		
		Theoretical Dose Level	Mean Measured Dose	Range	Theoretical Dose Level	Mean Measured Dose	Range
2	1-13	40	40.6		30	30.5	
3	1-13	90	92.4		75	75.4	
4	1-13	135	135.1		120	117.4	
5	1-6	200	188.6		180	172.2	
	7-9	155	158.5		140	136.5	
	9-10	135	155.8		120	129.1	

Ophthalmoscopy: Focal opacities in 1 male and 6 females at the high dose in week 7, corneal edema and lens lesions in groups 4 and 5 in week 10

Electrocardiography: Not done

Hematology:

In the animals sacrificed moribund: there was a treatment-related increase in polymorphonuclear neutrophils, decreased polymorphonuclear eosinophils and lymphocytes, increased hemoglobin, red blood cell count and packed cell volume (hemoconcentration) and decreased platelet count at the high dose compared to the control values

Group 2-4 animals measured in Week 13: there were significant increases in polymorphonuclear neutrophils and prothrombin time, and decreased lymphocytes and platelet count (11% to 24% in males and females of Grps 2-4), compared to controls; the mean values were within the range of historical control values

Group 5 animals treated for 10 weeks with a 4-week recovery period: Increased color index, mean hemoglobin concentration, mean corpuscular volume and polymorphonuclear neutrophils, and decreased hemoglobin, mean corpuscular hemoglobin concentration, and red blood cell count; the mean values were within the range of historical control values

Clinical chemistry:

In the animals sacrificed moribund: Increased sodium potassium, chloride, bun levels, liver enzymes, and decreased globulins, considered to be related to the moribund status of the animals

Groups 2-4 measured in Week 13: decreased sodium (-1% [Grp 2 males] and –2% [Grp 3 males]), chloride (-3% to –4% in Grps 2, 3, and 4 males), proteins (-7% in Grps 2 and 4 males and –8% to –13% in Grps 3 and 4 females), albumin (-9%, Grp 4 females), and globulins (-10% to –15% in Grps 2, 3, and 4 males, -10% to –19% in Grps 2, 3, and 4 females), and increased potassium (9% to 21% in Grps 3, and 4 females), phosphorus (24% in males and 34% in females of Grp 4), blood urea nitrogen (22% in males and 29% in females of Grp 4), albumin/globulin ratio, serum alkaline phosphatase (33% to 46% in Grps 2, 3, and 4 females), aspartate aminotransferase (102% to 144% in 5/9 Grp 4 females and 3/6 males, respectively), and alanine aminotransferase (40% in 6/10 Grp 4 females compared to control values; sodium, potassium, chloride and phosphorus levels within range of historical control values.
Group 5 animals treated for 10 weeks with a 4-week recovery period: increased phosphorus (28% in males, 43% in females) and serum alkaline phosphatase (40 % in males, 52% in females), and decreased proteins (6% in males), albumin (5% in males, 4% in females), and globulins (8% in males) compared to control values;
Urinalysis:
Groups 2-4 measured in Week 13: increased ketones (Grps 2, 3, and 4 males), blood in urine (Grp 4; males and females), epithelial cells (all groups), and casts (Grps 3 and 4 males, Grp 4 females), and decreased pH (Grp 4 males and Grps 3 and 4 females)
Group 5 animals treated for 10 weeks with a 4-week recovery period: Slightly decreased urine volume in males and females
Organ weights: Increased adrenal (Grps 3 and 4 males, Grps 3 and 4 females) and kidney (Grps 3, and 4 males, Grps 3 and 4 females) weights, and decreased thymus (Grps 3 and 4 males, Grp 4 females), testes (Grp 4 males), and uterus (Grp 4 females) weights
Gross pathology: Alopecia in Grps 3 and 4
Histopathology: lymphoid lesions (reversible), testicular and epididymal lesions (not reversible), and pulmonary macrophages (reversible) observed in Group 5 animals
Toxicokinetics: The results of the plasma Memantine measurements are presented in the following table:

Plasma Memantine Levels in Rats Administered Memantine HCl in the Diet for 13 Weeks

Group	Sex	Dose (mg/kg)	n	Memantine level (mcg/L, mean ± S.D.), Wk 13
1	M F	0 0	10 10	0 0
2	M F	40 30	10 10	584 ± 218 571 ± 239
3	M F	90 75	10 9	1917 ± 828 2437 ± 604
4	M F	135 120	6 7	3343 ± 1678 4623 ± 1649
5	M F	(200 reduced to 135) (180 reduced to 120)	10 10	0 0

The tissue Memantine levels in eyes with lesions are presented in the following table:

Memantine Levels in Lesioned Eye Tissues of Rats Administered Memantine HCl in the Diet for 13 Weeks

Animal #	Sex	Dose (mg/kg)	Inclusion		Rest	
			Weight (mg)	Memantine	Weight (mg)	Memantine (mcg/g)
67	Male	200-135	9.0	0	72.3	115.6
128	Female	180-120	12.6	0	75.3	103.6
134	Female	180-120	11.5	0	59.4	97.8
121 (2 eyes)	Female	180-120	19.5	0	121.2	117.7
Mean						**108.6 ± 9.5**

Study title: A thirteen week subacute toxicity study in rats fed diet containing memantine with a recovery period of 5 weeks

Key study findings:

- Deaths in 1/16 M at 90 mg/kg/day, 12/16 M and 9/16 F at 180 mg/kg/day, associated with clinical signs of hypersensitivity, decreased movement and staggering, chromodacryorrhea, unkempt fur, and emaciation secondary to malocclusion-induced malnourishment
- Treatment-related signs were unkempt fur, emaciation, hypersensitivity, and staggering at the highest dose of 180 mg/kg/day
- Body weights reduced 21% and 27% in M and F, respectively, at 90 mg/kg/day, 64% and 27% in M and F, respectively, at 180 mg/kg/day, reversed during recovery period
- Food consumption reduced at 90 and 180 mg/kg/day, reversed during recovery
- Drug intake measured at 19, 84, and 161 mg/kg/day, respectively, in M and 19, 88, and 153 mg/kg/day, respectively, in F at 20, 90 and 180 mg/kg/day
- Treatment-related adverse effects in cornea, (considered related to treatment-induced decreased blinking): membranous/striate opacities, punctate opacities, focal adhesion or detachment of the cornea or iris, and vascularization in one or both eyes, partially reversed during recovery period
- Treatment-related hematology findings at 90 and 180 mg/kg/day: increased hemoglobin, red blood cells, neutrophils, reticulocytes, and hematocrit, and decreased white blood cells and lymphocytes; After recovery: decreased lymphocyte ratio and increased neutrophils and mean corpuscular volume
- Clinical chemistry changes at 90 and 180 mg/kg/day (considered related to malnutrition) were decreased triglyceride, glucose, calcium, total protein, urea nitrogen, creatinine, alpha-1 globulin fraction and gamma globulin fraction, and increased A/G ratio, albumin fraction and alpha-2 globulin fraction; also increased GOT, GPT, and LDH possibly related to microscopic changes in liver, kidneys and skeletal muscle; after recovery: decreased LDH, triglyceride, A/G ratio, chloride, and albumin, and increased gamma globulin fraction
- Treatment-related effects in urinalysis: decreased pH, specific gravity, and excretion of sodium, potassium and chloride
- Increased relative and absolute lung weight, and slight decreases in absolute and relative thymus, spleen, ovary and uterus weights; After recovery: decreased absolute and relative thymus, testes and epididymides weights at high dose
- Gross necropsy: atrophy of thymus, spleen, mesenteric lymph nodes, ovaries, uterus, testes and epididymis in 1-2 animals at high dose

- Histopathology: multiple lesions (cytoplasmic vacuolation, foam cells, degeneration, necrosis, atrophy or enlargement) in many organs/tissues in several animals at 90 mg/kg/day, most animals at 180 mg/kg/day: including hypothalamus, cerebrum, cerebellum, pituitary, spinal cord, liver, thyroid, renal tubular epithelium, glomeruli of the kidney, adrenals, thymus, spleen, mesenteric lymph nodes, trachea, bronchi, alveoli, epididymis, urinary bladder, testes, seminal vesicle, seminiferous tubules, prostate, ovaries, uterus and vagina, tongue, duodenum, jejunum, and ileum, femoral muscle fibers, mammary gland, and skin cells; glandular stomach, corneal lesions, swelling of the pigment epithelium, and hypocellularity in the bone marrow; After the recovery period foam cells in lung alveoli were observed in 4/6 of the mid-dose females
- Target organs of toxicity: cornea (probably secondary to reduced blinking), liver, kidneys, and muscle; 90 and 180 mg/kg/day for 13 weeks resulted in microscopic lesions, including vacuolation, foam cells and degeneration or necrosis in nearly all organs and tissues in M and F rats
- Doses studied were approximately 10X, 43X, and 88X the MRHD of 20 mg/day in a 60 kg patient on a BSA basis
- NOAEL 20 mg/kg/day in agreement with the sponsor's conclusion; For the carcinogenicity study, the NOAEL can be considered to be <90 mg/kg/day

Study no: B-1717
Volume # 30, and page #1
Conducting laboratory and location: ——

Date of study initiation: December 11, 1989
GLP compliance: yes (x) no ( )
QA report: yes (x) no ( )
Drug Memantine HCl, **lot #** R7979, **radiolabel** Not applicable, **and % purity** 100.3%
Formulation/vehicle: Admixture of test article in the diet

Methods (unique aspects):
Dosing:

Species/strain: Crj:CD(SD) rats
#/sex/group or time point (main study): 10/sex/dose
Satellite groups used for toxicokinetics or recovery: 6/sex/dose recovery animals
Age: 4 weeks
Weight: 169-200 g males and 125-150 g females
Doses in administered units: 0 (diet alone), 20, 90, 180 mg/kg/day; due to high incidence of animal loss at the high dose, the high dose was administered for 6 weeks with a 12 week recovery period in the recovery group
Route, form, volume, and infusion rate: Oral in the diet, continuous for 13 weeks

Observations and times:

Clinical signs: 2X daily
Body weights: Baseline and 2x weekly
Food consumption: Baseline and 2X weekly for a 3-4-day period
Drug intake: Calculated based on body weights, drug concentration in the feed, and food consumption
Ophthalmoscopy: Baseline and Dosing Weeks 4-5, 8-9, and 12-13, Recovery Week 5

EKG: Not done
Hematology: At terminal autopsy and after the recovery period
Clinical chemistry: At terminal autopsy and after the recovery period
Urinalysis: Dosing Weeks 5 and 13, and Recovery Week 5
Gross pathology: At termination of dosing (Week 13) and after 6-week recovery period
Organs weighed: At termination of dosing (Week 13) and after 6-week recovery period: see under Histopathology Inventory, below
Histopathology: At termination of dosing (Week 13) and after 6-week recovery period; see under Histopathology Inventory, below
Toxicokinetics: 0.5 ml serum samples at termination of dosing (Week 13)
Other:

Results:

Mortality: Deaths in 1 male at 90 mg/kg/day (Day 56), 12 males (1 accidental and 11 treatment-related) and 9 females (all treatment-related) at 180 mg/kg/day
Clinical signs: Signs in the animals that died included incisor malocclusion, hypersensitivity, decreased spontaneous movement, staggering gait, lateral or prone position, chromodacryorrhea, unkempt fur and emaciation (probably secondary to inadequate nourishment due to malocclusion). In the animals that survived, treatment-related clinical signs were observed at the 180 mg/kg/day dose, and included unkempt fur, emaciation, hypersensitivity, peri-genitourinary area smudge, and staggering gait; reversible in the recovery period except for unkempt fur and hypersensitivity in one male.
Body weights: Sporadic reduction of body weight gain in females at 20 mg/kg/day on Days 80 and 91, reduced body weight gain at 90 mg/kg/day in males (21% by Day 91) and females (27% by Day 91), and at 180 mg/kg/day in males (64% by day 66, too few animals to measure thereafter) and females (27% by Day 91); tended to increase at 90 mg/kg/day and increased at 180 mg/kg/day during the recovery period
Food consumption: Reduced at 90 mg/kg/day and 180 mg/kg/day during dosing; increased compared to controls during the recovery period at both doses
Drug intake: The results of the drug intake calculations, based on body weights, concentration in the feed and food consumption, are presented in the following table:

Mean Drug Intake in Rats Administered Memantine in the Diet for 13 Weeks

Theoretical Dose (mg/kg/day)	Mean Memantine Intake (mg/kg/day ± S.D.) in Males	Mean Memantine Intake (mg/kg/day ± S.D.) in Females
20	19.2 ± 0.6	19.1 ± 1.2
90	84.3 ± 5.9	87.6 ± 2.9
180	161.2 ± 5.1	153.5 ± 4.2

Ophthalmoscopy: Treatment-related changes in the cornea: the results of the ophthalmological examination are presented in the following table:

Results of the Ophthalmological Investigation in Rats Administered Memantine HCl in the Diet for 13 Weeks

Dose (mg/kg/day)	Males	Females
0	Unilaterally striate opacity in 1M (Wk 5) Unilaterally punctate opacity in whole cornea in 1M (Wk 8)	No effects

20	Unilateral membranous/striate opacity in 1M (Wk 5) Unilateral punctate opacity in whole cornea in 1M (Wks 8,12) Unilateral membranous opacity in whole cornea in 1M (Wk 12)	Unilateral membranous/striate opacity in 1F (Wk 8)
90	Unilateral punctate opacity in whole cornea in 1M (Wk 5) Unilateral punctate opacity in whole cornea with bilateral opacity and vascularization in 1 M (Week 8, 12) Unilateral punctate opacity in whole cornea in 1M (Wk 12)	Bilateral punctate opacity in whole cornea in 1F (Wks 8, 12) Unilateral punctate opacity in whole cornea in 1 F (Wk 12)
180	Punctate opacity in whole cornea in 5/15 M (Wk 5, bilateral in 2 M) Punctate opacity in whole cornea in 5/6 M (Wk 8, bilateral in 5 M) Not reversible in 4 M after 6-wk recovery Reversed in 2/4 recovery males by recovery Wk 12 Focal adhesion of cornea and iris in 1M during dosing Focal detachment of iris with hemorrhage in 1M during recovery	Punctate opacity in whole cornea in 6/16 F (Wk 5, bilateral in 3 F) Punctate opacity in whole cornea in 7/8 F (Wk 8, bilateral in 5 F) Bilateral punctate opacity in whole cornea (1 w/unilateral vascularization of cornea) in 2 F (Wk 12) Not reversible in 6 F after 6-wk recovery Reversed in 5 F after 12-wk recovery

Electrocardiography: Not done

Hematology:

End of 13-Week Dosing Period: At 90 mg/kg/day: Increased hemoglobin and hematocrit in males, decreased WBC in males and females, decreased lymphocytes and increased segmented neutrophils in males; At 180 mg/kg/day were the above changes and increased RBC and decreased reticulocytes in the females

End of Recovery Period: Decreased lymphocyte ratio, increased segmented neutrophils in males and females at 90 mg/kg/day; Increased mean corpuscular volume in females at 180 mg/kg/day

Clinical chemistry:

End of 13-Week Dosing Period: Decreased triglyceride, calcium, total protein, urea nitrogen and increased A/G ratio, albumin fraction and alpha-2 globulin fraction and decreased alpha-1 globulin fraction in males at 90 mg/kg/day, decreased urea nitrogen, creatinine, and gamma globulin fraction in females at 90 mg/kg/day; increased GOT, GPT, and LDH, and decreased triglyceride, free fatty acid, glucose and total protein in the females at 180 mg/kg/day

End of Recovery Period: Decreased LDH, triglyceride, A/G ratio and albumin, and increased gamma globulin fraction in the females at 90 mg/kg/day, and decreased LDH, chloride in the females at 180 mg/kg/day when compared to controls

Urinalysis:

Dosing Week 5: Trend toward decreased pH, significant decrease in excretion of sodium potassium, chloride in males and females at 90 mg/kg/day, decreased specific gravity in males and females at 180 mg/kg/day

Dosing Week 13: Trend toward decreased pH in males and females, significant increase in urine volume and decreased specific gravity in males at 90 mg/kg/day, decreased pH and total excretion of sodium, potassium and chloride in females at 180 mg/kg/day

Recovery Week 5: Increased urine volume in males at 90 mg/kg/day

Organ weights:
End of Dosing Period: Increased relative lung weight in males and females at 90 mg/kg/day, slightly decreased absolute and relative thymus, spleen, ovary and uterus weights and increased absolute and relative lung weights in the females at 180 mg/kg/day, additional decreases in organ weights and increases in relative organ weights were attributed to decreased body weight
End of Recovery Period: Increased absolute and relative prostate weights in males at 90 mg/kg/day, decreased absolute and relative thymus weights in females and decreased absolute and relative testes and epididymides weights in the males at 180 mg/kg/day
Gross pathology:
Animals that died prior to scheduled necropsy: Malnutrition due to malocclusion of teeth, atrophy of thymus, spleen, mesenteric or cervical lymph nodes and seminal vesicle, discolored spleen, red spots on glandular stomach, swelling or white spots on kidneys, enlarged adrenals
Animals examined at the scheduled necropsy: Malnutrition, unkempt fur, atrophy of thymus, testes, seminal vesicle, prostate, and swelling of lung in 1 M, and swelling of ovaries in 1F, red eyeball in 1F at 90 mg/kg/day, unkempt fur, emaciation, atrophy of thymus, spleen, mesenteric lymph nodes, ovaries, and uterus in 1 F at 180 mg/kg/day,
Recovery animals: Atrophy of testes and epididymides in 2M at 180 mg/kg/day
Histopathology:
Animals that died during the study: Foam cells and degeneration/necrosis of muscle fiber in tongue and femur, foam cells in lamina propria mucosa of the duodenum, jejunum and ileum, uterus, lamina propria mucosa and vellel wall of the vagina, foam cells and atrophy of thymus and lymph nodes, foam cells in marginal zone and atrophy of white pulp in spleen, dilatation of renal tubules, vacuolation in renal tubular and urinary bladder epithelium, foam cells in glomeruli of kidneys, vessel wall of epididymis, and femoral muscle fibers, cytoplasmic vacuolation and eosinophilic round bodies in neurocytes in the cerebrum, cytoplasmic vacuolation of Kupffer's cells and hepatocytes in the liver, parenchymal cells of the pituitary and thyroid glands, adrenal cortical cells, Purkinje cells in the cerebellum, neurocytes of the spinal cord, epithelial cells of the trachea, bronchial epithelium, epithelium of the epididymis, Leydig cells of the testes, seminal vesicles and prostate, lutein cells of the ovaries, mucosal epithelium of the uterus and vagina, and eosinophilic materials and foam cells in alveoli, vacuolation in alveolar epithelium, cellular infiltration in alveolar septa, single cell necrosis of hepatocytes, atrophy of seminiferous tubules and epididymis, skin cells, eye ball lesions in the cornea, hypocellularity in bone marrow, of nearly all animals that died during the study, increased herring body-like material in hypothalamus in most females and some males, enlargement of chief cells/erosion of glandular stomach in 1-2 deaths,
20 mg/kg/day: Inflammatory cellular infiltration in substantia propria and calcium deposition in the cornea in 1M
90 mg/kg/day: Eosinophilic round bodies in neurocytes with increased Herring body materials in hypothalamus in 1 F, cytoplasmic vacuolation in cerebellum and spinal cord in 1M, eosinophilic material and foam cells in lung alveoli in 2M and 5F, foam cells and degeneration/necrosis in tongue in 1M, enlargement of chief cells in the stomach in 1 M, foam cells in lamina propria mucosa of duodenum in 1 M and 1F, adrenal enlargement with vacuoles in cortical cells in 1M, foam cells and atrophy of thymus, mesenteric lymph nodes and spleen in 1M, dilatation of renal tubules with vacuolation in the renal tubular epithelium and foam cells in the glomeruli of the kidney in 1M, cytoplasmic

vacuolation in the urinary bladder epithelium in 1M, cytoplasmic vacuolation in the Leydig cells and atrophy of seminiferous tubules in 1M, vacuolation of the epithelium of the epididymis with foam cells in vessel wall and atrophy in 1-3 M, vacuolation and atrophy in the seminal vesicle and prostate in 1M, vacuolation in the mucosal epithelium and foam cells in the lamina propria mucosa in the uterus in 3-4 F, atrophy of mammary gland in 1M, corneal lesions and swelling of pigment epithelium in 1M and 2F, foam cells and degeneration/necrosis of muscle fibers in 1M

180 mg/kg/day: Cytoplasmic vacuolation with eosinophilic round bodies in neurocytes of cerebrum in 1F, cytoplasmic vacuolation in cerebellum, pituitary, spinal cord, epithelial cells of trachea, parenchymal cells in thyroid in 1F, eosinophilic material and foam cells in lung alveoli in 1F, foam cells and degeneration/necrosis in tongue in 1F, enlargement of chief cells in the stomach in 1 F, foam cells in lamina propria mucosa of duodenum, jejunum, and ileum in 1F, cytoplasmic vacuolation of Kupffer's cells with single cell necrosis of hepatocytes in liver of 1F, adrenal enlargement with vacuoles in cortical cells in 1F, foam cells and atrophy of thymus, mesenteric lymph nodes and spleen in 1F, dilatation of renal tubules with vacuolation in the renal tubular epithelium and foam cells in the glomeruli of the kidney in 1M, cytoplasmic vacuolation in the urinary bladder epithelium in 1F, vacuolation in the lutein cells of the ovaries and mucosal epithelium of the uterus and vagina in 1F, thin/atrophied skin in 1F, corneal lesions and swelling of pigment epithelium in 1F, hypocellularity in bone marrow in 1F, foam cells and degeneration/necrosis of muscle fibers in 1F

Recovery animals: Foam cells in the lung alveoli in 4/6 F at 90 mg/kg/day

Toxicokinetics: The results of the serum memantine measurements are presented in the following table:

Serum Memantine in Rats Administered Memantine in the Diet for 13 Weeks

Group	Dose (mg/kg/day)	Sex	Serum Memantine (ng/ml)
1	0	M F	- -
2	20	M F	92 164
3	90	M F	1136 1388
4	180	M F	5819 3391

Study title: Subacute, oral toxicity study on D 145 in the dog (3 months)

Key study findings:

- Tremor, apathy, slight dehydration after dose escalations in the high dose group (incremental from 5 to 10 mg/kg/day)
- Body weight gain reduced 20% at 2 mg/kg/day, 14% at 5 mg/kg/day, 74% at 10 mg/kg/day
- Opal turbidity of the cornea at 2 months of dosing, lasted through study termination, at 10 mg/kg/day
- Slight edema in the hypophysis and small Langerhans islets with incipient fibrosis in one high dose female

- Doses represented up to 16X the MRHD of 20 mg in a 60 kg patient on a BSA basis
- NOAEL between 5 and 10 mg/kg/day

Study no: — 3-2-171-72
Volume # 17, and page # 129
Conducting laboratory and location: ———

Date of study initiation: Report date May 1973
GLP compliance: yes ( ) no (x)
QA report: yes ( ) no (x)
Drug D 145 (Merz & Co.), **lot #** Not provided, **radiolabel** Not applicable, **and % purity** Not provided
Formulation/vehicle: Test article in gelatin capsules

Methods (unique aspects):
Dosing:

Species/strain: Preliminary study: Crossbreed dogs; Main study: Beagle dogs
#/sex/group or time point (main study): 1/sex/dose in the 3-week preliminary (range finding) study, 2/sex/group in the main experiment
Satellite groups used for toxicokinetics or recovery: None
Age: Not provided
Weight: Preliminary study: 8 kg; Main study: 7-9 kg
Doses in administered units: Dose range-finding study: 2, 5, and 10 mg/kg/day; main study: 0, 2, 5, and 10 mg/kg/day; high dose dogs were administered 5 mg/kg/day for the first 5 days of treatment, followed by 7 mg/kg/day, and then increasing by 1 mg/kg/day every 4 days to a maximum dose of 10 mg/kg/day for the remainder of the study
Route, form, volume, and infusion rate: Oral in gelatin capsules, once daily, 5 days/week

Observations and times: The following observations were made in the 3-week preliminary experiment: clinical signs, mortality, body weights, food and water consumption, gross necropsy, and organ weights. The following observations were made in the 3-month toxicology study:

Clinical signs: Daily
Body weights: Weekly
Food consumption: Weekly
Ophthalmoscopy: 14-day intervals
EKG: End of dosing period
Hematology: Baseline, after 2 months dosing, and end of study
Clinical chemistry: Baseline, after 2 months dosing, and end of study
Urinalysis: Baseline, after 2 months dosing, and end of study
Gross pathology: Cranial, abdominal, thoracic cavities
Organs weighed: Heart, liver, brain, spleen, kidneys, adrenals, thyroids, gonads (prostate and testicles, or uterus and ovaries)
Histopathology: Cerebrum, cerebellum, hypophysis, spinal cord, thyroid, heart, aorta, lung, stomach, colon, duodenum, bladder, gonads (ovary, testicles, epididymides, uterus, prostate), muscle, bone ~~marrow~~, kidneys, adrenals, stomach, pancreas, spleen, gall bladder, liver, lymph nodes (mesenteric and cervical)
Toxicokinetics: Not done

Other: None

Results:

Dose range-finding study:

The results of the preliminary, 3-week, dose range-finding study showed deaths in both high dose (10 mg/kg/day) animals on treatment day 6. The high dose dogs displayed decreased food consumption, increased water consumption, salivation, tremor, decreased respiration and tonoclonic spasms after 4 days of treatment. The necropsy showed congested duodenal blood vessels in the high dose dogs. There were no treatment-related effects on body weights and organ weights. The NOAEL was <10 mg/kg/day.

Main Study:

Mortality: No deaths
Clinical signs: Tremor and apathy after each dose escalation in the high dose group, slight dehydration indicated by increased latency to smoothing of the coat when back skin lifted
Body weights: Dose-related decrease in body weight gain (20%, 14%, and 74% at 2, 5, and 10 mg/kg/day, respectively), significant at the high dose in weeks 1-4, 9-12, and 1-12
Food consumption: No treatment-related effects
Ophthalmoscopy: Opal turbidity of the cornea at 2 months lasting through study termination at the high dose
Electrocardiography: No treatment-related effects
Hematology: No treatment-related effects
Clinical chemistry: No treatment-related effects
Urinalysis: No treatment-related effects
Organ weights: No treatment-related effects
Gross pathology: No treatment-related effects
Histopathology: Slight edema in the hypophysis in the HDF, small Langerhans islets with incipient fibrosis in HDF, remaining findings (e.g., fine-droplet fatty degeneration in the heart, subintimal relaxation in the aorta, interstitial pneumonia, liver RHS activation, fat deposition in cortical zone cells in adrenal) were observed in controls and treated dogs to a similar extent
Toxicokinetics: Not done

Study title: Memantine 13-week oral toxicity study in baboons with a 4-week withdrawal period

Key study findings:

- Treatment-related vomiting (HD, first day), dose-related quietness, nervousness, huddled posture, glazed eyes, ptosis, unsteadiness, and limb tremors
- Quietness, piloerection loss of appetite at HD during recovery, suggested mild withdrawal
- Body weights reduced slightly (2%-13%, dose-related, Wk 1), reduced overall in all treated males (12%-23% without dose-relationship) and MD (29%) and HD (19%) females throughout the study, no effect on body weight gain compared to controls
- Food consumption reduced in males (6%-25%, not dose-related, Wk 1) and females (10%-34%, dose-related, Wk 1), slightly reduced when averaged over 13-week dosing period in the males (4%-11%, not dose-related) and females (0.3%-5%, not dose-related)

- Hematology: PT increased 8%-16% (not dose-related, males and females combined, Wk 13)
- Urine volume decreased in Wk 13 at HD (24%).
- Decreased absolute adrenal weights (33% at MD, 21% at HD), increased absolute thyroid weights (47% at MD, 47% at HD), decreased absolute kidney weights (16% at HD)
- TK analysis confirmed memantine absorption, mean memantine plasma concentrations in Wk 7 below limit of detection at LD, 22.4 and 14.0 mcg/l in the MD males and females, respectively, and 102.4 and 49.9 mcg/l in the HD males and females, respectively; At 24 hours after last dose, mean plasma memantine levels below the level of detection at LD and MD, and 94.6 and 37.7 mcg/l in HD males and females, respectively
- Plasma and organ memantine concentrations 2X higher in males than in females
- No increase in plasma memantine with repeated dosing for 13 wks
- Memantine concentrations high in bile and urine
- Organ memantine concentrations highest in lung, liver and eye, lower concentrations in brain, spinal cord, lacrimal gland, parotid gland, and saliva, in order of decreasing concentration; Memantine found only in eye after the recovery period.
- No definitive organs of toxicity identified
- The baboons tolerated memantine HCl well at up to 8 mg/kg/day (13X the MRHD of 20 mg in a 60 kg patient on a BSA basis) by the oral route for 13 wks

Study no: PTX 46/861238
Volume # 36, and page # 78
Conducting laboratory and location:

Date of study initiation: February 5, 1986
GLP compliance: yes (x) no ( )
QA report: yes (x) no ( )
Drug Memantine HCl, **lot #** R 7979, **radiolabel** Not applicable, **and % purity** 100%
Formulation/vehicle: Test article dissolved in distilled water, concentrations confirmed by chemical analysis in Weeks 1, 6, and 13

Methods (unique aspects):
Dosing:

Species/strain: Wild-caught baboons (*Papio sp.*,

#/sex/group or time point (main study): 3/sex/dose
Satellite groups used for toxicokinetics or recovery: 2/sex/group recovery (HD only)
Age: 2-4 years
Weight: 4.1-6.5 kg
Doses in administered units: 0, 2, 4, and 8 mg/kg/day
Route, form, volume, and infusion rate: Oral by gastric intubation, at 4 ml/kg, once daily for 13 weeks

Observations and times:

Clinical signs: Daily
Body weights: Weekly
Food consumption: Daily
Ophthalmoscopy: Baseline and during Weeks 6, 13, and end of recovery period

EKG: Not done
Hematology: Baseline and Weeks 6 and 13, and end of recovery period
Clinical chemistry: Baseline and Weeks 6 and 13, and end of recovery period
Urinalysis: 16-h collection periods at baseline and Weeks 6 & 13, and end of recovery
Gross pathology: at 13 weeks
Organs weighed: at 13 weeks, see under Histopathology Inventory, below
Histopathology: Bone marrow examination, at 13 weeks; histopathology at 13 weeks, see under Histopathology Inventory, below
Toxicokinetics: Blood withdrawn (4 ml) 24 hours after dosing in Weeks 6, and 13, and in Weeks 2 and 4 of the recovery period
Other: Determination of tissue memantine levels, at necropsy

Results:

Mortality: No deaths
Clinical signs: Treatment-related vomiting (predominantly on Day 1 in HD animals), quietness (% incidence as percent total number of doses during dosing period: 5.49, 25.09, 52.38, and 79.56% at 0, LD, MD, and HD, respectively), nervousness (0.73, 1.10, 3.48, and 18.02% at 0, LD, MD, and HD, respectively), huddled posture (0.18, 2.56, 4.58, and 14.84% at 0, LD, MD, and HD, respectively), glazed eyes and ptosis (0, 2.93, 53.48, and 88.90% at 0, LD, MD, HD, respectively), unsteadiness and limb tremors (0.18, 0.18, 10.07, and 22.64% at 0, LD, MD, and HD, respectively); during recovery quietness (HD), piloerection (HD), loss of appetite (HD); no treatment-related effects on rectal temperature
Body weights: Reduced at LD (4%, Week 1), MD (2% and 5% in males and females, respectively, Week 1) and HD (8% 13% in males and females, respectively, Week 1), reduced at end of study (mean of weeks 0-13) 23%, 16%, and 12% in LD, MD, and HD males, respectively, compared to controls and 29% and 19% in MD and HD females, respectively, compared to controls; no statistically significant treatment-related effects on overall body weight gain during study
Food consumption: Reduced during Week 1 at LD (25% in males and 10% in females), MD (9% in males, 11% in females) and HD (6% in males, 34% in females); overall mean food consumption in weeks 1-13 was decreased 11%, 5%, and 4% in LD, MD, and HD males, respectively, and 2%, 0.3%, 5% in LD, MD, and HD females, respectively; reduced in 1 male during first recovery week
Ophthalmoscopy: No treatment-related effects
Electrocardiography: Not done
Hematology: No treatment-related effects in Week 6 and after the recovery period; In Week 13 increased PT at 2 (16%), 4 (8%) and 8 (14%) mg/kg/day
Clinical chemistry: No treatment-related effects during dosing and after recovery
Urinalysis: No treatment-related effects in Week 6 and after recovery period; in week 13 decreased urine volume at 8 (24%) mg/kg/day, decreased pH at 8 mg/kg/day (6%)
Organ weights: Decreased absolute adrenal weights (33% at 4 mg/kg/day, 21% at 8 mg/kg./day), increased absolute thyroid weights (47% at 4 mg/kg/day, 47% at 8 mg/kg/day), decreased absolute kidney weights (16% at 8 mg/kg/day); decreased relative adrenal weight (30% at 4 mg/kg/day, 19% at 8 mg/kg/day), kidney (12% at 2 and 8 mg/kg/day) and increased relative thyroid (22% at 2, 58% at 4, and 52% at 8 mg/kg/day); however relative organ weight differences from controls not statistically significant; no treatment-related differences in organ weights after the recovery period

Gross pathology: No treatment-related effects
Histopathology: No treatment-related effects on bone marrow; No treatment-related effects in the microscopic pathology examination
Toxicokinetics: Mean memantine plasma concentrations in Week 7 were below the limit of detection in the LD groups, 22.4 and 14.0 mcg/l in the MD males and females, respectively, and 102.4 and 49.9 mcg/l in the HD males and females, respectively. At 24 hours after the last dose, the mean plasma memantine levels were below the level of detection at 2 and 4 mcg/l, and 94.6 and 37.7 mcg/l in the HD males and females, respectively. Plasma and organ memantine concentrations 2X higher in males than in females; no increase in plasma memantine was observed with repeated dosing for 13 weeks.

Memantine concentrations were high in bile and urine. Organ memantine concentrations were highest in lung, liver and eye, and lower concentrations were found in brain, spinal cord, lacrimal gland, parotid gland, and saliva, in order of decreasing concentration. After the 4-week recovery period, memantine was found only in the eye.

Study title: Six month chronic oral toxicity study of NEU 3004 in the rat

Key study findings:

- Treatment-related clinical signs: increased mucoid feces, corneal opacities, red eye discharge, and swollen eye region
- Treatment-related reduction in mean body weights at 20 and 40 mg/kg/day in males (7% and 12%, respectively) and females (9% and 11%, respectively)
- Dose-related reduction of body weight gain by 12% and 21% in the males at 20 and 40 mg/kg/day, respectively, by 17%, 23%, and 26% in the females at 10, 20 and 40 mg/kg/day, respectively
- Food consumption increased in males and females at 20 and 40 mg/kg/day
- Increase in glucose (8%-19% in HD males and females on Days 22 and 183), alkaline phosphatase (15%-23% in MD and HD males on days 92 and 183), A/G ratio (8%-30% in the MD and HD males on days 183 and 211), phosphorus (8%-21% in the MD and HD males and females on days 92 and 183), and decreased creatinine (8% in the HD males on days 183 and 211)
- No treatment-related effects in the hematology, urinalysis, gross and microscopic examinations
- Decreased absolute and relative (to brain weight) spleen weight (19%-35%) in the MD and HD males rats compared to controls at 13-weeks, increased absolute and relative (to body weight) kidney (13%-21% in HD males) and relative (to body weight) liver (10% in HD males) weights, and decreased absolute and relative (to brain weight) spleen (18%-22% in HD females) and absolute and relative (to brain weight) thyroid (29%-33% in HD females) weights; no treatment-related effects on organ weights in recovery animals
- Dose proportional increase in plasma concentration, accumulation with increasing duration of treatment, no differences in plasma concentrations in males and females
- NOAEL 10 mg/kg/day NEU 3004 in males, not established in females (<10 mg/kg/day)
- No definitive target organs of toxicity identified, clinical chemistry and organ weight changes were of small magnitude, and not consistent across timepoints or sexes

- Doses studied (10-40 mg/kg/day) represented 5X to 19X the MRHD of 20 mg/day in a 60 kg patient on a BSA basis

Study no: —— ; Study No. N002171A
Volume # 30, and page # 96
Conducting laboratory and location: ——

Date of study initiation: June 25, 1996
GLP compliance: yes (x) no ( )
QA report: yes (x) no ( )
Drug NEU 3004, **lot #** 960029, **radiolabel** Not applicable, **and % purity** Not provided
Formulation/vehicle: Test article dissolved in Sterile Water

Methods (unique aspects):
Dosing:

Species/strain: Sprague Dawley rats ——
#/sex/group or time point (main study): 18/sex/group (6/sex/group in the 3-month evaluation, and 12/sex/group in the 6-month evaluation)
Satellite groups used for toxicokinetics or recovery: 6/sex/group for toxicokinetic evaluation
Age: 7-8 weeks at start of dosing
Weight: 232.0-300.3 g males and 185.8-253.8 g females
Doses in administered units: The dosing schedule is presented in the following table:

Dosing Schedule in the 6-Month Toxicology Study in Rats

Group	Study Week	Dose (mg/kg/day)	N 3-Month Evaluation		N 6-Month Evaluation		N Toxicokinetic Evaluation	
			Males	Females	Males	Females	Males	Females
1	Weeks 1-26	0	6	6	12	12	6	6
2	Week 1 Week 2 Week 3 Weeks 4-26	0.8 2.5 5.0 10.0	6	6	12	12	6	6
3	Week 1 Week 2 Week 3 Weeks 4-26	2.5 5.0 10.0 20.0	6	6	12	12	6	6
4	Week 1 Week 2 Week 3 Weeks 4-26	5.0 10.0 20.0 40.0	6	6	12	12	6	6

Route, form, volume, and infusion rate: Oral by gavage at 4 ml/kg, once daily for 6 months (concentrations of 0.2, 0.625, 1.25, 2.5, 5.0, and 10.0 mg/ml at 0.8, 2.5, 5.0, 10.0, 20.0, and 40.0 mg/kg dose)

Observations and times:

Clinical signs: 2X daily, prior to dosing and 1-2 hours post-dose
Body weights: Baseline, Day 1, and weekly thereafter

Food consumption: Weekly
Ophthalmoscopy: Baseline and Week s 13, 26, and 30
EKG: Not done
Hematology: Baseline, Week 4, prior to necropsy in Weeks 14, 27, and 31
Clinical chemistry: Baseline, Week 4, prior to necropsy in Weeks 14, 27, and 31
Urinalysis: Baseline, Week 4, prior to necropsy in Weeks 14, 27, and 31
Gross pathology: Week 14 (3-month groups), Week 27 (6-month evaluation), and Week 31 (Recovery groups)
Organs weighed: See under Histopathology Inventory, below
Histopathology: See under Histopathology Inventory, below
Toxicokinetics: 1 ml blood samples from the retro-orbital sinus at 1 hour post-dose in Weeks 4, 13, 26, and 30
A separate study was conducted in male and female Crl:CD®(SD)BR [redacted] rats with identical administration at the same doses (up to 10, 20, and 40 mg/kg/day) for 5 weeks, to determine the toxicokinetic profile at the doses used in this study (see Study to Develop the Toxicokinetic profile of NEU 3004 in the Rat using the Oral Route of Administration, Study # MPI 775/001, Vol. 65, p. 1). The rats (n=3/sex/timepoint/dose) were bled (1 ml) at 0.5, 1, 2, 4, 8, 12, and 24 hours after dosing in Week 5
Other: None

Results:

Mortality: 6 deaths: 1M and 1F control (both on Day 22, due to trauma), 1F at 10 mg/kg/day on Day 100, 1M and 1F at 20 mg/kg/day on Days 184 and 85 (sacrificed), 1F at 40 mg/kg/day on day 26; no deaths considered related to treatment with test article
Clinical signs: Treatment-related increase in mucoid feces, corneal opacities, red eye discharge and swollen eye region
Body weights: Reduced mean body weights at 20 mg/kg/day (up to 7% in Males on Days 29-92 and 141-183, and up to 9% in Females on Days 85, 141, 155, and 162) and 40 mg/kg/day (up to 12% in Males on Days 29-197, and up to 11% in Females on Days 36-183). Reduced body weight gain at 10 mg/kg/day (up to 17% in Females on Days 113, 141, 148, and 162), 20 mg/kg/day (up to 13% in Males on Days 29-183 and up to 23% in Females on Days 43-183) and 40 mg/kg/day (up to 21% in Males on Days 8-204, and up to 26% in Females on Days 29-183)
Food consumption: Increased at 20 mg/kg/day (Males on Days 50-113 and 155-183, and Females on Days 64-92 and 190-197), and at 40 mg/kg/day (Males on Days 57-99, and Females on Days 64, 78, 92, and 155-211)
Ophthalmoscopy: No treatment-related effects
Electrocardiography: Not done
Hematology: The results of the hematology measurements are presented in the following table:

Hematology Results in Rats Administered NEU 3004 by Oral Gavage Once Daily for 6 Months*

Parameter	10 mg/kg/day	20 mg/kg/day	40 mg/kg/day
Basophils (10^3/mcL)		100%↑, M, Day 92	100%↑, M, Day 183
Monocytes (10^3/mcL)			203%↑, M, Day 183 74%↑, F, Day 92
Eosinophils (10^3/mcL)	[redacted]		32%↓, M, Day 183
Neutrophils (10^3/mcL)		20%↓, F, Day 183	

Lymphocytes (10^3/mcL)	5%↑, F, Day 183		
Platelets (10^3/mcL)			10%↓, F, Day 22
Activated Partial Thromboplastin times (sec)	18%↑, F, Day 92	16%↑, F, Day 92 17%↓, M, Day 183	

*Values represent differences from control values; M=males and F=females

Clinical chemistry: The results of the serum chemistry measurements are presented in the following table:

Serum Chemistry Results in Rats Administered NEU 3004 by Oral Gavage Once Daily for 6 Months*

Parameter	10 mg/kg/day	20 mg/kg/day	40 mg/kg/day
Glucose (mg/dL)			8%↑M, Day 22 9%%↑F, Day 22 10%↑M, Day 183 19%↑F, Day 183
Aspartate Aminotransferase (IU/L)		15%↓F, Day 22 19%↓F, Day 92	11%↓F, Day 22
Alanine Aminotransferase (IU/L)	21%↑M, Day 211	21%↓F, Day 22 27%↓F, Day 92	
Alkaline Phosphatase (IU/L)		15%↑M, Day 92 19%↑M, Day 183	18%↑M, Day 92 23%↑M, Day 183
Creatine Kinase (IU/L)		47%↓F, Day 22	
Blood Urea Nitrogen (mg/dL)		8%↑M, Day 92 8%↑M, Day 183	7%↓F, Day 22 13%↓F, Day 92 8%↑M, Day 92
Total Protein (g/dL)	4%↑F, Day 22		4%↑F, Day 22
Albumin (g/dL)			4%↑F, Day 22
Triglycerides (mg/dL)			30%↑F, Day 92
A/G Ratio		30%↑M, Day 211	8%↑M, Day 183 28%↑M, Day 211
Creatinine (mg/dL)	8%↓M, Day 183		8%↓M, Day 183 8%↓M, Day 211
Cholesterol (mg/dL)		20%↓F, Day 183	
Indirect Bilirubin (mg/dL)		100%↑F, Day 211	
Chloride (mEq/L)	2%↑M, Day 183		2%↓F, Day 22 2%↓F, Day 92
Calcium (mg/dL)	5%↑M, Day 183	3%↑M, Day 183	3%↑F, Day 92
Phosphorus (mg/dL)		8%↑F, Day 92 11%↑M, Day 183 14%↑F, Day 183	7.5%↑M, Day 92 12%↑F, Day 92 21%↑F, Day 183
Sodium (mEq/L)	2%↑M, Day 183 1%↑F, Day 183		

*Values represent differences from control values; M=males and F=females

Urinalysis: The results of the urinalysis measurements are presented in the following table:

Urinalysis Results in Rats Administered NEU 3004 by Oral Gavage Once Daily for 6 Months*

Parameter	10 mg/kg/day	20 mg/kg/day	40 mg/kg/day
pH	5%↓M, Day 22 10%↓F, Day 22	4%↓M, Day 22 11%↓F, Day 22 7%↓F, Day 92	16%↓F, Day 22
Specific gravity	1%↑M, Day 22 1%↑F, Day 22	1%↑M, Day 22 1%↑F, Day 22 1%↑F, Day 92 1%↑F, Day 211	1%↑M, Day 22 1%↑F, Day 22 1%↑F, Day 211
Sodium	65%↑M, Day 22 37%↑F, Day 22 53%↑M, Day 92 71%↑M, Day 183	81%↑M, Day 22 50%↑M, Day 92 75%↑M, Day 183	108%↑M, Day 22
Potassium	50%↑M, Day 22 34%↑F, Day 22	36%↑M, Day 22 61%↑F, Day 211	24%↓M, Day 183 58%↑F, Day 211
Volume	45%↓M, Day 22 29%↓F, Day 22	35%↓M, Day 22	36%↓M, Day 22 50%↑M, Day 183
Crystals			100%↑M, Day 22
Epithelial Cells	100%↑F, Day 92	100%↑F, Day 22 500%↑M, Day 183	300%↑F, Day 92 400%↑M, Day 183 137%↑F, Day 183
Mucus	100%↑F, Day 22	100%↑F, Day 22	100%↑F, Day 22

*Values represent differences from control values; M=males and F=females

The changes in urinalysis parameters are attributed to changes in hydration status in the rats, due to absence of changes in urea, nitrogen and creatinine, the small magnitude of the observed changes, and absence of consistency of the changes across dose groups, measurement times, and gender groups.

Organ weights: The results of the organ weight measurements are presented in the following table:

Changes in Organ Weights in Rats Administered NEU 3004 Daily by Oral Gavage for 3 and 6 Months*

Organ	10 mg/kg/day	20 mg/kg/day	40 mg/kg/day
13-Week Necropsy			
Spleen		23%↓absolute, M 25%↓relative to brain, M	36%↓absolute, M 35%↓relative to brain, M 19%↓relative to brain, F
26-Week Necropsy			
Kidney	12%↑ relative to BW, M		13%↑absolute, M 13%↑relative to brain, M 21%↑ relative to BW, M
Spleen			18%↓absolute, F 22%↓relative to brain, F
Thyroid			29%↓absolute, F 33%↓relative to brain, F
Liver	9%↑ relative to BW, M		10%↑ relative to BW, M

Recovery Groups			
Thyroid		67%↑absolute, M 67%↑relative to brain, M 100%↑relative to BW, M	

*Values represent differences from control weights; M=males and F=females; BW=body weight

Gross pathology: In the rats that died during the treatment period, the gross observations were swollen feet (1 rat), enlarged liver and spleen (1 rat), discolored eye (1 rat), fluid in the abdominal cavity (1 rat), enlarged right atrium of the heart (1 rat) and opaque discoloration of the eye (2 rats); no treatment-related gross observations in the rats sacrificed at the 3-month timepoint; at 6 months, the observations were liver abnormalities (deformities/nodules, 2HDM, 1HDF), cysts on the mammary gland (1 HDF); sporadic observations in the recovery groups indicated no irreversible or delayed treatment-related macroscopic effects

Histopathology: There were no treatment-related histopathology findings in the rats examined at 3 months; in the rats sacrificed at 6 months, chronic liver inflammation was observed in 1 high-dose female, and thyroid follicular adenoma in 1 high-dose female; retinal detachment was observed in 1 high-dose female, and chronic heart inflammation in 1 mid-dose male and 1 high-dose female

Toxicokinetics: Plasma NEU 3004 concentrations observed in the main study are presented in the following table:

Plasma NEU 3004 Concentrations in Rats Treated for 6 Months*

Dose (mg/kg/day)	Time (Weeks)							
	Male Rats				Female Rats			
	4	13	26	30	4	13	26	30
Vehicle	8.13±11.1	0	0	0	3.57±3.11	0	0.72±1.24	0.46±1.13
10	437±150	654±124	806±171	0	571±193	829±157	985±281	0
20	886±210	1306±467	1545±383	0	1184±350	1339±379	2063±642	0
40	1531±171	2271±312	2371±312	0	2029±1067	1839±886	2386±1203	0

*Values represent group means ± S.D.; samples collected at 1-hour post-dose

The results of the toxicokinetic study are presented in the following table:

Toxicokinetics of NEU 3004 in Rats (Week 5)

Parameter	10 mg/kg/day		20 mg/kg/day		40 mg/kg/day	
	Males	Females	Males	Females	Males	Females
Tmax (h)	0.5	0.5	1	2	2	2
Cmax (ng/ml)	369	833	1206	1331	1481	3010
T1/2 (h)	3.0	2.7	3.2	3.6	4.3	3.8
AUC (1-8 h)	1298	2776	4888	6151	8437	17260
AUC (0-24 h)	1808	3782	NC*	NC	12950	27344
Cmax/Dose	37	83	60	67	37	75
AUC(1-8h)/Dose	130	278	244	308	211	432
AUC(0-24h)/Dose	181	378	NC	NC	324	684

*NC: not calculated

At steady state (5 weeks) the NEU 3004 peak plasma concentrations and exposure (AUC values) were higher in the females than in the males. Plasma concentrations and exposure increased approximately proportionally with dose. Absorption was rapid, with peak plasma levels attained

by 0.5-2 hours. The half life of NEU 3004 was approximately 3-4 hours, slightly higher at the high dose of 40 mg/kg/day.

Study title: Six-month chronic oral toxicity study of NEU 3004 in dogs

Key study findings:

- 1 HD male found dead (Wk 24), and 1 HD male euthanized *in extremis* (Wk 16)
- Clinical signs in dogs that died and were sacrificed: incoordination, pacing, nervousness, rapid respiration, chomping, hypoactivity, tonic rigidity, prostration, and vocalization, with convulsions 4 hours after dosing (dog found dead) and unremitting convulsions (euthanized dog)
- Gross pathology: dark red GI contents in dog that was found dead, pituitary cyst in dog that was euthanized
- No treatment-related clinical signs or effects on body weights, food consumption, ophthalmoscopy and electrocardiography examinations, clinical pathology (hematology, clinical chemistry, urinalysis), and necropsy evaluations (organ weights, gross pathology, histopathology) in the dogs that survived to the end of the study
- No differences in kinetics between males and females, increase in exposure slightly greater than dose-proportional, no differences in exposure with repeated dosing from Weeks 3 through 25, no accumulation and no induced metabolism
- Main target organ of toxicity: CNS, based on the convulsions induced in 2 high dose dogs (18 mg/kg/day, 29X the MRHD of 20 mg in 60 kg patient on BSA basis, AUC = 15002 ng.h/ml, Cmax = 1278 ng/ml)
- NOAEL 9 mg/kg/day (15X the MRHD of 20 mg in a 60 kg patient on a BSA basis, AUC = 5902 ng.h/ml, Cmax = 587 ng/ml)

Study no: [redacted]-244006
Volume # 18, and page # 1
Conducting laboratory and location: [redacted]

Date of study initiation: June 21, 1996
GLP compliance: yes (x) no ( )
QA report: yes (x) no ( )
Drug NEU 3004, **lot #** 960029 and 960045, **radiolabel** Not applicable, **and % purity** >99%
Formulation/vehicle: Test article in [redacted] gelatin capsules

Methods (unique aspects):
Dosing:

Species/strain: Beagle dogs [redacted]
#/sex/group or time point (main study): 6/sex/dose
Satellite groups used for toxicokinetics or recovery: 2/sex/dose
Age: Approximately 6 months
Weight: Mean weights 7.9-8.1 kg males and 6.9-7.1 kg females at start of dosing
Doses in administered units: The following dosing schedule was used:

Study Week	Dosing Week	Low Dose (mg/kg/day)	Mid-Dose (mg/kg/day)	High Dose (mg/kg/day)
0	1	0.25	0.75	1.5
1	2	0.75	1.5	3.0
2	3	1.5	3.0	6.0
3-9	4-10	3.0	6.0	12.0
10	11	3.0	9.0	15.0
11-25	12-26	3.0	9.0	18.0

Empty capsules administered as negative control (0 mg/kg/day) article.

Route, form, volume, and infusion rate: Oral by capsule, once daily for 6 months

Observations and times:

Clinical signs: 2X daily
Body weights: Baseline and weekly
Food consumption: Baseline and daily, reported as weekly averages
Ophthalmoscopy: Baseline and Week 25
EKG: Baseline and Week 25, 4 hours after dosing
Hematology: Baseline, Weeks 3, 12, 25, and 29
Clinical chemistry: Baseline, Weeks 3, 12, 25, and 29
Urinalysis: Baseline, Weeks 3, 12, 25, and 29
Gross pathology: External surface, all orifices, cranial, thoracic, abdominal and pelvic cavities and contents
Organs weighed: See under Histopathology Inventory, below
Histopathology: See under Histopathology Inventory, below
Toxicokinetics: Pre-dose and 0.5, 1, 2, 4, 8, 12, and 24 hours after dosing in Weeks 3 and 12; additional blood draws at 30, 48 and 72 hours in the recovery animals
Other: None

Results:

Mortality: 1 HD (18 mg/kg/day) male found dead in Week 24, associated with incoordination, prostration, shallow respiration, convulsions observed in this dog at 4 hours after dosing in Week 16; 1 HD (18 mg/kg/day) male euthanized *in extremis*, showing incoordination, pacing, nervousness, rapid respiration, chomping, tonic rigidity, hypoactivity, prostration, vocalization, periods of convulsions, episode of unremitting convulsions
Clinical signs: No treatment-related effects
Body weights: No treatment-related effects
Food consumption: No treatment-related effects
Ophthalmoscopy: No treatment-related effects
Electrocardiography: No treatment-related effects
Hematology: Decreased absolute lymphocyte count in 6/9 mg/kg/day females in Week 3, increased mean percent lymphocyte count in 12/18 mg/kg/day females in Week 25 compared to controls (no change from baseline); after 4-week recovery: decreased WBC at LD, MD, and HD males and increased MCHC in MD females; no changes attributed to effects of treatment
Clinical chemistry: Increased mean cholesterol and lactate dehydrogenase in males at 12 and 18 mg/kg/day in Weeks 3, 12, and 25 compared to controls (no change from

baseline), no changes in clinical chemistry parameters considered to be treatment-related
Urinalysis: Increased sodium in MD females and HD males and females in Week 3, Increased urine volume and decreased sodium in the MD females in Week 29 (after recovery); no changes considered to be treatment-related
Organ weights: Increased relative (to body weight) lung weight in the MD females at 26 weeks (no differences in absolute lung weights, no effects at the high dose or in the male dogs), decreased absolute thyroid weights in the MD females (no differences in the relative thyroid weights, and no effects at the HD or in the male dogs); No changes in organ weights attributed to treatment
Gross pathology: dark red gastrointestinal tract contents in the HD male that was found dead, pituitary cyst in the HD dog that was euthanized *in extremis*; no treatment-related effects in the dogs that survived to the scheduled Week 26 and Week 30 necropsies
Histopathology: No treatment-related findings in the HD male dogs found dead or euthanized *in extremis*; No treatment-related effects in the dogs that survived to scheduled Week 26 and Week 30 necropsies
Toxicokinetics: The results of the toxicokinetic analysis are presented in the following table:

Results of Toxicokinetic Analysis in Dogs Administered Oral Memantine HCl for 6 Months*

Parameter	Low Dose	Mid-Dose	High Dose
	Week 3		
	3 mg/kg/day	**6 mg/kg/day**	**12 mg/kg/day**
Tmax (h)	3.8 ± 4.0	4.8 ± 4.4	2.6 ± 1.1
Cmax (ng/ml)	129 ± 39.5	332 ± 150	908 ± 232
T1/2 (h)	4.4 ± 0.7	4.8 ± 0.6	5.7 ± 0.9
AUC0-24h (ng.h/ml)	1008 ± 224	2841 ± 899	8554 ± 1848
Cmax/dose	43 ± 13	55 ± 25	76 ± 19
AUC/dose	336 ± 74	474 ± 150	711 ± 155
	Week 12		
	3 mg/kg/day	**9 mg/kg/day**	**18 mg/kg/day**
Tmax (h)	3.6 ± 2.4	3.6 ± 2.9	5.3 ± 2.6
Cmax (ng/ml)	164 ± 56	679 ± 143	1296 ± 264
T1/2 (h)	5.0 ± 1.0	5.4 ± 0.8	6.7 ± 1.0
AUC0-24h (ng.h/ml)	1281 ± 286	5516 ± 938	13938 ± 3222
Cmax/dose	55 ± 19	75 ± 16	72 ± 15
AUC/dose	427 ± 95	613 ± 105	774 ± 179
	Week 25		
	3 mg/kg/day	**9 mg/kg/day**	**18 mg/kg/day**
Tmax (h)	3.7 ± 2.8	4.1 ± 2.6	6.0 ± 3.3
Cmax (ng/ml)	170 ± 36	587 ± 185	1278 ± 230
T1/2 (h)	5.5 ± 1.0	5.8 ± 0.9	6.8 ± 1.1
AUC0-24h (ng.h/ml)	1534 ± 339	5902 ± 1664	15002 ± 2118
Cmax/dose	57 ± 12	65 ± 21	71 ± 13
AUC/dose	512 ± 113	656 ± 185	834 ± 118

*Values are means ± S.D.

Study title: Chronic (12-month) oral toxicity study on D 145 in the rat (Includes Report entitled "12-month oral toxicity study with D 145 in rats: Compilation of study results using modern statistical methods" dated August 1983)

Key study findings:

- Irwins Activity Test showed slight treatment-related decreases in vitality and response to environment
- Body weights dose-dependently reduced compared to control body weights during dosing weeks 26 and 52 at all doses tested: overall reduction during the 52-week study at 3 (16%), 15 (27%) and 30 (30%) mg/kg/day in the males, and at 3 (23%), 15 (21%), and 30 (25%) in the females
- Body weight gain reduced in males 13%-76% at 3 (first 36 weeks), 179% at 15 (throughout study), and 26%-96% at 30 mg/kg/day (throughout study) and females up to 134% at 3, 189% at 15, and 268% at 30 mg/kg/day (throughout study)
- Food consumption reduced 9%-13% at all doses in males throughout the study, 5%-10% at 3 and 15 mg/kg/day in females throughout study
- Water consumption reduced in high dose males 14% over 52 weeks
- Treatment-related nuclear polymorphism in the liver at 3 months but not in later examinations, suggesting initial metabolic loading
- Hemosiderin accumulation in the macrophages in the lung in 1 high dose male, spermiogenesis disturbance with vacuolar degeneration in the germinal epithelium in 1-2 treated males at each dose
- No definitive target organs of toxicity identified
- Doses studied, 3, 15, and 30 mg/kg/day were 1.5X, 7X, and 15X the MRHD of 20 mg in a 60 kg patient on a BSA basis
- NOAEL not identified

Study no: Not provided
Volume # 31A, and page # 202
Conducting laboratory and location: Not provided. Report address:

Date of study initiation: 1972
GLP compliance: yes ( ) no (x)
QA report: yes ( ) no (x)
Drug D145 (Merz & Co.), **lot #** Not provided, **radiolabel** Not applicable, **and % purity** Not provided
Formulation/vehicle: 0.03, 0.15, and 0.30% aqueous solutions

Methods (unique aspects):

Dosing:

Species/strain: SPF-Wistar albino rats
#/sex/group or time point (main study): 15/sex/dose
Satellite groups used for toxicokinetics or recovery: None
Age: Not provided
Weight: Mean 65-66 g

Doses in administered units: 0, 3, 15, 30 mg/kg/day
Route, form, volume, and infusion rate: Oral by esophageal intubation at 10 ml/kg

Observations and times:

Clinical signs: Daily
Irwins Activity Test: Including consciousness, emotional behavior, activity/reactivity, central excitation, coordination, muscle tone, reflexes, and autonomic functions; At 2 and 6 months and end of study
Body weights: Weekly
Food consumption: Weekly
Ophthalmoscopy: Examination of cornea, iris and lens, time not provided
Hearing Test: Time not provided
EKG: Not done
Hematology: At 6 months and end of study
Clinical chemistry: At 6 months and end of study
Urinalysis: At 6 months and end of study
Gross pathology: End of study
Organs weighed: End of study, see under Histopathology Inventory, below
Histopathology: End of study, see under Histopathology Inventory, below
Toxicokinetics: Not done
Other: None

Results:

Mortality: No treatment-related deaths; 1 control male, and 3 LD males and 1 LD female died during weeks 28-50
Clinical signs: No treatment-related effects
Irwins Activity Test: Slight treatment-related decrease in vitality and response to environment in the males
Body weights: Dose-related decrease in weight gain; the results of the body weight measurements are presented in the following table:

Body Weights and Body Weight Gain in Male Rats Administered D 145 By Oral Gavage for 12 Months

Dosing Week(s)	0 mg/kg/day	3 mg/kg/day	15 mg/kg/day	30 mg/kg/day
Mean Body Weight (difference from control values in parentheses)				
0	65.7 ± 3.20	66.0 ± 3.38	65.7 ± 3.20	66.0 ± 3.38
1	116.5 ± 5.36	117.6 ± 6.45	113.3 ± 3.85	112.1 ± 5.84
26	409.8 ± 30.72	337.9 ± 56.46 (-18%)	353.5 ± 31.80 (-14%)	321.3 ± 25.83 (-22%)
52	418.1 ± 47.27	363.3 ± 40.19 (-13%)	322.6 ± 23.41 (-23%)	311.1 ± 34.51 (-25%)
1-52	352.4 ± 47.87	297.6 ± 40.97* (-16%)	256.3 ± 23.42*** (-27%)	245.1 ± 34.25*** (-30%)
Mean Body Weight Gain (difference from control values in parentheses)#				
5-9	68.3 ± 14.77	49.9 ± 23.15 (-27%)	67.5 ± 20.44 (-1%)	37.3 ± 19.18 (-45%)
9-12	46.5 ± 17.13	38.5 ± 14.40 (-17%)	26.9 ± 15.11 (-42%)	34.6 ± 14.80 (-26%)
17-20	24.5 ± 13.82	16.1 ± 16.64 (-34%)	23.1 ± 11.73 (-6%)	7.8 ± 15.74 (-68%)

25-28	25.1 ± 21.22	-7.9 ± 22.48 (-76%)	1.7 ± 11.34 (-93%)	1.1 ± 26.35 (-96%)
33-36	7.9 ± 27.05	6.9 ± 15.92 (-13%)	5.4 ± 9.68 (-32%)	4.3 ± 8.69 (-46%)
45-48	-4.5 ± 13.10	9.9 ± 24.68	-14.8 ± 26.92 (-129%)	-7.0 ± 20.75 (-45%)
49-52	6.7 ± 6.40	9.1 ± 10.03	-12.0 ± 26.36 (-179%)	-3.5 ± 12.02 (-52%)

*p<0.05; **p<0.01; ***p<0.001; #body weight changes shown for months in which changes in the treated groups were different from controls, only

Body Weights and Body Weight Gain in Female Rats Administered D 145 By Oral Gavage for 12 Months

Dosing Week(s)	0 mg/kg/day	3 mg/kg/day	15 mg/kg/day	30 mg/kg/day
Mean Body Weight (difference from control values in parentheses)				
0	66.0 ± 3.87	66.0 ± 3.87	66.0 ± 3.87	66.0 ± 3.87
1	104.3 ± 5.07	105.2 ± 3.82	101.1 ± 4.98	98.9 ± 4.91
26	231.9 ± 20.77	210.6 ± 15.14 (- 9%)	206.5 ± 10.47 (-11%)	198.4 ± 11.54 (-14%)
52	251.2 ± 24.49	208.8 ± 18.55 (-17%)	213.0 ± 15.60 (-15%)	205.1 ± 13.06 (-18%)
1-52	185.2 ± 22.44	142.8 ± 18*** 142.9 (-23%)	146.6 ± 15.31*** 146.7 (-21%)	139.1 ± 13.47*** 139.2 (-25%)
Mean Body Weight Gain (difference from control values in parentheses)#				
1-4	86.1 ± 8.34	80.8 ± 6.46	80.2 ± 8.02	67.3 ± 11.44 (-22%)
13-16	15.7 ± 14.80	10.9 ± 4.27 (-31%)	9.4 ± 4.85 (-40%)	8.9 ± 4.41 (-43%)
33-36	6.3 ± 5.79	-0.0 ± 7.32 (-99%)	1.2 ± 5.96 (-81%)	1.1 ± 6.73 (-83%)
37-40	-1.8 ± 4.25	-4.8 ± 6.09 (-167%)	-2.1 ± 7.29 (-17%)	-2.7 ± 5.10 (-50%)
41-44	4.1 ± 7.93	3.3 ± 7.27 (-20%)	-2.4 ± 8.13 (-158%)	1.2 ± 6.87 (-71%)
45-48	1.9 ± 9.11	-2.9 ± 9.89 (-253)	5.5 ± 4.97 (+189%)	-3.2 ± 7.06 (-268%)
49-52	7.1 ± 6.05	-2.4 ± 10.43 (-134%)	0.2 ± 6.74 (-97%)	3.3 ± 6.91 (-46%)

*p<0.05; **p<0.01; ***p<0.001; #body weight changes shown for months in which changes in the treated groups were different from controls, only

Food consumption: Statistically significant reduction in males at all doses and in the LD and MD females. Decreased food effectiveness (increase in required food) with dose in males and females. The results of the measurements of food consumption, averaged over 26-week and 52-week periods, are presented in the following table:

Food Consumption in Rats Administered D 145 By Oral Gavage for 12 Months

Dosing Week(s)	0 mg/kg/day	3 mg/kg/day	15 mg/kg/day	30 mg/kg/day
Males (difference from control values in parentheses)				
1-26	3347.5 ± 214.41	3024.7 ± 416.34	3165.8 ± 185.14* (-5%)	3041.7 ± 183.94** (-9%)
27-52	3475.9 ± 259.03	2947.1 ± 336.54** (-15%)	3072.8 ± 135.16** (-12%)	3171.1 ± 246.54** (-9%)

1-52	6823.4 ± 392.17	5932.6 ± 703.39** (-13%)	6216.1 ± 267.35** (-9%)	6212.8 ± 409.77** (-9%)
Females (difference from control values in parentheses)				
1-26	2544.5 ± 167.82	2286.5 ± 157.06* (-10%)	2428.5 ± 113.19	2343.6 ± 120.21
27-52	2568.9 ± 194.65	2321.0 ± 144.85* (-10%)	2437.1 ± 117.86	2578.5 ± 148.72
1-52	5113.4 ± 347.03	4607.5 ± 244.92** (-10%)	4879.1 ± 207.67* (-5%)	4922.1 ± 254.40

*p<0.05; **p<0.01

Water consumption: Statistically significant reduction in the high dose males (14% compared to controls), when averaged over 52 weeks.
Ophthalmoscopy: No treatment-related effects
Hearing Test: No treatment-related effects
Electrocardiography: Not done
Hematology:

- Significantly increased hematocrit at 12 months at the low dose (0.3898, 8%), mid-dose (0.4376, 21%) and high dose (0.4174, 15%) compared to control values (0.3620) in females, within range of historical control values (0.3-0.5)
- Increased mean corpuscular volume (MCV) in the females at 12 months at the mid-dose (64.216 fl, 21%) and high dose (61.428 fl, 16%%) compared to controls (52.94 fl), within range of historical control values (50-65 fl)
- Decreased mean corpuscular concentration (MCHC) in the females at 12 months at the mid-dose (21.550 mmol/L, 17%) and high dose (22.742 mmol/L, 12%) compared to controls (25.868 mmol/L), within range of historical control values (10-27 mmol/L)
- Increased prothrombin time in the high dose females at 6 months (13.60 sec, 28%) and 12 months (13.60 sec, 28%) in the high dose rats compared to the control values (10.60 and 10.60 sec, respectively), within range of historical control values (8-14 sec)
- Dose-related increase in coagulation time, in the high dose males at 6 months (78.8 sec, 52%) and in the high dose females at 12 months (76.8 sec, 70%) compared to controls (51.8 sec and 45.1 sec, respectively), within range of historical control values (35-80 sec)

Clinical chemistry: No treatment-related effects
Urinalysis: No treatment-related effects
Organ weights: In the males, reduced absolute liver weights at 3 (16%), 15 (30%), and 30 (28%) mg/kg/day, reduced absolute kidney weights at 3 (15%), 15 (20%), and 30 (19%) mg/kg/day, reduced absolute spleen weights at 15 (21%) and 30 (27%) mg/kg/day, reduced absolute adrenal weights at 30 (38%) mg/kg/day compared to controls, compared to controls; in the females, reduced absolute liver weights at 3 (17%), 15 (15%), and 30 (20%) mg/kg/day, reduced kidney weights at 3 (15%), 15 (12%), and 30 (13%) mg/kg/day, reduced adrenal weights at 3 (58%), 15 (49%), and 30 (55%) mg/kg/day, reduced spleen weights at 3 (30%), 15 (29%), and 30 (32%) mg/kg/day, reduced ovary weights at 30 (47%) mg/kg/day compared to controls; increased relative heart weights at 30 mg/kg/day (7%) compared to controls
Gross pathology: No treatment-related effects

Histopathology: At 3 months, nuclear polymorphism in the liver was observed in some treated rats that was attributed to initial metabolic loading by the examining pathologist because the observation was not present at the 6 month and 12 month examinations, and was therefore reversible after adaptation of the animals; moderate hemosiderin accumulation in the macrophages in the lung in 1/5 high dose males, spermiogenesis disturbance with vacuolar degeneration in the germinal epithelium in 1/5 (both testicles), 1/5 (both testicles) and 2/5 (1 testicle only) males at 3, 15, and 30 mg/kg/day respectively; the remaining findings, including chronic trachitis, lymphocytic reaction in the duodenum and colon propria and in the kidney interstitium, fine-droplet fatty degeneration, lymphocytic reaction in the periportal and intralobular region of the liver, and golden brown pigment in the spleen and interstitium of the ovary and uterus were observed in the treated and control rats with similar incidence.
Toxicokinetics: Not done

Study title: MEMANTINE hydrochloride – 52 week oral (dietary administration) toxicity study in the rat followed by a 6 week treatment-free period

Key study findings:

- Treatment-related dirty fur and focal hairloss
- Dose-related reduction in body weights (9%, 13%, and 24% at 20, 40, and 70 mg/kg/day in males, respectively, and 8%, 16%, and 23% at 15, 30, and 50 mg/kg/day in females, respectively), reduced body weight gain (13%, 18%, 34% in males, respectively, 13%, 26%, 36% in females, respectively) compared to controls, partially reversed during 6-week recovery
- Food consumption reduced in dose-related manner in males, water consumption increased in a dose-related manner in the LD, MD, HD males and LD, MD females
- Appropriate memantine HCl intake confirmed by analysis of test article composition in feed, dietary intake, and plasma drug level analysis
- Treatment-related hematology changes were increased packed cell volume (MD and HD) and mean corpuscular volume (LD and HD) in the females, and decreased lymphocytes in the MD and HD males, lymphocytes decreased 25%-34% at all timepoints, not reversible
- Treatment-related increase in urine volume with corresponding decrease in specific gravity in the MD and HD males and females throughout dosing; reversed during recovery, pH decreased 8%-25% in MD and HD males and females, ketones increased in HD males, crystals decreased in MD and HD males.
- Dose-related alopecia, small testes (males only), mottled kidneys with dark focus, enlargement or pale kidneys, pale focus on the lungs observed with dose-related increases in incidence in the MD and HD males and females, reversible except for small testes
- Main target organs of toxicity in the histopathology examination: kidneys, lungs and skin: irreversible dose-related increases in severity and incidence of renal papillary congestion and hemorrhage, pigment accumulation and mineralization in the kidney with tubulointerstitial nephritis in the MD and HD males and females, irreversible pulmonary histiocytosis at all dose levels in males and females, intraalveolar amorphous material with macrophages and foamy or vacuolated cytoplasm at the MD and HD in both sexes, and reversible cutaneous acanthosis in the HD females; After the recovery period kidney papilla congestion,

hemorrhage, pigment accumulation and mineralization, tubulointerstitial nephritis and histiocytosis were still present in HD animals
- No evidence of "Olney Lesion" in retrosplenial and posterior cingulate cortices
- No severe toxicity in the cornea except for increased corneal epithelial thickness without inflammatory reaction in treated rats
- Electron microscopy of the retina showed abnormal lysosomal storage in the ganglion cells and retinal pigment epithelial cells at end of treatment, partially reversed after recovery period in the HD males and females, no structural damage of the retinal layers or retinal atrophy
- Memantine blood levels confirmed adequate intake, suggested accumulation with increased duration of dosing
- Main target organs of toxicity: kidneys, lungs and skin
- Doses studied represented 10X-34X in males and 7X-24X in females the MRHD of 20 mg/day in a 60 kg patient on a BSA basis
- NOAEL was not identified in this study, due to reduced body weights and body weight gain, kidney mineralization, tubulointerstitial nephritis, and pulmonary histiocytosis in all treated rats (≥20 mg/kg/day in the males and ≥15 mg/kg/day in the females)

Study no: 442/007
Volume # 33, and page # 1
Conducting laboratory and location: —

Date of study initiation: August 24, 1988
GLP compliance: yes (x) no ( )
QA report: yes (x) no ( )
Drug Memantine hydrochloride, **lot #** R 8825, **radiolabel** Not applicable, **and % purity** 99.8%
Formulation/vehicle: Test article mixed into diet (standard powder rodent diet — homogeneity evaluated

Methods (unique aspects):
Dosing:
Species/strain: — SD. —) Sprague-Dawley rat , —
#/sex/group or time point (main study): 30/sex controls and high dose, 20/sex/dose at the low and mid-dose
Satellite groups used for toxicokinetics or recovery: TK: 10/sex/group; recovery groups: 10/sex/dose (control and high dose only)
Age: 6 weeks
Weight: 181-225 g males, 143-182 g females
Doses in administered units: 0, 20, 40, and 70 mg/kg/day in the males, 0, 15, 30, and 50 mg/kg/day in the females
Route, form, volume, and infusion rate: Oral by admixture in the diet, *ad libitum*, 24 hours/day, daily for 365 days, homogeneity of test article chow confirmed by analysis of samples from the right, middle and left of the feed containers in weeks 1 and 13

Observations and times:
Clinical signs: 2X daily—

Body weights: Weekly during weeks 1-12, every 4 weeks during weeks 13-52, every 2 weeks during the recovery period
Food consumption: Weekly during weeks 1-12, every 4 weeks during weeks 13-52, every 2 weeks during the recovery period
Water consumption: Weekly during weeks 1-12, every 4 weeks during weeks 13-52, every 2 weeks during the recovery period
Memantine HCl intake: Weekly for weeks 1-12, every 4 weeks thereafter, calculated as concentration of memantine in the diet X mean daily food consumption divided by the mean body weight
Ophthalmoscopy: Baseline and weeks 13, 26, 39, and 50, control and high dose only
EKG: Not done
Hematology: 10/sex/group during weeks 13, 26, 39, and 20/sex/group during week 52
Clinical chemistry: 10/sex/group during weeks 13, 26, 39, and 20/sex/group during week 52
Urinalysis: 10/sex/group during weeks 13, 26, 39, and 20/sex/group during week 52
Gross pathology: External surface, all orifices, cranial cavity, external surface of brain and spinal cord, thoracic, abdominal and pelvic cavities and viscera, cervical tissues and organs, carcass
Organs weighed: See under Histopathology Inventory, below
Histopathology: See under Histopathology Inventory, below
Toxicokinetics: Blood samples withdrawn from retro-orbital sinus before dosing (weeks 2, 10, 11, 13, 17, 26, 39, and 52) and 10 hours after first sample (weeks 17, and 26)
Other:

Results:

Mortality: Deaths in 2M at 0 mg/kg/day (days 285 and 408), 1M at 20 mg/kg/day (day 285), 1M at 70 mg/kg/day (day 323), and 3F (days 26, 207, and 276) at 50 mg/kg/day; the causes of death were undetermined (control animals, 1 HDM), associated with right agenesia of the kidney and enlarged thyroids (LDM), or anesthesia errors (1 HDF) and accidental injury (2 HDF)
Clinical signs: No treatment-related or dose-related signs, except for dirty fur and diffuse or focal hairloss at the high dose
Body weights: Reduced from week 20 and week 48 in the LD males and females, respectively, and from the first week of treatment in the MD and HD rats, compared to controls: The following reductions in mean body weights were observed at week 52:

Males:	-9% at 20 mg/kg/day	-13% at 40 mg/kg/day	-24% at 70 mg/kg/day
Females:	-8% at 15 mg/kg/day	-16% at 30 mg/kg/day	-23% at 50 mg/kg/day

The mean body weight gains (from start of study to week 52) are presented in the following table:

Mean Body Weight Gain in Rats Administered Memantine HCl (Dietary) for 52 Weeks

Parameter	0 mg/kg/day	Low Dose*	Mid-Dose*	High Dose*
		Males		
Mean Body Weight Gain over 52	464.7 g	406.4 g	381.5 g	306.4 g

Weeks				
Difference from Control Gain	Reference	-58.3 g	-83.2 g	-158.3
Percent Difference from Control Gain	Reference	-13%	-18%	-34%
Mean Body Weight Gain During 6-wk Recovery Period (percent gain in parenthesis)	30.5 g (+5%)	Not done	Not done	104.4 g (+21%) 242% higher gain than in controls
Females				
Mean Body Weight Gain over 52 Weeks	245.6 g	214.2 g	181.2 g	156.7 g
Difference from Control Gain	Reference	-31.3 g	-64.4 g	-88.9 g
Percent Difference from Control Gain	Reference	-13%	-26%	-36%
Mean Body Weight Gain During 6-wk Recovery Period (percent gain in parenthesis)	34.3 g (+8%)	Not done	Not done	53.4 g (+18%) 16% higher gain than in controls

*Low dose 20 mg/kg/day in males and 15 mg/kg/day in females, Mid-dose 40 mg/kg/day in males and 30 mg/kg/day in females, High dose 70 mg/kg/day in males and 50 mg/kg/day in females

After the recovery period, mean body weights increased 5% and 8% in the control males and females, respectively, and 21% and 18% in the high dose males and females, respectively.

Food consumption: Reduced in the high dose (70 mg/kg/day) males from week 1 and in the low (20 mg/kg/day) and mid-dose (40 mg/kg/day) males from week 13 to the end of the study.
Water consumption: Dose related increase in water consumption in the males at 20 (+20 to +40 g/animal/wk, from week 32), 40 (+9 to +100 g/animal/wk, from week 5), and 70 (+150 to +170 /animal/wk, from week 3) mg/kg/day compared to controls; increased in the females at 15 (+15 to +20 g/animal/wk, from week 8) and 30 (+50 to +60 g/animal/wk, from week 4) compared to controls; reversible during the recovery period.
Memantine HCl intake: The following table summarizes the mean memantine HCl intake during the study

Mean Test Article Intake in Rats Administered Dietary Memantine for 1 Year

Males			Females		
Theoretical Dose (mg/kg/day)	**Mean Value (mg/kg/day)**	**Range (mg/kg/day)**	**Theoretical Dose (mg/kg/day)**	**Mean Value (mg/kg/day)**	**Range (mg/kg/day)**
20	**20.1**		**15**	**15.2**	
40	**40.0**		**30**	**30.4**	
70	**70.0**		**50**	**50.7**	

Ophthalmoscopy: No treatment-related effects
Electrocardiography: Not done

Hematology:

- Increased packed cell volume in the females in Week 52 at 30 (5%) and 50 (5%) mg/kg/day compared to controls
- Increased mean corpuscular volume in the females in Week 52 at 15 (3.5%) and 30 (3.5%) mg/kg/day compared to controls
- Increased prothrombin time in the males at 40 (weeks 39 [5%] and 52 [4%]) and 70 (weeks 13 [9%], 26 [6%], 39 [8%], and 52 [8%]) mg/kg/day compared to controls; within range of historical control values, reversible in the recovery period
- Decreased activated partial thromboplastin time in males at 40 (week 39) and 70 (week 52 [9%]) mg/kg/day compared to controls; within range of historical control values, reversible in the recovery period
- Decreased lymphocytes in the males at 40 (weeks 26 [28%] and 52 [25%]) and 70 (weeks 13 [28%], 26 [32%], 39 [34%], and 52 [29%]) compared to controls; not reversible (-31% compared to controls) after the recovery period in the high dose group

Clinical chemistry:

- Increased potassium in females at 50 mg/kg/day (week 39 [12.5%]) and males at 20 mg/kg/day (week 52 [7%])
- Decreased chloride in males at 70 mg/kg/day (weeks 13 [3%] and 52 [6%]) and females at 30 (week 26 [2%]) and 50 (week 26 [2%]) mg/kg/day
- Increased calcium in the females at 30 (week 26 [5%]) and 50 (weeks 13 [4%], 26 [6%], and 39 [5%]) mg/kg/day
- Decreased inorganic phosphorus in the males at 40 (week 26 [26%]) and 70 (week 26 [26%]) mg/kg/day
- Decreased glucose in the females at 50 mg/kg/day (week 13 [9%])
- Increased blood urea nitrogen in the males at 20 (week 26 [13%]) and 70 (end of recovery period [25%]) mg/kg/day and females at 30 (week 52 [15%]) and 50 (week 52 [17%]) mg/kg/day
- Decreased cholesterol in the males at 40 (weeks 39 [20%] and 52 [21%]) and 70 (weeks 39 [27%] and 52 [22%]) mg/kg/day, 43% after the recovery period at 70 mg/kg/day) and females at 50 mg/kg/day (28% after the recovery period)
- Increased bilirubin in the males at 20 (week 52 [19%]) and 70 (weeks 13 [26%] and 52 [19%]) mg/kg/day
- Decreased globulin in the males at 20 (week 39 [9%]) and 40 (week 39 [9%]) mg/kg/day
- Increased albumin/globulin ratio in the males at 20 (week 39 [70%]), 40 (week 52 [8%]) and 70 (week 52 [8%]) mg/kg/day
- Increased creatinine in the males at 40 (weeks 13 [7%], 26 [23%], and 52 [12%]) and 70 (weeks 13 [3.5%] and 26 [19%]) mg/kg/day
- Increased alkaline phosphatase activity in the males at 40 mg/kg/day (week 52 [27%])
- Decreased aspartate aminotransferase activity in the females at 30 mg/kg/day (week 52 [35%])
- Decreased alanine aminotransferase activity in the females at 30 (week 52 [55%]) and 50 (week 52 [56%]) mg/kg/day
- Decreased gamma glutamyl transferase activity in the males at 70 mg/kg/day (week 26 [50%]) and females at 30 mg/kg/day (week 52 [50%])

The changes in clinical chemistry values were within the range of historical control values, were without a dose-relationship, and were not consistently observed across timepoints and sexes. Therefore the changes are not considered to be treatment-related.

Urinalysis:

- Increased volume in the males at 40 (85% to 152%) and 70 (87% to 102%) mg/kg/day and females at 30 (113% to 123%) and 50 (92% to 135%) mg/kg/day throughout dosing
- Decreased specific gravity in the males at 40 (1% to 2%) and 70 (2%) mg/kg/day and females at 15 (1%) 30 (1%) and 50 (1%) mg/kg/day throughout dosing
- Decreased pH in the males at 40 (week 51 [12.5%]) and 70 (14% to 25%) throughout dosing) mg/kg/day and females at 30 (week 25 [14%]) and 50 (8% to 17%) throughout dosing) mg/kg/day
- Increased ketones in the males at 70 mg/kg/day throughout dosing
- Decreased crystals in the males at 40 (week 39) and 70 (from week 25) mg/kg/day

Organ weights:

- Decreased absolute thyroid weights in females at 50 mg/kg/day (14%), after recovery period mean absolute thyroid weights decreased 27% in the HD females
- Decreased absolute prostate weights in males at 70 mg/kg/day (17%)
- Decreased absolute (13%) and increased relative (to body weight, 10%) liver weights in males at 70 mg/kg/day; decreased absolute liver weight in females at 30 (15%) and 50 (13%) mg/kg/day, increased relative liver weight in females at 50 mg/kg/day at the end of dosing (10%) and at the end of the recovery period (16%)
- Increased relative (to body weight) kidney weights in the males at 40 (9%) and 70 (41%) mg/kg/day and after the recovery period in the HD males (23%), and in the females at 30 (16%) and 50 (30%) mg/kg/day
- Decreased absolute spleen weights in males at 70 mg/kg/day (25%) and females at 30 (21%) and 50 (20%) mg/kg/day, increased relative spleen weights in the HD males after the recovery period (16%)
- Decreased absolute heart weights in males at 40 (10%) and 70 (10%) mg/kg/day and females at 50 mg/kg/day (7%), increased relative (to body weight) heart weights in the males at 70 mg/kg/day at the end of dosing (13%) and after the recovery period (18%) and females at 30 (14%) and 50 (17% after dosing, 19% after recovery) mg/kg/day
- Decreased absolute thymus weights in males at 40 (33%) and 70 (38%) mg/kg/day and females at 50 mg/kg/day (37%)
- Increased relative (to body weight) pituitary weights in the males at 70 mg/kg/day after treatment (25%) and after the recovery period (59%)
- Increased relative (to body weight) brain weights in the males at 40 (11%) and 70 (28% after dosing, 25% after recovery period) mg/kg/day and females at 30 (16%) and 50 (25% after dosing period and 34% after recovery period) mg/kg/day
- Decreased absolute adrenal weights in the HD recovery females (16%), increased relative (to body weight) adrenal weights in the males at 70 mg/kg/day (22%) and females at 30 (20%) and 50 (31%) mg/kg/day, after recovery period increased relative adrenal weights in the high dose males (24%)
- Decreased absolute ovary weights in the HD recovery females (17%), increased relative (to body weight) ovary weights in the HD females (39%)

- Decreased absolute testes weights in the HD recovery males (22%), increased relative (to body weight) at 40 (14%) and 70 (25%) mg/kg/day
- Increased relative (to body weight) uterus weight in the HD females at the end of dosing (54%) and after the 6-week recovery period (39%)

The absolute and relative organ weight changes are considered to be secondary to decreased body weights.

Gross pathology: Alopecia in 16/30 high dose females, stained fur in 1 control, 3 mid-dose, and 4 high dose males, small testes in 1 mid-dose and 6 high dose males, increased incidence of mottled kidneys (1/20, 1/19, 6/20, and 9/20 males at 0, 20, 40, and 70 mg/kg/day, respectively) with dark focus, enlargement or pale kidneys in high dose males, increased incidence of pale focus on the lungs in the high dose males and females, after the recovery period small testes was observed in 3/9 high dose males

Histopathology: renal papillary congestion (16/20 and 20/20 males at MD and HD, respectively, and 9/20 and 15/20 MD and HD females, respectively) and hemorrhage (mid-dose and high dose terminal and recovery rats), pigment accumulation (2/20 and 19/20 MD and HD males, respectively and 1/20 and 9/20 MD and HD females, respectively) and mineralization (11/19, 20/20, and 17/20 LD, MD, and HD males, respectively and 3/20, 9/20, 14/20, and 13/20, controls, LD, MD, and HD females, respectively) in the kidney with tubulointerstitial nephritis (higher incidence and more severe in the males, 8/19, 11/20, 14/20 LD, MD, and HD males, respectively, and 1/20 and 2/20 MD and HD females, respectively); dose-related increase in pulmonary histiocytosis (11/20, 11/19, 13/20, and 20/20 control, LD, MD, and HD males, respectively, and 8/20, 8/20, 13/20, and 19/20 control, LD, MD, and HD females, respectively) with intraalveolar amorphous material (macrophages with foamy or vacuolated cytoplasm) in the mid-dose and high dose rats, cutaneous acanthosis in 10/20 high dose females; after the recovery period, kidney papilla congestion and/or hemorrhage was observed in 6/9 HD males and 2/7 HD females, pigment accumulation and mineralization in the papilla in 9/9 HD males and 5/7 HD females, tubulointerstitial nephritis in 5/9 HD males, histiocytosis in the lung in 9/9 HD males and 4/7 HD females

Tissue samples [redacted] from the retrosplenial and posterior cingulate cortices (n=5/sex/ group) showed no evidence of necrosis or progressive degeneration; however, perinuclear vacuolation was observed in the cortical cells of 1-2 males and females in each group (including controls) and axonal vacuolation was observed in 1 HD male in the cerebellum and brain stem and was attributed to formalin fixation artifacts.

Special histopathology examination of the eyes showed no severe toxicity in the cornea except for increased corneal epithelial thickness without inflammatory reaction in the treated rats compared to controls. Additionally, electron microscopy of the retina was performed (n=3/sex/timepoint, controls and HD animals, examined at end of treatment and after 6-week recovery period) because memantine was found to concentrate in the eyes in several studies in rats, dogs, and monkeys, memantine is amphiphilic and accumulates in lysosomes which is associated with retinal damage by other drugs, corneal lesions and focal lens turbidities were observed in a 13-week toxicity study in rats, and some changes in the retina may not be observable by light microscopy. [redacted] sections were contrasted with uranyl acetate and lead citrate for the electron microscopic evaluation. The high dose males and females showed abnormal lysosomal storage in the ganglion cells and retinal pigment epithelial cells at end of treatment, partially reversed after the 6-week recovery period. No structural damage of the retinal layers or retinal atrophy was found.

Toxicokinetics: The memantine blood levels are presented in the following table:

Memantine Blood Levels (mcg/L, ± S.D.) in Rats Treated by Oral Gavage for 52 Weeks

Weeks	Low Dose*	Mid-Dose*	High Dose*
Males			
2	112 ± 46	294 ± 63	804 ± 187
10	225 ± 55	ND	1974 ± 187
11	ND	610 ± 141	ND
13	195 ± 33	587 ± 136	1916 ± 536
17(a.m.)	217 ± 39	690 ± 172	1778 ± 360
17(p.m.)	163 ± 27	262 ± 36	1065 ± 366
26(a.m.)	246 ± 54	706 ± 142	2031 ± 471
26(p.m.)	149 ± 32	243 ± 42	837 ± 337
39	352 ± 113	ND	ND
52	228 ± 95	729 ± 224	3248 ± 1160
Females			
2	128 ± 32	289 ± 138	565 ± 129
10	293 ± 120	ND	1102 ± 341
11	ND	553 ± 117	ND
13	226 ± 54	530 ± 201	957 ± 298
17(a.m.)	231 ± 78	580 ± 177	1434 ± 660
17(p.m.)	159 ± 38	320 ± 92	690 ± 203
26(a.m.)	323 ± 108	875 ± 368	1770 ± 403
26(p.m.)	193 ± 41	402 ± 136	852 ± 248
39	400 ± 118	ND	ND
52	256 ± 86	766 ± 289	2128 ± 289

*The low, mid- and high doses were 20, 40, and 70 mg/kg/day, respectively, in the males, and 15, 30, and 50 mg/kg/day, respectively, in the females; ND = not done

Study title: Subacute oral toxicity study on D 145 over 12 months in the dog

Key study findings:

- Tremors and apathy after the incremental dose-escalations from 5 to 18 mg/kg/day, slight dehydration during first 10 dosing months in the HD group
- Dose-related decrease in body weight gain in HD dogs compared to controls during dose-escalation period; Reduced body weight gain at end of study in HD dogs compared to controls (39% in males and female combined, 23% in males, 55% in females); Absolute body weights reduced at HD compared to controls at end of study (13% in males and females combined, 19% in males, and 5% in females)
- Food consumption reduced 10% throughout study in the HD males and females combined (15% in males, 6% in females)
- Opal clouding of cornea from Months 2-8, no treatment-related effects in eyes at end of study
- Clinical chemistry: increased alkaline phosphatase at 3 (26%), 6 (39%), 9 (85%), and 12 (75%) months (in HD males and females combined)
- Increased thyroid weights (46%-48%, left-right) at the HD; increased relative (to body weight) adrenal weights at the LD (27%-23%, left-right) and HD (15%-10%, left-right),

thyroid weights at the MD (33%-35%, left-right) and HD (63%-64%, left-right), and liver (16%) and kidney (20%-17%, left-right) weights at the HD (males and females combined).
- Definitive target organs of toxicity and NOAEL not identified
- Doses studied represented approximately 3X-29X MRHD of 20 mg in a 60 kg patient on a BSA basis

Study no: Not provided
Volume # 21, and page # 1
Conducting laboratory and location: [redacted]

Date of study initiation: Report date January 1974
GLP compliance: yes ( ) no (x)
QA report: yes ( ) no (x)
Drug D 145, **lot #** Not provided, **radiolabel** Not applicable, **and % purity** Not provided
Formulation/vehicle: Test article in gelatin capsules

Methods (unique aspects):
Dosing:

Species/strain: Beagle dogs
#/sex/group or time point (main study): 2/sex/dose
Satellite groups used for toxicokinetics or recovery: None
Age: Not provided
Weight: 7-9 kg
Doses in administered units: 0, 2, 5, and 18 mg/kg/day (the high dose was initially 5 mg/kg/day, increased to 7 mg/kg after 5 days, then increased by 1 mg/kg every 4 days for 14 days, and by 2 mg/kg until the dose reached 18 mg/kg/day)
Route, form, volume, and infusion rate: Oral in gelatin capsules, once daily for 5 days/week, for 52 weeks

Observations and times:

Clinical signs: Daily
Body weights: Weekly
Food consumption: Weekly
Ophthalmoscopy: Every 14 days
EKG: End of study
Hematology: Baseline and at 2, 3, 6, 9, and 12 months
Clinical chemistry: Baseline and at 2, 3, 6, 9, and 12 months
Urinalysis: Baseline and at 2, 3, 6, 9, and 12 months
Gross pathology: End of study
Organs weighed: See under Histopathology Inventory, below
Histopathology: See under Histopathology Inventory, below
Toxicokinetics: Not done
Other: None

Results:

Mortality: No deaths
Clinical signs: In the HD group, tremors and apathy were observed after incremental dose escalations, slight dehydration up to 10 months

Body weights: Dose-related decrease in body weight gain in the HD dogs during the dose-escalation period from 5-18 mg/kg/day, compared to controls; reduced body weight gain at end of study in the HD dogs (39% in males and female combined, 23% in males, 55% in females); absolute body weights reduced 13% in males and females combined, 19% in males, 5% in females compared to controls
Food consumption: Decreased 10% throughout the 52-week study in the HD males and females combined (15% in males, 6% in females)
Ophthalmoscopy: Opal clouding of cornea from Month 2 through Month 8, with regression thereafter in the HD dogs, no treatment-related effects observed at the end of the study
Electrocardiography: No treatment-related effects
Hematology: No treatment-related effects
Clinical chemistry: Slight increase (26%, males and females combined) in alkaline phosphatase at 3 months in the HD dogs (within normal range), increased significantly at 6 (39%), 9 (85%), and 12 (75%) months.
Urinalysis: No treatment-related effects
Organ weights: In the males and females combined: increased thyroid weights (46%-48%, left-right) at the HD; increased relative (to body weight) adrenal weights at the LD (27%-23%, left-right) and HD (15%-10%, left-right), thyroid weights at the MD (33%-35%, left-right) and HD (63%-64%, left-right), and liver (16%) and kidney (20%-17%, left-right) weights at the HD
Gross pathology: No treatment-related effects
Histopathology: No treatment-related effects
Toxicokinetics: Not done

Study title: Memantine Toxicity to Baboons by Repeated Oral Administration for 52 Weeks Followed by a 4-Week Withdrawal Period

Key study findings:

- Treatment-related clinical signs were dose-related vomiting, quietness, ptosis, and huddled posture
- Body weights reduced 6%-12% in MD and HD males and 6%-15% in LD, MD and HD females during 1st week of dosing period
- Clinical chemistry: slightly decreased alpha2 globulin (33%, LD, MD, and HD in Week 51), decreased beta globulin (20%, LD, MD and HD in Week 13, 18%, D and MD, 9%, HD in Week 51), decreased globulin (13%, MD and HD in Week 13, and 14%-21%, LD, MD, and HD in Week 51), decreased T4 (22%, HD in Week 51), decreased cortisol (27%, HD in Week 51) (changes in thyroxine without corresponding changes in thyroid weights and histopathology)
- Gross pathology: pale raised foci and dark red mucosal discoloration on mucosal surface of stomach fundus in HD females after the 4-week recovery period
- Bone marrow: moderate increases in erythroid cells in 1 MD female and 1 HD male and 2 high dose female baboons, without anemia or microscopic pathology indicating marrow stimulation, no differences from controls after recovery period
- TK confirmed absorption of test article, no evidence of accumulation, no differences between the males and females