CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-697

PHARMACOLOGY REVIEW

MEMORANDUM
Dec. 22, 2005

TO: File
FROM: Kenneth L. Hastings, Dr.P.H., D.A.B.T.

SUBJECT: NDA 21-697

This application is approvable based on submitted nonclinical pharmacology/toxicology data. The product label should be amended as recommended by Drs. Karen Davis-Bruno and Fred Alavi.

_____
Kenneth L. Hastings, Dr.P.H., D.A.B.T.
Associate Director for Pharmacology and Toxicology
Office of Drug Evaluations II & III

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/s/

Kenneth Hastings
12/22/2005 02:36:41 PM
PHARMACOLOGIST

MEMORANDUM
Nov. 23, 2004

TO: File
FROM: Kenneth L. Hastings, Dr.P.H., D.A.B.T.

SUBJECT: NDA 21-697

I have read the pharmacology/toxicology review (Dr. Fred Alavi) and the supervisor's memorandum (Dr. Karen Davis-Bruno) for Conivaptan hydrochloride (Vaprisol®) and concur that the application is approvable with appropriate changes to the proposed product label. As recommended by Dr. Davis-Bruno, the label should contain the following statement in the Pregnancy section of the label: "Conivaptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." This is consistent with the recommendation that conivaptan should be labeled Pregnancy Category C. Other changes in the product label recommended by Dr. Davis-Bruno should also be incorporated.

_____
Kenneth L. Hastings, Dr.P.H., D.A.B.T.
Associate Director for Pharmacology and Toxicology
Office of Drug Evaluations II & III

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/s/

Kenneth Hastings
11/23/04 01:38:13 PM
PHARMACOLOGIST

Supervisor's Memo
To: NDA 21-697
From: Karen Davis-Bruno; PhD; HFD-510
Date: 9/9/04

Introduction: Conivaptan hydrochloride is a nonpeptide dual antagonist of arginine vasopressin (AVP) V_{1A} and V_{1B} receptors. Selective V_2 receptor antagonism has been associated with reflexively increased plasma AVP levels possibly stimulating the undesired V_{1A} mediated vasoconstriction and platelet aggregation. The proposed clinical use is for treatment of the syndrome of inappropriate anti-diuretic hormone (SIADH) using a bolus IV 20 mg dose on day 1 followed by 3 day IV infusion at 40 mg/day in a hospital setting. Human PK in SIADH patients has not been provided. The Pharmacology/Toxicology review has used an averaged AUC=3580 ng h/ml based on the proposed clinical dose in healthy volunteers to calculate safety margins. The safety margins described in the label may need modification pending submission of human PK in the proposed patient population. Hyponatremia is a common disorder associated with fluid and electrolyte imbalance the principal causes include: hypovolemia, euvolemia (including SIADH) and hypervolmeia including congestive heart failure and hepatic cirrhosis. Moderate to severe hyponatremia increases the potential risks of intractable seizures and death. The standard of care is fluid restriction, IV infusion of hypertonic saline alone or in combination with loop diuretics. Exaggerated correction of plasma sodium may aggravate hyponatremic encephalopathy. In general inconsistent efficacy and compliance has been associated with current therapy. In rats and dogs Conivaptan increases urine flow accompanied by a decrease in urine osmolality (aquaresis) and exhibits potent inhibition of the pressor response induced by exogenous AVP. Conivaptan is metabolized via CYP3A4. Since many drugs are metabolized by this enzyme drug interactions are quite possible. The proposed clinical use has attempted to minimize this potential.

Summary of Nonclinical Findings: An extensive toxicology program has been performed with conivaptan including oral and intravenous (bolus, infusion) routes in acute and repeat dosing conditions in several species. Conivaptan is not genotoxic, carcinogenic or teratogenic in animals. Target organ toxicity includes: bone marrow in dogs, hepato- and renal toxicity in rat and dog, effects on estrus cycle and reproduction in rats and vascular irritation in rats, rabbits and dogs and adrenal gland in rat. The bone marrow toxicity consisting of focal/multifocal necrosis and degeneration, decreased erthroblastic islands, myeloid hyperplasia, hypocellularity and fibrosis occurred at systemic exposures only at high sustained exposures (>40X the therapeutic exposure for durations of exposure beyond one week of dosing). These findings were reversed following a 6 week drug recovery phase as part of a 13 week oral dog toxicity study. This suggests limited clinical risk. Likewise hepatotoxicity occurs at high exposures given for durations greater than 1 week. Liver findings included: elevated enzymes, bile duct hyperplasia, sinusoidal dilatation, hepatocyte hypertrophy, inflammation, jaundice, cholestasis, hepatocte necrosis at 40X therapeutic exposures. Slight increases in liver enzymes, hepatocellular hypertrophy and hepatocyte necrosis were observed in a one week IV rat study at 15X therapeutic exposure which was the lowest exposure for these findings. Exposures >5X therapeutic exposure are generally needed to see even slight increases in liver enzymes. Renal tubular degeneration is observed in rats at exposures 4X therapeutic exposure after one week IV dosing along with elevations in BUN suggesting some clinical relevance. However the indicated patient population might be expected to have underlying renal pathology consistent with this finding. Thus renal function would likely be monitored in this patient population during clinical use. It should be noted that the exposures described in animal studies are based on a clinical AUC=3580 ng h/ml which is an averaged value for a 20 mg bolus on day 1 followed by continuous IV infusion at 40 mg/day for 4 days in healthy volunteers. Clinical PK has not been provided in SIADH patients.

Effects on estrus cycles and reproduction in rats occurred at doses comparable to human clinical exposure. Conivaptan caused delayed partuition and physical and function developmental deterioration in offspring. Conivapatan is contraindicated during pregnancy and lactation based on these findings. The parturition delays and impaired ability to nurse and lactate were attributed to conivaptan inhibition of oxytocin receptors (Ki~44 nM; ~24 mg/ml) in rat. Parturition in rats is much more dependent on oxytocin receptors than rabbits or humans. In fact maternal toxicity was observed in the rabbit, but didn't involve parturition delays instead decreased body weight, food consumption were observed. Distribution studies in pregnant rats reveals placental (2-3X higher than maternal plasma levels) and milk transfer (maximal at 1 h post dose

IV and reaches 2-3X higher than plasma levels) of conivaptan. Tissue levels in the fetuses <10% of maternal plasma concentrations but clearance was much slower (even after 24h post IV dose fetal levels were 39% of the Cmax) and accumulation in the fetus is possible. The sponsor attributes the prolonged estrus and adrenal hypertrophy/hyperplasia to the effect of conivaptan on steroidogenesis. Conivaptan increases progesterone, AVP and ACTH after ≥10 mg/kg oral doses in rats and decreases corticosterone via inhibition of 21-hydroxylase; which converts progesterone to 11-deoxycorticosterone. Negative feedback results in secretion of pituitary ACTH with decreased plasma corticosterone resulting in stimulation of progesterone from the adrenal cortex. The ACTH is implicated in the adrenal hypertrophy/hyperplasia observed in the toxicology studies. Distribution studies reveal elevated conivaptan in rat adrenal glands relative to the plasma which may implicate a direct effect in addition. Adrenal findings occur as early as 4-weeks in rat at 2.5 mg/kg IV infusion (at therapeutic exposures) however the finding appears in the one-year oral dog toxicity study at 20 mg/kg (exposures >25X therapeutic exposure).

Tissue distribution studies in rats show testicular exposure to conivaptan is greater than plasma exposure although rats did not have histopathology and tissue distribution studies were not performed in dogs. In the 4-week continuous IV infusion study in dogs, 2/3 males given 20 mg/kg had mild-slight multi-focal degeneration of seminiferous tubules, immature sperm and epididymal vasculitis. The sponsor attributes this finding to deteriorating health of the two dogs. Exposures in these dogs were >30X therapeutic exposure the NOAEL for the study provides a 3X safety margin relative to clinical exposures. This finding was not observed in a 1 week continuous IV infusion study in dogs at higher exposures. No changes in male fertility were observed in rat reprotoxicity studies at doses up to 2.5 mg/kg/day. This finding only occurs with relatively high, prolonged (>1 week) exposures and is not likely to be clinically relevant.

Summary of Nonclinical Safety Issues Relevant to Clinical Use: Administration of conivaptan PG/EtOH clinical formulation is recommended in large veins typically used for humans to minimize the significant vascular irritation observed in nonclinical studies. The degree of inflammation was severe enough to terminate a 4 week rat IV infusion and dog IV bolus study.

Conivaptan caused significant aquaresis leading to dehydration in normal animals as a function of its pharmacologic action. This should not be a major problem in the indicated SIADH population. Conivaptan is primarily biliary/fecal excreted (90%). The metabolic profile among species is quite similar although plasma levels of metabolites are <10% of the administered dose suggesting a minimal contribution of metabolites to pharmacologic activity. This would suggest that renal/hepatic impairment will not be problematic in clinical use. SIADH patients may have renal and hepatic pathology and these organs are identified target organs of toxicity with conivaptan administration however functional changes will likely be monitored in the patient population. The liver toxicity requires relatively high exposures; which are above systemic therapeutic exposures for prolonged durations. The renal findings were observed after one week IV infusions in rats at 4 times therapeutic exposure.

Effects on estrus cycles and female reproduction occurred in rats at therapeutic exposures. Conivaptan delayed parturition and physical/functional development including reflexes in offspring in rats. These effects were largely absent in rabbits and have been associated with oxytocin receptor interactions in rats. Parturition and maternal care are less influenced by oxytocin in rabbits and humans. Caution should exercised with Conivaptan use during pregnancy and lactation based on these findings.

Recommendation: Approval; pending labeling changes.

Labeling comments:

Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard lifetime (104 week) carcinogenicity bioassays were conducted in mice and rats. Mice were given oral doses of 3, 10, 30 mg/kg/day in males and 1, 3, 10 mg/kg/day in females by gavage. Rats were given oral doses of 0.3, 1, 3, 10 mg/kg/day in males and 1, 3, 10, 30 mg/kg/day in females by gavage. No

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Pharm/Tox- 1

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/s/

Karen Davis-Bruno
9/13/04 10:48:17 AM
PHARMACOLOGIST
P/T label

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-697**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**02/03/04**
DRUG NAME:	**Conivaptan (Vaprisol ®)**
INDICATION:	**hyponatremia**
SPONSOR:	**Yamanouchi**
DOCUMENTS REVIEWED:	**Vol. (electronic)**
REVIEW DIVISION:	**DMEDP (HFD-510)**
PHARM/TOX REVIEWER:	**Fred Alavi**
PHARM/TOX SUPERVISOR:	**Karen Davis-Bruno**
DIVISION DIRECTOR:	**David Orloff**
PROJECT MANAGER:	**Lina Aljuburi**

Date of review submission to Division File System (DFS): **Sept 22, 04**

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: approvable

B. Recommendation for nonclinical studies: There is sufficient non-clinical data to support safety of the intravenous conivaptan PG/EtOH formulation in humans (20 mg bolus intravenous dose followed by [redacted] in SIADH patients. No further studies are needed.

C. Recommendations on labeling:

Carcinogenesis, Mutagenesis, Impairment of Fertility
Standard lifetime (104 week) carcinogenicity bioassays were conducted in mice and rats. Mice were given oral doses of 3, 10, 30 mg/kg/day in males and 1, 3, 10 mg/kg/day in females by gavage. Rats were given oral doses of 0.3, 1, 3, 10 mg/kg/day in males and 1, 3, 10, 30 mg/kg/day in females by gavage. No increased incidence of tumors was observed at doses up to 30mg/kg/day in mice (6X systemic exposure of an IV bolus of 20 mg on day I followed by IV infusion 40 mg for 3 days based on AUC comparison) or rats (2X systemic exposure of an IV bolus of 20 mg on day 1 followed by IV infusion 40 mg for 3 days based on AUC comparison).
Conivaptan was not mutagenic or clastogenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* and *Escherichia coli,* in human peripheral blood lymphocytes, or *in vivo* rat micronucleus assay.

In fertility studies after 4-weeks treatment by intravenous bolus at 0.5, 1.25 and 2.5 mg/kg/day, male fertility was unaffected. However, in females given IV bolus conivaptan 15 days before mating through gestation day 7 there was prolonged diestrus, decreased fertility and increased pre- and post-implantation loss at 2.5 mg/kg/day (systemic exposures less than the therapeutic dose).

Pregnancy Category C
Conivaptan has been shown to have adverse effects on the fetus when given to animals during pregnancy at systemic exposures less that achieved at a therapeutic dose based on AUC comparisons. There are no adequate and well controlled studies in pregnant women. Conivaptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The patient should be apprised of the potential hazard to the fetus. Conivaptan crosses the placenta and is found in fetal tissue. Fetal tissue levels are <10% of maternal plasma concentrations [redacted] milk levels are up to 3X higher than maternal plasma levels following an intravenous dose of 1 mg/kg (systemic exposures less than therapeutic based on AUC comparisons).
In female rats given intravenous bolus dose of 0.5, 1.25 and 2.5 mg/kg/day conivaptan before mating and continuing through gestation day 7 prolonged diestrus, decreased

fertility and increased pre- and post-natal implantation loss at 2.5 mg/kg/day (systemic exposures less than the therapeutic dose).
In pregnant rats given intravenous doses of 0.5, 1.25, 2.5 mg/kg/day from gestation day 7 through 17 (organogenesis) no significant maternal or fetal effects were observed at systemic exposures less than therapeutic exposure based on AUC comparisons.

In pregnant rabbits given intravenous doses of 3, 6, 12 mg/kg/day from gestation day 6 through 18 (organogenesis) there were no fetal findings however, maternal toxicity was observed in all groups. (systemic exposures less than the therapeutic dose).

Labor and Delivery
The effect of conivaptan on labor and delivery has not been studies in humans.
Conivaptan delayed delivery in rats given 10 mg/kg/day by oral gavage (systemic exposures equivalent to the therapeutic dose based on AUC comparisons).
Administration of conivaptan at 2.5 mg/kg/day intravenously increased peripartum pup mortality ; systemic exposures less than the therapeutic dose based on AUC comparisons.

Lactating Women
It is not known whether Conivaptan is excreted in human milk. Because many drugs are excreted in human milk caution should be exercised when conivaptan is administered to a lactating woman. Conivaptan is excreted in milk and detected in neonates when given by intravenous to lactating rats. Milk levels in rats reach maximal levels at 1 h post dose following intravenous administrations which are up to 3 times greater than maternal plasma levels. Administration of conivaptan at 2.5

mg/kg/day intravenously [redacted] increased peripartum pup mortality [redacted] systemic exposures less than the therapeutic dose based on AUC comparisons.

II. Summary of nonclinical findings

A. Marked aquaresis mediate via the V_2 receptor was observed in studies with conivaptan in mice, rats and dogs. Decreased body weight in repeat dose studies can be attributed to the increased water consumption, decreased food consumption and increased urine output. An extensive toxicology program has been performed with conivaptan including oral and intravenous (bolus, infusion) routes in acute and repeat dosing conditions in several species. Conivaptan is not genotoxic, carcinogenic or teratogenic in animals. Target organ toxicity includes: bone marrow in dogs, hepato- and renal toxicity in rat and dog, effects on estrus cycle and reproduction in rats and vascular irritation in rats, rabbits and dogs and adrenal gland in rat. The bone marrow toxicity consisting of focal/multifocal necrosis and degeneration, decreased erythroblastic islands, myeloid hyperplasia, hypocellularity and fibrosis occurred at systemic exposures only at high sustained exposures (>40X the therapeutic exposure for durations of exposure beyond one week of dosing). These findings were reversed following a 6 week drug recovery phase as part of a 13 week oral dog toxicity study. This suggests limited clinical risk. Likewise hepatotoxicity occurs at high exposures given for durations greater than 1 week. Liver findings included: elevated enzymes, bile duct hyperplasia, sinusoidal dilatation, hepatocyte hypertrophy, inflammation, jaundice, cholestasis, hepatocyte necrosis at 40X therapeutic exposures. Slight increases in liver enzymes, hepatocellular hypertrophy and hepatocyte necrosis were observed in a one week IV rat study at 15X therapeutic exposure which was the lowest exposure for these findings. Exposures >5X therapeutic exposure are generally needed to see even slight increases in liver enzymes. Renal tubular degeneration is observed in rats at exposures 4X therapeutic exposure after one week IV dosing along with elevations in BUN suggesting some clinical relevance. However the indicated patient population might be expected to have underlying renal pathology consistent with this finding. Thus renal function would likely be monitored in this patient population during clinical use. It should be noted that the exposures described in animal studies are based on a clinical AUC=3580 ng h/ml which is an averaged value for a 20 mg bolus on day 1 followed by continuous IV infusion at 40 mg/day for 4 days in healthy volunteers. Clinical PK has not been provided in SIADH patients.

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maternal plasma concentrations but clearance was much slower (even after 24h post IV dose fetal levels were 39% of the Cmax) and accumulation in the fetus is possible. The sponsor attributes the prolonged estrus and adrenal hypertrophy/hyperplasia to the effect of conivaptan on steroidogenesis. Conivaptan increases progesterone, AVP and ACTH after ≥10 mg/kg oral doses in rats and decreases corticosterone via inhibition of 21-hydroxylase; which converts progesterone to 11-deoxycorticosterone. Negative feedback results in secretion of pituitary ACTH with decreased plasma corticosterone resulting in stimulation of progesterone from the adrenal cortex. The ACTH is implicated in the adrenal hypertrophy/hyperplasia observed in the toxicology studies. Distribution studies reveal elevated conivaptan in rat adrenal glands relative to the plasma which may implicate a direct effect in addition. Adrenal findings occur as early as 4-weeks in rat at 2.5 mg/kg IV infusion (at therapeutic exposures) however the finding appears in the one-year oral dog toxicity study at 20 mg/kg (exposures >25X therapeutic exposure).

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Administration of conivaptan PG/EtOH clinical formulation is recommended in large veins typically used for humans to minimize the significant vascular irritation observed in nonclinical studies. The degree of inflammation was severe enough to terminate a 4 week rat IV infusion and dog IV bolus study.
Conivaptan was not mutagenic or carcinogenic in a series of studies designed to address this potential.

Ratio of systemic exposures at NOAEL doses in animals to clinical dose AUC_{0-24} in healthy volunteers. AUC data for the 4-day IV clinical dose in SIADH patients is not available at present time; AUC from healthy volunteers was used in calculating safety margins. Since conivaptan AUC_{0-24} in SIADH patients is expected to be significantly higher (up to 3 fold), the safety margins are likely to be lower than noted in table below:

Species	NOAEL dose, mg/kg/day	AUC_{0-24}, ng.h/ml	Ratio of animal / human dose based on AUC_{0-24}
Rat, 13-WK, oral	M: 1 F: 3	M: 59.6 F: 549	M: 0.16 F: 0.15
Rat, 13-WK oral	2	M: 13517 F: 10141	M: 3.8 F: 2.8
Rat, 26 WK, oral	1	M: 86 F: 117	M: 0.024 F: 0.03
Rat, 4 WK, IV bolus	1.25	1339	0.4
Rat, 4 WK, IV infusion	10	M: 9288 F: 4944	M: 2.6 F: 1.4
Dog, 13 WK, oral	10	M: 39700 F: 41000	M: 11 F: 11.45
Dog, 52 WK, oral	10	M: 75092 F: 111683	M: 21 F: 31.2
Dog, 4 WK, IV bolus	2	M: 13517 F: 10141	M: 3.8 F: 2.8
Dog, 4 WK, IV infusion	10	M: 137447 F: 120168	M: 38 F: 33.6
Rat, embryofetal develop., IV	2.5	3803	1
Rabbit, embryofetal Develop., IV	3	3458	0.96
Rat, pre- & post-natal develop., IV	0.5	203	0.06
Human dose 20 mg IV bolus followed by 40 mg IV infusion for 4 days in healthy volunteers		3580	

M =male, F= female

B. Pharmacologic activity

Conivaptan hydrochloride (YM087, PD185718, CI-1025, Vaprisol®) is a nonpeptide antagonist of arginine-vasopressin (AVP) V_{1A} and V_2 receptors. The V_{1A} receptor mediates contraction in human blood vessels and aggregation of human platelets. The V_2 receptor modulates water clearance through its functional coupling to aquaporine channels in the apical membrane of the collecting tubules in the human kidney. According to the sponsor, conivaptan does not bind to V_{1B} receptors located in anterior pituitary β cells of pancreas and adrenal medulla, although increase in adrenal weight and high conivaptan concentration in adrenal gland suggest it is a target organ. As a new molecular entity and first in class, conivaptan is indicated for treatment of Syndrome of Inappropriate Antidiuretic Hormone (SIADH). Conivaptan has been shown to significantly increase plasma sodium concentrations and urine volume excretion with minimal effect on urinary electrolyte excretion. In conscious dogs and rats, IV and oral conivaptan increased urine volume (V_2 antagonist) and reduced urine osmolality (from $\geq$1500 to $\leq$100 mOsm/kg

H_2O) dose-dependently. In a rat model of SIADH, intravenous (0.01-0.1 mg/kg) and oral (0.3-3 mg/kg) conivaptan inhibited AVP induced hyponatremia. Systemic exposure at these doses is 100X clinical based on body surface area (mg/m^2) comparisons.

The sponsor [redacted]
IV therapeutic agent. However, since conivaptan is metabolized by CYP3A4 system. There is significant potential for the drug to interact with other CYP3A4 metabolized drugs, limited the development to acute IV treatment. The current therapeutic regimen is 20 mg IV bolus followed by 40 mg IV infusion for 4 days in SIADH patients in a hospital setting (AUC_{0-24} 3580 ng.h/ml). As a V_2 antagonist conivaptan can increase free water clearance correcting plasma sodium levels. By inhibiting platelet aggregation and vasoconstriction by V_{1A} receptors, it blocks reflex mediated AVP caused by V_2 blockade.

C. Nonclinical safety issues relevant to clinical use
Administration of conivaptan PG/EtOH clinical formulation is recommended in large veins typically used for humans to minimize the significant vascular irritation observed in nonclinical studies. The degree of inflammation was severe enough to terminate a 4 week rat IV infusion and dog IV bolus study. Conivaptan caused significant aquaresis leading to dehydration in normal animals as a function of its pharmacologic action. This should not be a major problem in the indicated SIADH population. Conivaptan is primarily biliary/fecal excreted (90%). The metabolic profile among species is quite similar although plasma levels of metabolites are <10% of the administered dose suggesting a minimal contribution of metabolites to pharmacologic activity. This would suggest that renal/hepatic impairment will not be problematic in clinical use. SIADH patients may have renal and hepatic pathology and these organs are identified target organs of toxicity with conivaptan administration however functional changes will likely be monitored in the patient population. The liver toxicity requires relatively high exposures; which are above systemic therapeutic exposures for prolonged durations. The renal findings were observed after one week IV infusions in rats at 4 times therapeutic exposure.
Effects on estrus cycles and female reproduction occurred in rats at therapeutic exposures. Conivaptan delayed parturition and physical/functional development including reflexes in offspring. Conivaptan is contraindicated during pregnancy and lactation based on these findings. Conivaptan was not mutagenic or carcinogenic.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

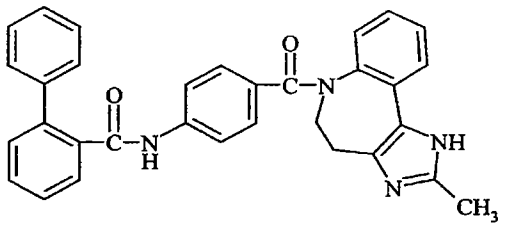
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-697
Review number: 1
Sequence number/date/type of submission: NDA
Information to sponsor: Yes (x) No ( )
Sponsor and/or agent: Yamanouchi, Mack Centre IV, S, 61 Paramus Road, Paramus, NJ, 07652
Manufacturer for drug substance: Yamanouchi

Reviewer name: Fred K. Alavi, Ph.D.
Division name: Division of Metabolic and Endocrine Drug Products
HFD #: 510
Review completion date: Aug 25, 04

Drug:

Trade name: Vaprisol®
Generic name: Conivaptan
Code name: YM087 (CI-1025),
Chemical name: N-[4-[(1,4,5,6-tetrahydro-2-methyl-6-imidazo[4,5-d] [1] benzazepinyl) carbonyl] phenyl][1,1-biphenyl]-2-carboxamide monohydrochloride
CAS registry number: 168626-94-6
Molecular formula/molecular weight: $C_{32}H_{26}N_4O_2$ / 535.04
Structure:



• HCl

Relevant INDs/NDAs/DMFs: IND : [redacted] IND 56,813
Drug class: arginine-vasopressin (AVP) V_{1A} and V_2 receptors antagonist.
Indication: Hyponatremia in euvolemic or hypervolemic patients
Clinical formulation:

Active drug: conivaptan hydrochloride, 5 mg/ml
Inactive Ingredients: [redacted]propylene glycol,[redacted] ethanol in water per ml of injectable solution

Route of administration: intravenous, 5 mg/ml , 4 ml per ampule
Proposed use: hyponatremia (MRHD, 20 mg bolus followed by [redacted] average AUC_{0-24} **3580** ng.h/ml/day, total AUC_{0-96h} 14320 ng.h/ml in healthy volunteers)

Disclaimer: Use of sponsor's material was restricted to the molecular structure and PK/TK and other data tables. Scanned tables pasted as images in the review, can be easily recognized by their skewed line and text alignments. Some of the introductory text that was found to represent the drug background accurately were modified and incorporated into the INTRODUCTION section.

Toxicology studies reviewed:
In this submission, intravenous and oral toxicology studies in rats and dogs, intravenous reproductive toxicity and oral mouse and rat carcinogenicity studies were reviewed.

Studies not reviewed within this submission:
Most of the early toxicology studies were performed with oral gavage administration of conivaptan. Toxicology, genotoxicity and oral reproductive toxicity studies reviewed by Tim Link from Cardiorenal Division were not reviewed (reviews are in DFS, IND [redacted]

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Conivaptan hydrochloride (YM087, PD185718, CI-1025, Vaprisol®) is a nonpeptide antagonist of arginine-vasopressin (AVP) V_{1A} and V_2 receptors. This is a new molecular entity first in class. There are no approved AVP antagonists in the market to date. YM087 was originally licensed from Yamanouchi by Parker Davis-Warner Lambert group. After acquisition of Warner Lambert-Parker Davis by Pfizer, the development rights were transferred back to Yamanouchi. Yamanouchi is developing YM087 for the treatment of hyponatremia in euvolemic or hypervolemic patients and congestive heart failure (CHF). The hyponatremia indication will involve acute treatment with YM087 with the primary outcome measure being an increase in serum sodium. Effects of conivaptan in animals models suggests that it would be effective for treatment of hyponatremia in patients with CHF or SIADH unlike hypertonic saline combined with loop diuretic (standard care) conivaptan is not associated with hypokalemia of fluid overload.

According to the sponsor, approximately 1% to 1.5% of the 30 million people in United States (300,000-450,000) and 4 million Canadian hospitalized every year (40,000-60,000) are complicated by hyponatremia. Fourthly nine to 78% of the hyponatremic episodes occur during hospitalization/treatment for a concurrent disease. In patients with serum sodium <125 mmol/L: euvolemic patients constitute 34% to 39% of the hyponatremic population, while hypervolemic patients constitute 10% to 17%. Duration of hyponatremia averages 6 days, with a mortality of 41.7% in patients with serum sodium 110 to 125 mmol/L.

YM087 has been shown to significantly decrease body weight (aquaresis) and increase plasma sodium concentrations and urine volume excretion without a significant reduction in urinary electrolyte excretion in rats and dogs. In rat model of Syndrome of Inappropriate Antidiuretic Hormone (SIADH), oral administration of YM087 (0.3-3 mg/kg/day) reversed the AVP-induced decrease in plasma sodium concentration (hyponatremia).

In healthy subjects under physiological conditions, V_1-antagonists were found to have no or little effect on blood pressure, while V_2-antagonists increased diuresis. Under conditions of increased vasopressin levels, V_{1A}- and V_2-antagonists have altered blood pressure and displayed "aquaretic" effects, respectively. Hyponatremia is a common and potentially serious electrolyte disturbances in medicine and thiazide diuretics are the most common cause of drug-induced hyponatremia.

The effects of conivaptan on CNS, cardiovascular and respiratory function were evaluated in various animal models. Conivaptan had no notable CNS effect in male mice. At doses up to 0.01 mg/kg conivaptan had no effect on cardiovascular and respiratory function in anesthetized dogs. Respiratory rate increased by 33 to 44% at doses >0.03 mg/kg. Left ventricular pressure increased by 11% and femoral arterial blood flow decreased by 15% at 0.3 mg/kg. ECG parameters in anesthetized dogs were not affected at doses up to 0.3 mg/kg. In the hERG channel assay, the IC_{50} was 2.24 μM. Generally, an IC_{50} less than 1 μM suggest some potential to cause QT prolongation and biological significance. The potential effect of conivaptan on cardiac action potential was examined using guinea pig papillary muscle. The action potential duration (APD) was not affected at concentrations less than 1 μM, however, at 10 μM conivaptan slightly prolonged APD30, APD60 and APD90 by 3.4, 3.3 and 2.7%, respectively. The analyzed concentration of conivaptan hydrochloride in the 0.1, 1 and 10 μM perfusion solutions in the chamber in the advanced study was 0.0855, 0.746 and 7.76 μM, respectively.

The slight increase in prolongation of ADP was considered to have minimal biological impact, since 10 μM (5.35 mg/ml) is significantly greater than clinical exposure.
Initially the sponsor had planned to develop YM087 for [redacted] parenteral (IV route) [redacted] In this NDA conivaptan is indicated for hyponatremia associated with SIADH. The hyponatremia indication will involve acute treatment with YM087 with the primary outcome measure being an increase in serum sodium. The proposed dosage is 20 mg on day 1 followed by 40 mg/day infusion for 4 days. To get animal to human exposure, the AUC for IV clinical formulation was obtained from AUC_{0-i} divided by number of days (10740 ng.h/ml/3= 3580 ng.h/ml/day).

2.6.2.2 Primary pharmacodynamics

Mechanism of action:
YM087 is a V_{1A} and V_2 vasopressin antagonist. The V_{1A} receptor mediates contraction in human blood vessels and aggregation of human platelets. The V_2 receptor modulates water clearance through its functional coupling to aquaporine channels in the apical membrane of the collecting tubules in the human kidney. YM087 antagonizes these effects. Arginine vasopressin (AVP) or antidiuretic hormone (ADH) is a centrally derived neuropeptide hormone primarily responsible for water conservation. It is synthesized in the magnocellular neurosecretory cells of the paraventricular and supraoptic nuclei of the hypothalamus and stored in the posterior pituitary for release into the circulation after activation of the neurosecretory cells. Vasopressin (V) receptors are subdivided into V_1 (including V_{1A} and V_{1B} receptor subtypes) and V_2-receptors with distinct localization, function and signaling pathways. The V_{1A} receptor affects vasomotor tone in blood vessels and is also found on platelets as a mediator of platelet aggregation. The V_{1B}-receptor is involved in the stimulating effect of AVP on adrenocorticotropic hormone (ACTH) secretion. The V_1 receptor is linked to phosphatidylinositol metabolism and calcium mobilization. The V_2 receptor is functionally coupled to aquaporine channels in the apical membrane of the collecting tubules in the human kidney, modulating water clearance. Activation of V_2 receptors conserves water and concentrates urine by enhancing hydro-osmotic flow of water from the luminal fluid through the cells of the collecting tubule of the kidney to the medullary interstitium. This is the major means by which the body maintains osmolality and body fluid volume. The intracellular signaling system of the V_2 receptor is via adenylate cyclase. In conscious rats and dogs, IV or oral conivaptan increased urine volume (V_2 receptor antagonism) and reduced urine osmolality (from $\geq$1500 to $\leq$ 100 mOsm/kg H20) dose-dependently. In a rat model of SIADH, intravenous (0.01-0.1 mg/kg) and oral (0.3-3 mg/kg) conivaptan inhibited AVP induced hyponatremia

Drug activity related to proposed indication:
Elevated AVP is observed in most patients with hyponatremia despite hyposomolality of the plasma. Inappropriate AVP (SIADH) occurs in euvolemic and hypervolemic hyponatremic patients. Severe hyponatremia can lead to convulsions and mortality. Usually stringent restriction of water intake and IV hypertonic saline plus a loop diuretic are used to treat hyponatremia. However rapid and exaggerated correction of hyponatremia can aggravate hyponatremic encephalopathy. V_2 antagonists are expected to correct plasma sodium through their aquaretic action without increasing sodium excretion and to be more effective in these cases of difficult to treat hyponatremia.

Euvolemic hyponatremia is often associated with sustained or intermittently elevated levels of antidiuretic hormone (ADH) that are inappropriate in the face of osmotic and volume stimuli that normally inhibit ADH secretion. This condition is known as Syndrome of Inappropriate ADH (SIADH) secretion. SIADH now is known to be associated with many disease states that involve stress: malignant tumors, central nervous system disorders (i.e. meningitis, head trauma, brain abscess, encephalitis), diseases of the lung (i.e. pneumonia, tuberculosis), drugs (ie, vincristine, vinblastine, chlorpropamide), acute psychosis, and the postoperative period. Risk of symptomatic hyponatremia is greater in women (pre-menopausal) and may be linked to the menstrual cycle.

Hypervolemic hyponatremia is observed when total body sodium is increased but total body water is increased to a greater extent. This condition is difficult to treat and recurs frequently because of irreversible dysfunction of the liver, heart, or kidney. In heart failure, cirrhosis, and nephrotic syndrome, reduced effective arterial volume results in the nonosmotic stimulation of arginine vasopressin and an increase in thirst. One of the methods of treatment has been restriction of water intake. However, compliance with water restriction is difficult and uncomfortable. Diuretics are the primary agents for symptomatic relief of edema. Thiazide diuretics impair urinary dilution and may exacerbate hyponatremia. Nonspecific loop diuretics cause sodium excretion, and volume loss may trigger thirst and promote ingestion of water. The standard of care is generally hypertonic saline with loop diuretics. Conivaptan is not associated with hypokalemia or fluid overload associated with standard care.

Inhibition of rodent V_1 and V_2 receptor binding:

As noted before, YM087 is antagonist at both V_{1A} and V_2 receptors. The primary efficacy of YM087 is thought to be due to blockade of AVP at V_2 receptors leading to aquaresis. YM087 was examined by the sponsor for at least 20 other receptors. YM087 had no affinity (IC_{50} > 10,000 nM) for adenosine, adrenergic, dopamine, t-aminobutyric (GABA), histamine, serotonin, muscarinic, benzodiazepine, angiotensin II, endothelin, neuropeptide Y, TRH (thyrotropin releasing hormone), VIP (vasoactive intestinal peptide), ANF (atrial natriuretic factor), CRF (corticotropin releasing factor), EGF (epidermal growth factor), forskolin, phorbol ester, inositol triphosphate, estradiol, or testosterone receptors. OPC-21268 and OPC-31260 are two experimental AVP antagonists [redacted]

Binding Affinity of YM087 and Reference Compounds for AVP Receptor Subtypes From Rat Tissue Membrane Preparations

Drug	K_i (nM)		
	V_{1A} (liver)	V_{1B} (pituitary)	V_2 (kidney)
AVP	1.09 ± 0.25	0.23 ± 0.03	3.23 ± 1.26
YM087	0.48 ± 0.07	>100,000	3.04 ± 1.51
OPC-21268	23.5 ± 4.39	>2,000,000	152,000 ± 77000
OPC-31260	193 ± 76.9	36500 ± 9400	42.3 ± 14.3

Inhibition of human V_1 and V_2 receptor binding:

Membrane fractions isolated from human liver, pituitary, and kidney, respectively, and transfected in COS-1 cells were obtained from cells expressing the V_1 and V_2 receptors,

respectively. YM087 inhibited binding of [^{3}H] AVP to V_{1A} and V_2 receptors. YM087 did not reduce specific binding to V_{1B} receptors.

$V_{1A/B}$ receptors mediate phospholipase C activation and intracellular calcium mobilization. V_2 receptors are coupled to adenylate cyclase. V_{1A} present in vascular smooth muscle, hepatocytes, platelets, mesangial cells, cardiomyocytes and are thought to be important in maintenance of vascular tone and platelet aggregation. V_{1B} receptors are located in anterior pituitary β cells of pancreas and adrenal medulla where they stimulate ACTH, insulin and catecholamine release respectively.

V_2 receptors are coupled to aquaporine water channels in the apical membrane of renal collecting duct. Activation of V_2 results in H_2O reabsorption and urine concentration by increasing hypo-osmotic H_2O plus ions from the lumen to medullary collecting duct. Systemic V_2 antagonist causes a reflex mediated increase in plasma AVP resulting in the potential for undesirable V_{1A} activity hence the need for a dual V_{1A}, V_2 receptor antagonist to treat hyponatremic patients with CHF.

Inhibition of Presser Responses to AVP (V_1 Antagonist Activity) Rat, Dog

Orally administration of YM087 in conscious rats dose dependently inhibited the presser response to AVP (30 mU/kg), a measure of V_{1A} antagonist activity (see table below). The inhibition was maximal at 30 minutes postdose with an ID_{50} (dose which inhibited 50% of AVP-induced presser response) of 0.32 mg/kg. The inhibitory effect of a 1 mg/kg oral dose of YM087 was sustained for over 8 hours. In pithed rats, IV administration of YM087 dose-dependently inhibited AVP-induced increases in blood pressure. In contrast, YM087 had no effect on the presser responses to angiotensin II or norepinephrine.

In dogs, YM087 (0.003-0.1 mg/kg, IV) inhibited the presser response to AVP in a dose-related manner with an ID_{50} value of 0.026 mg/kg (98 times more potent than OPC-21268).

Inhibitory Effects of YM087 and OPC-21268 on the Pressor Response to AVP (V_{1A} Receptor Antagonistic Activity)

Species	Drug	ID_{50} (mg/kg, PO)	ID_{50} (mg/kg, IV)	Ref
Rat	YM087	0.32	0.013	10
Rat	OPC-21268	7.02	0.35	10
Dog	YM087	ND	0.026	10,11
Dog	OPC-21268	ND	2.55	10,11

All doses were based on the molecular weight of the HCl salt of YM087.

Diuretic Effects (V_2 Antagonist Activity)

The aquaretic effect of YM087 was studied in water deprived (16-20 hr) male Wistar rats. Water deprivation was made to stimulate endogenous AVP secretion. YM087 administered orally (0.01-3 mg/kg) or IV (0.1-0.3 mg/kg) increased urine volume (from about 0.5 to 10 ml) and reduced urinary osmolality (from about 2000-200 mOsm/kg H20) in a dose-dependent manner in water deprived conscious rats.

Water Diuretic Effects in Dogs

In conscious female beagle dogs, administration of YM087 orally (0.03-0.3 mg/kg) or IV (0.01-0.1 mg/kg) exerted a water diuretic effect, by increasing the urine volume from about 0.1 ml/min to 1.5 ml/min and reducing the urinary osmolality from about 1500 to less than 100 mOsm/kg H20 in a dose-dependent manner with little or no effect on urinary electrolyte excretion. In dogs with pacing-induced congestive heart failure, YM087 (0.1 mg/kg, IV)

increased urinary flow 3-fold and reduced urine osmolality markedly by increasing free water clearance.

YM087 activity in the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) Model
SIADH models in male Wistar rats were produced by implanting an osmotic pump for continuous AVP release (3 μg/day). Water was administered by oral gavage 3 times a day (30 ml/kg each). Animals receiving a continuous AVP infusion (control group) showed a significant decrease in plasma sodium concentration (hyponatremia) as compared with a non-AVP infusion (sham) group. Oral administration of YM087 (0.3-3 mg/kg/day) reversed the AVP-induced decrease in plasma sodium concentration. Furosemide (100 mg/kg/day PO) was ineffective at correcting the hyponatremia and also caused hypokalemia in this model.

2.6.2.3 Secondary pharmacodynamics
Aquaretic effects are observed in rats with CHF due to myocardial infarction over the dose range 0.03-0.3 mg/kg/d and in dogs with rapid RV pacing-induced CHF at 0.1 mg/kg/d. Intra venous conivaptan at 0.1-0.3 mg/kg/d significantly improved hemodynamic parameter: LVEDP, RAP and TPR in several rat and dog models of CHF. Male Wistar rats with A-V shunts given IV 0.1 mg/kg conivaptan showed an acute impairment of RAP, RVEDP and decreased LVEDP. Conivaptan (0.1 mg/kg IV) significantly ameliorated AVP-induced heart failure in dogs.

2.6.2.4 Safety pharmacology

CNS effect:
For CNS evaluations, 4 groups of male mice were treated with YM087 and different CNS active test drugs. In the first group mice were treated with single oral doses of YM087 in 0.5% methylcellulose (MC) by gavage at 0.3, 3, or 30 mg/kg, and rectal temperature and CNS functions (1 hour post dose) were assessed. The second group was dosed with hexobarbital at 85 mg/kg (IP) and effects on length of sleep time were observed. The third group was given pentetrazol at 5 mg/ml (IV) and the time of clonic convulsion, tonic extensor, tonic flexor, and death was recorded. The fourth group was given an electroshock (25 mA for0.2 seconds) and the number of tonic convulsions were evaluated. YM087 had no effect on behavior, body temperature, induced sleep time, or frequency of pentetrazol-induced or electroshock induced convulsions observed following single doses up to 30 mg/kg.

Cardiovascular and Respiratory effects:
Respiratory rate, arterial blood pressure, heart rate, left ventricular pressure, blood flow, and ECG parameters were evaluated continuously in anesthetized dogs given vehicle or YM087 at 0.001, 0.003, 0.01, 0.10, or 0.30 mg/kg. Doses were administered by intravenous infusion in rising doses at 10 to 13 minute intervals. There were no effects observed at <0.01 mg/kg. Respiratory rate increased 33% to 44% at >0.03 mg/kg. Left ventricular pressure increased 11% and femoral arterial blood flow decreased 15% at 0.3 mg/kg. Electrocardiographic parameters were unaffected. In conscious and anesthetized dogs, IV administration of 15 and 30 mg/kg respectively did not prolong QTc. Furthermore, repeated dose oral and bolus IV dog studies did not shown QTc prolongation.

Effects on the hERG current

To assess the QT potential of YM087 (conivaptan hydrochloride), the inhibitory effect of YM087 on the hERG (human ether-à-go-go-related gene) potassium channel expressed in human embryonic kidney 293 (HEK293) cells was evaluated and compared to that of E-4031, an IKr inhibitor, by patch clamp technique. The effect of conivaptan hydrochloride on hERG current was studied at concentrations of 0.1, 1 and 10 μM (n = 4 in each concentration). Conivaptan hydrochloride inhibited hERG current in a concentration-dependent manner, with statistically significant inhibition of it observed at all concentrations examined ($P<0.05$, compared to DMSO vehicle). The analyzed content of conivaptan hydrochloride in the 0.1, 1 and 10 μM perfusion solutions was 0.134 ± 0.024, 0.850 ± 0.028 and 8.47 ±0.66 μM, respectively. Potassium currents observed in the presence of YM087 were corrected for the mean vehicle rundown. The IC_{50} value for YM087 inhibition of hERG current was 2.24 μM. The drug concentrations between 0.1 and 1 μM have been considered biologically significant. At concentrations of 1 to 10 μM, the general consensus is to do further evaluations. Inhibition of hERG channel at doses greater than 10 μM has been considered biologically insignificant since most drugs at high concentrations will give false positive hERG channel inhibition.

Effect on cardiac action potential in isolated guinea pig papillary muscles

The sponsor also examined the effects of conivaptan hydrochloride on action potentials in isolated guinea pig papillary muscles. The 6 isolated papillary muscles in each experimental group were perfused with YM087 at 0.1, 1 and 10 μM for 45 minutes to determine the effects on resting membrane potentials (RMP) and action potential amplitude (APA). RMP, APA and maximal upstroke velocity (dV/dtmax) and action potential durations (APD) at 30%, 60% and 90% repolarization (APD30, APD60 and APD90) before and 45 minutes after application of the test substance were analyzed. E-4031, an IKr blocker, was used as the reference compound, had no effect on RMP, APA and dV/dtmax at a concentration of 0.1 μM. In contrast, E-4031 extended the APD30, APD60 and APD90 by 22.5%, 29.8% and 29.1%, respectively and the changes were significantly different from those of the vehicle control. Conivaptan hydrochloride had no effects on RMP, APA and dV/dtmax at up to 10 μM. The APD were also not affected by the treatments of conivaptan hydrochloride at concentrations of 0.1 and 1 μM. However, conivaptan hydrochloride at the highest concentration of 10 μM slightly prolonged APD30, APD60 and APD90 by 3.4, 3.3 and 2.7%, respectively, and the prolongation observed in APD60 and APD90 were statistically significant. The analyzed concentration of conivaptan hydrochloride in the 0.1, 1 and 10 μM perfusion solutions in the chamber in the advanced study was 0.0855, 0.746 and 7.76 μM, respectively. Although conivaptan hydrochloride showed statistically significant prolongation effects on APD in isolated guinea pig papillary muscles at the highest concentration, the magnitude of prolongation was rather small (almost 3% changes). The slight increase in prolongation of ADP was considered to have minimal biological impact, since 10 μM is significantly greater than clinical exposure.

The effects of M1, M2, M4 and M7 on hERG channel expressed in HEK293 cells and APD in isolated papillary muscle suggest no significant effect at concentration of 10 μM.

2.6.2.5 Pharmacodynamic drug interactions

No specific pharmacodynamic drug interaction studies were performed in animals. Since both loop diuretic and YM087 may interact pharmacodynamically, it is expected that a lower dose of loop diuretic may be needed to reduce the risk of hypokalemia in patients with CHF given conivaptan.

At the end of the Phase 2 meeting the sponsor present the table below showing the IC_{50} for CYP3A4 inhibition of several VAP receptor antagonists. It appears that all AVP antagonist except for [redacted] are powerful inhibitors of CYP3A4 enzyme, thus all are suspected to increase exposure to drugs that are metabolized by CYP3A4 (i.e. simvastatin).

Company	Compound	CYP3A4 IC_{50}, μM
[redacted]	[redacted]	43
		0.93
		0.15
Yamanouchi	Conivaptan (YM087)	0.47

2.6.3 PHARMACOLOGY TABULATED SUMMARY

The dual V_{1A} and V_2 receptor activity of conivaptan *in vitro* and *in vivo* studies in hyponatremic models suggest that conivaptan will improve condition of hyponatremia in SIADH (pure H_2O retention) and in CHF which is complicated by sodium and H_2O retention. Based on animal studies, there is a demonstrated pharmacologic profile for treatment of euvolemic and hypervolemic hyponatremia.

Pharmacology Tabulated Summary ***Test Article: Conivaptan Hydrochloride***

Type of Study	Test System	Method of Administration	Testing Facility	Study Number
Primary pharmacodynamics				
Selectivity and specificity for arginine vasopressin (AVP) receptor subtypes				
Affinity and binding characteristics for rat AVP receptor subtypes	Rat liver V_{1A}, pituitary V_{1B} and kidney V_2 and uterus oxytocin receptors	In vitro	Yamanouchi	R087-PH-002
	Rat liver V_{1A} and kidney V_2 receptors	In vitro	Yamanouchi	R087-PH-001
Affinity and binding characteristics for human AVP receptor subtypes	Human cloned V_{1A}, V_{1B} and V_2 receptors expressed in CHO cells	In vitro	Yamanouchi	R087-PH-004
	Human cloned V_{1A} and V_2 receptors expressed in CHO cells	In vitro	Yamanouchi	R087-PH-005
Affinity for various receptors	Various receptors	In vitro	—	R087-PH-024
***In vitro* functional anti-AVP activity**				
Effect on AVP-induced second messenger activation				
Effect on AVP-induced intracellular calcium elevation	Human cloned V_{1A} and V_{1B} receptors expressed in CHO cells	In vitro	Yamanouchi	R087-PH-009
Effect on AVP-induced intracellular cAMP production	Human cloned V_2 receptor expressed in CHO cells	In vitro	Yamanouchi	R087-PH-008
***In vivo* V_2 antagonistic activity**				
Aquaretic effect	Conscious (water deprived) rats	Intravenous/Oral	Yamanouchi	R087-PH-012
Aquaretic effect and electrolyte excretion	Conscious dogs	Intravenous/Oral	Yamanouchi	R087-PH-022
Diuretic effect and electrolyte metabolism	Conscious dogs	Intravenous (combination with furosemide)	—	R087-PH-014

AVP; arginine vasopressin, CHO; Chinese hamster ovary, cAMP; cyclic adenosine monophosphate.
Yamanouchi; Yamanouchi Pharmaceutical Co., Ltd.

Type of Study	Test System	Method of Administration	Testing Facility	Study Number
***In vivo* V_{1A} antagonistic activity**				
Effect on AVP-induced pressor responses	Pithed rats	Intravenous	Yamanouchi	R087-PH-010
	Conscious rats	Oral	Yamanouchi	R087-PH-010
	Anesthetized dogs	Intravenous	Yamanouchi	R087-PH-022
Improvement of hyponatremia				
Effect on syndrome of inappropriate secretion of antidiuretic hormone (SIADH)				
Effect on plasma sodium concentration	AVP-infused and water-loaded rats	Intravenous	Yamanouchi	R087-PH-017
	AVP-infused and water-loaded rats	Oral	Yamanouchi	R087-PH-013
Effect on hypervolemic hyponatremia				
Effect on plasma sodium concentration	AVP-infused and water-loaded CHF rats	Oral	Yamanouchi	R087-PH-039
Pharmacological profile of human metabolites				
Affinity for AVP receptor subtypes and oxytocin receptor	Rat liver V_{1A}, kidney V_2 and uterus oxytocin receptors	In vitro	[redacted]	R087-PH-028
	Human cloned V_{1A}, V_{1B} and V_2 receptors expressed in CHO cells, and uterus oxytocin receptors	In vitro	Yamanouchi	R087-PH-018
Affinity for various receptors	Various receptors	In vitro	[redacted]	R087-PH-028
Secondary pharmacodynamics				
Effect on congestive heart failure (CHF) in rats				
Aquaretic and hemodynamic effects	Myocardial infarction-induced CHF rats	Intravenous	Yamanouchi	R087-PH-049
Hemodynamic effect	Aortocaval shunt-induced CHF rats	Intravenous	Yamanouchi	R087-PH-050
Effect on CHF in dogs				
Hemodynamic effect	AVP-induced heart failure dogs	Intravenous	Yamanouchi	R087-PH-047
Aquaretic and hemodynamic effects	Rapid RV pacing-induced CHF dogs	Intravenous	Yamanouchi	R087-PH-048

AVP; arginine vasopressin, CHF; congestive heart failure, CHO; Chinese hamster ovary, RV; right ventricular.
Yamanouchi: Yamanouchi Pharmaceutical Co., Ltd.
[redacted]

Organ Systems Evaluated	Species/ Strain	Method of Admin.	Concentrations/ Doses [a]	Gender [b] and No. per Group	Noteworthy Findings [c]	GLP Compliance	Study Number
***In vivo* functional anti-AVP activity**							
V_2 antagonistic activity							
Aquaretic effect in conscious rats	Wistar rats	Intravenous	0.01, 0.03, 0.1 and 0.3 mg/kg	5 to 14M	Increased urine volume and reduced urine osmolality with ED_3 value of 0.028 mg/kg.	No	R087-PH-012
		Oral	0.1, 0.3, 1 and 3 mg/kg	5 to 10M	Increased urine volume and reduced urine osmolality with ED_3 value of 0.24 mg/kg.		
Aquaretic effect, urinary electrolyte excretion in conscious dogs	Beagle dogs	Intravenous	0.01, 0.03 and 0.1 mg/kg	2 to 5F	Increased urine volume (UV) and reduced urine osmolality (U_{osm}) with little effect on urinary electrolyte excretion.	No	R087-PH-022
		Oral	0.03, 0.1 and 0.3 mg/kg	4 to 7F	Increased UV and reduced U_{osm} with little effect on urinary electrolyte excretion.		
Diuretic effect and electrolyte metabolisms in combination with low dose furosemide in conscious dogs	Beagle dogs	Intravenous	0.03 mg/kg (alone) 0.01 mg/kg together with 0.03 mg/kg furosemide	6E	Aquaretic effect with no effect on electrolyte metabolism (alone). The combination together with low dose furosemide can produce a diuretic effect without affecting blood electrolyte levels.	No	R087-PH-014
V_{1A} antagonistic activity							
Effect on AVP-induced pressor responses in pithed and conscious rats	Wistar rats (pithed)	Intravenous	0.003, 0.01 and 0.03 mg/kg	4M	Inhibition AVP-induced increase in diastolic blood pressure with ID_{50} value of 0.014 mg/kg.	No	R087-PH-010
	Wistar rats (conscious)	Oral	0.1, 0.3 and 1 mg/kg	5 to 7M	Inhibition pressor response to AVP with ID_{50} value of 0.32 mg/kg. The effect was sustained for over 8 h after dosing.		
Effect on AVP-induced pressor responses in anesthetized dogs	Mongrel dogs	Intravenous	0.003, 0.01, 0.03 and 0.1 mg/kg	3E	Inhibition AVP-induced increase in mean blood pressure with ID_{50} value of 0.0269 mg/kg.	No	R087-PH-022

ED_3; dose required to increase urine flow to 3 mL, UV; urine volume, U_{osm}; urine osmolality, AVP; arginine vasopressin, ID_{50}; dose required to induce 50% inhibition.
a - Single dose unless specified otherwise.
b - M, male; F, female; E, either sex.
c - Findings relate to conivaptan unless specified otherwise.

Type of Study	Test System	Method of Administration	Testing Facility	Study Number
Safety pharmacology				
General pharmacology studies				
Effect on central nervous system	Mice	Oral	Yamanouchi	R087-PH-015
Effect on respiratory and cardiovascular systems	Anesthetized dogs	Intravenous	Yamanouchi	R087-PH-016
Potential for QT prolongation				
Effect on the potassium current via hERG channels	Human cloned hERG expressed in HEK293 cells [a]	In vitro	[redacted]	R087-PH-055
	Human cloned hERG expressed in HEK293 cells	In vitro	[redacted]	R087-PH-020
Effect on cardiac action potential parameters	Guinea pig papillary muscles [a]	In vitro	[redacted]	R087-PH-056
	Guinea pig papillary muscles	In vitro	Yamanouchi	R087-PH-021
Effect on general condition and cardiovascular systems	Conscious dogs [a]	Intravenous	[redacted]	R087-PH-019
	Anesthetized dogs [a]	Intravenous		R087-PH-025
Potential for QT prolongation of human metabolites				
Effect of human metabolites on the potassium current via hERG channels	Human cloned hERG expressed in HEK293 cells [a]	In vitro	[redacted]	R087-PH-057
Effect of human metabolites on cardiac action potential parameters	Guinea pigs papillary muscles [a]	In vitro	[redacted]	R087-PH-058
	Guinea pigs papillary muscles	In vitro		R087-PH-027

hERG; human *ether-à-go-go*-related gene. HEK293: human embryonic kidney 293.
a - GLP compliance.
Yamanouchi: Yamanouchi Pharmaceutical Co., Ltd.

[redacted]

Organ Systems Evaluated	Species/ Strain	Method of Admin.	Concentrations/ Doses [a]	Gender [b] and No. per Group [c]	Noteworthy Findings [d]	GLP Compliance	Study Number
Selectivity and specificity for AVP receptor subtypes							
Radioligand binding to rat liver V_{1A}, pituitary V_{1B}, kidney V_2 and uterus oxytocin receptors	Rat	In vitro	Multiple concentrations	3 to 11	Affinity constants (Ki value) for V_{1A}, V_2 and oxytocin receptors were 0.505, 2.84 and 41.6 nM, respectively. No reduction in the specific binding to V_{1B} receptors.	No	R087-PH-002
Radioligand binding to rat liver V_{1A} and kidney V_2 receptors	Rat	In vitro	0.1, 0.3, 1 and 3 nM	5 to 6	Concentration-dependent increase in Kd without reduction in Bmax (competitive manner).	No	R087-PH-001
Radioligand binding to human cloned receptors expressed in CHO cells	Human	In vitro	Multiple concentrations	5	Ki value for V_{1A} and V_2 receptors were 4.45 and 1.81 nM, respectively. No reduction in the specific binding to V_{1B} receptors.	No	R087-PH-004
Radioligand binding to human cloned V_{1A} and V_2 receptors	Human	In vitro	0.3, 1 and 3 nM	4	Concentration-dependent increase in Kd without reduction in Bmax (competitive manner).	No	R087-PH-005
Radioligand binding to various receptors	Various	In vitro	0.1, 1 and 10 µM	1 to 2	No effect on the radioligand binding to 28 different receptors except for the non-selective opiate receptor. Ki value for rat opiate receptor was 1.72 µM.	No	R087-PH-024
***In vitro* functional anti-AVP activity**							
Effect on AVP-induced second messenger activation							
Effect on AVP-induced intracellular calcium elevation in cloned V_{1A} and V_{1B} receptors expressing CHO cells	Human	In vitro	Multiple concentrations	3 to 4	Inhibited AVP-induced intracellular calcium elevation mediated through V_{1A} receptors with IC_{50} value of 1.05 nM, but not through V_{1B} receptors. Did not show intrinsic agonistic activity up to 10 µM.	No	R087-PH-009
Effect on AVP-induced cAMP production in cloned V_2 receptor expressing CHO cells	Human	In vitro	Multiple concentrations	3 to 8	Inhibited AVP-induced cAMP production mediated through V_2 receptors, with IC_{50} value of 1.67 nM. Did not show intrinsic agonistic activity up to 10 µM.	No	R087-PH-008

AVP; arginine vasopressin, Ki; inhibitory constant, Kd; dissociation constant, Bmax; receptor density, CHO; Chinese hamster ovary, IC_{50}; concentration required to induce 50% inhibition, cAMP; cyclic adenosine monophosphate.
a - Single dose unless specified otherwise.
b - M, male; F, female; E, either sex
c - In the case of in vitro studies, the numbers of independent determinations were indicated.
d - Findings relate to conivaptan unless specified otherwise.

Organ Systems Evaluated	Species/ Strain	Method of Admin.	Concentrations/ Doses [a]	Gender [b] and No. per Group [c]	Noteworthy Findings [d]	GLP Compliance	Study Number
Improvement of hyponatremia							
Effect on euvolemic hyponatremia (SIADH; syndrome of inappropriate secretion of antidiuretic hormone)							
Effect on plasma sodium concentration in AVP-infused SIADH rats	Wistar rats	Intravenous	0.01, 0.1 and 1 mg/kg	5 to 6M	Dose-dependent reverse of AVP-induced hyponatremia.	No	R087-PH-017
		Oral	0.3, 1 and 3 mg/kg (2 days)	5M	Dose-dependent reverse of AVP-induced hyponatremia.	No	R087-PH-013
Effect on hypervolemic hyponatremia (CHF; congestive heart failure)							
Effect on plasma sodium concentration in AVP-infused CHF rats with aortocaval-shunt	Wistar rats	Oral	1 mg/kg (3 days) 1 mg/kg (13 days)	8 to 9M	Inhibition body weight gain and decrease in plasma sodium concentration (3 days treatment), and reduced mortality rates (13 days treatment).	No	R087-PH-039
Pharmacological profile of human metabolites							
Affinity for AVP receptor subtypes and oxytocin receptor	Rat	In vitro	Multiple concentrations	3	Affinity for rat V_{1A}, V_2 and oxytocin receptors were comparable or lower than that of parent compound.	No	R087-PH-028
	Human (cloned AVP and uterus receptors)	In vitro	Multiple concentrations	4	Affinity for human V_{1A}, V_2 and oxytocin receptors were comparable or lower than that of parent compound. No specific binding to V_{1B} receptors.	No	R087-PH-018
Affinity for various receptors	Various	In vitro	10 µM	1	All metabolites showed no effect on the radioligand binding to 27 different receptors including the non-selective opiate receptor.	No	R087-PH-028

AVP; arginine vasopressin.
a - Single dose unless specified otherwise.
b - M, male; F, female; E, either sex.
c - In the case of in vitro studies, the numbers of independent determinations were indicated.
d - Findings relate to conivaptan unless specified otherwise.

Organ Systems Evaluated	Species/ Strain	Method of Admin.	Concentrations/ Doses [a]	Gender [b] and No. per Group	Noteworthy Findings [c]	GLP Compliance	Study Number
Congestive heart failure (CHF) models in rats							
Myocardial infarction (MI)-induced CHF							
Aquaretic effect in MI rats	SD rats	Intravenous	0.03, 0.1 and 0.3 mg/kg	6M	Dose-dependent increase of urine volume (UV) and reduction of urine osmolality (U_{osm}).	No	R087-PH-049
Effect on heart and lung weight, and hemodynamic parameters in MI rats	SD rats	Intravenous	0.1 and 0.3 mg/kg	9 to 11M	Reduction of the pulmonary congestion and cardiac preload. More beneficial effect was observed on cardiac contractility than selective V_2 antagonist.		
Aortocaval shunt (A-V shunt)-induced CHF							
Effect on urine volume, heart weight, and hemodynamic parameters in A-V shunt rats	Wistar rats	Intravenous	0.1 mg/kg	7 to 17M	Increased urine volume and reduced left ventricular end-diastolic pressure (LVEDP).	No	R087-PH-050
Congestive heart failure models in dogs							
AVP-induced heart failure							
Effect on hemodynamic parameters in AVP-infusion dogs	Beagle dogs	Intravenous	0.1 mg/kg	5E	Amelioration of the AVP-induced cardiac depression and systemic vasoconstriction.	No	R087-PH-047
Rapid right ventricular (RV) pacing-induced CHF							
Aquaretic effect in rapid RV pacing dogs	Beagle dogs	Intravenous	0.1 mg/kg	5E	Increased urine flow (3.8-fold) and free water clearance, and decreased urine osmolality.	No	R087-PH-048
Effect on hemodynamic parameters in rapid RV pacing dogs	Beagle dogs	Intravenous	0.1 mg/kg	5E	Amelioration of cardiac function (LV dP/dt_{max}, cardiac output and stroke volume), and afterload (total peripheral resistance). Tended to decrease in LVEDP, an index of preload.		

SD; Sprague-Dawley, AVP; arginine vasopressin, LV dP/dt_{max}; maximum first derivative of left ventricular pressure.
a - Single dose unless specified otherwise.
b - M, male; F, female; E, either sex.
c - Findings relate to conivaptan unless specified otherwise.

Organ Systems Evaluated	Species/ Strain	Method of Admin.	Concentrations/ Doses [a]	Gender [b] and No. per Group [c]	Noteworthy Findings [d]	GLP Compliance	Study Number
General Pharmacology Studies							
Effect on central nervous system	ICR mice	Oral	0.3, 3 and 30 mg/kg	3 to 8M	No effect on general behavior, body temperature, hexobarbital-induced sleep, pentetrazol-induced convulsion or maximum electroshock convulsion.	No	R087-PH-015
Effect on respiratory and cardiovascular systems in anesthetized dogs	Beagle dogs	Intravenous	0.001, 0.003, 0.01, 0.03, 0.1 and 0.3 mg/kg	5E	No effect at up to 0.01 mg/kg. Slight increase in respiratory rate at 0.03 mg/kg or more, and LV dP/dt_{max} and slight decrease in femoral-arterial blood flow at 0.3 mg/kg.	No	R087-PH-016
Potential for QT prolongation							
Effect on the potassium current in cloned hERG expressing HEK293 cells	Human	In vitro	0.1, 1 and 10 µM (0.134, 0.850 and 8.47 µM in analyzed conc.)	4	Inhibition hERG current in a concentration-dependent manner with IC_{50} value of 2.24 µM. The reference compound (E-4031) at 100 nM inhibited hERG current by 92.4%.	Yes	R087-PH-055
			0.3, 1, 3 and 10 µM	4 to 5	Inhibition hERG current in a concentration-dependent manner with IC_{50} value of 2.76 µM. IC_{50} value of reference compound (dofetilide) was 36 nM.	No	R087-PH-020
Effect on cardiac action potential parameters in isolated papillary muscles	Hartley Guinea pigs	In vitro	0.1, 1 and 10 µM (0.086, 0.746 and 7.76 µM in analyzed conc.)	6M	No biologically significant effect on cardiac action potential parameters.	Yes	R087-PH-056
			1 and 3 µM	5 to 6M	No significant effect on cardiac action potential parameters.	No	R087-PH-021

LV dP/dt_{max}; maximum first derivative of left ventricular pressure, hERG; human *ether-à-go-go*-related gene, HEK293; human embryonic kidney 293, IC_{50}; concentration required to induce 50% inhibition, conc.; concentrations.
a - Single dose unless specified otherwise.
b - M, male; F, female; E, either sex.
c - In the case of in vitro studies, the numbers of independent determinations were indicated.
d - Findings relate to conivaptan unless specified otherwise.

Organ Systems Evaluated	Species/ Strain	Method of Admin.	Concentrations/ Doses [a]	Gender [b] and No. per Group [c]	Noteworthy Findings [d]	GLP Compliance	Study Number
Safety Pharmacology Studies							
Effect on cardiovascular systems in conscious and anesthetized dogs	Beagle dogs (conscious)	Intravenous	0.15, 1.5 and 15 mg/kg	4M	No changes in ECG and general conditions up to 15 mg/kg.	Yes	R087-PH-019
	Beagle dogs (anesthetized)	Intravenous	30 mg/kg (0.5 mg/kg/min for 60 min)	5M	No changes in ECG except RR interval. Lowering diastolic blood pressure and increasing heart rate (resulting in shortened RR interval).	Yes	R087-PH-025
***In vitro* studies on potential for QT prolongation of human metabolites**							
Effect of human metabolites on the potassium current in cloned hERG expressing HEK293 cells	Human	In vitro	10 µM (8.85 to 10.64 µM in analyzed conc.)	4 to 5	No effect on hERG current.	Yes	R087-PH-057
Effect of human metabolites on cardiac action potential parameters in isolated papillary muscles	Hartley guinea pigs	In vitro	0.1, 1 and 10 µM (7.99 to 10.44 µM in analyzed conc. at 10 µM)	4 to 8M	M1, M2 and M7 showed no effects. M4 also showed no effects except for APD_{30} at the nominal concentration of 10 µM, which was reduced with no biological significance.	Yes	R087-PH-058
	Hartley guinea pigs	In vitro	10 µM	5M	All metabolites showed no effect on cardiac action potential parameters.	No	R087-PH-027

ECG; electrocardiogram, hERG; human *ether-à-go-go*-related gene, HEK293; human embryonic kidney 293, conc.; concentrations, APD_{30}; action potential duration at 30% repolarization.
a - Single dose unless specified otherwise.
b - M, male; F, female; E, either sex.
c - In the case of in vitro studies, the numbers of independent determinations were indicated.
d - Findings relate to conivaptan unless specified otherwise.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Although the sponsor is pursuing the intravenous formulation, early oral bioavailability studies showed conivaptan is rapidly absorbed in both rats and dogs (20%, following a 1 mg/kg dose in rat and 0.1 mg/kg in dogs). It should be noted that the drug was administered to animals as conivaptan HCl salt but the pharmacokinetic parameters were expressed as free base to make AUC comparisons easier across species.
Conivaptan is widely distributed into tissues, extensively metabolized (by CYP3A4 and it inhibits), and predominantly excreted in feces following biliary excretion. In both animal and human studies, conivaptan demonstrated a nonlinear pharmacokinetic behavior; AUC values increased with repeated administration of conivaptan.

Radiography studies showed radioactivity was widely distributed to all tissues except for central nervous system. High concentrations were observed in liver and kidney. After 24 hrs drug levels were detectable in liver, kidney and adrenal glands. Following IV administration, tissue concentrations rapidly declined except for adrenal gland and testes. The adrenal hypertrophy noted in toxicology studies was likely due to prolonged residence and higher concentrations in adrenal glands. Studies in pregnant rats have shown presence of radioactivity in amnion, mammary gland, placenta relative to blood. Conivaptan appears to transfer to fetus but at very low levels. In reproduction and lactation study tissue analysis, the concentrations in the fetuses 24 hours after oral dosing declined to 32% of the fetal Cmax and 39% after IV dosing. The fetal/plasma concentration ratio increased over time after the oral and IV dose, suggesting that clearance of radioactivity from the fetus is slower than from maternal plasma, and, therefore, accumulation may occur. In a single dose study (3 mg/kg po, 1 mg/kg IV) in dams with neonates, radioactivity has been found in maternal milk, blood and plasma and in neonate blood, plasma and tissue.
YM087 had high and similar protein binding in rats, dogs and humans (99.1, 99.2 and 99.5%, respectively). Conivaptan is metabolized by CYP3A4 and is potent inhibitor of CYP 3A4. CYP3A4 inhibition will play a critical role in the safety of conivaptan when co-administered with CYP3A4 metabolized drugs. Metabolic profile of conivaptan was similar across species examined (rats, dogs and humans). Two major metabolites, M1 and M2 were identified in liver microsomes derived from mice, rats, dogs and humans. M1, M2, M4 and M7 metabolites are present in human plasma and have been found in rat and dog plasma, suggesting that rat and dog are appropriate species for pharmacology and toxicology studies of conivaptan. The affinity of metabolites M1, M2, M4 and M7 to V_{1A} and V_2 receptors has been evaluated in rats. M1 affinity is similar to parent product. M2 and M4 affinities were 5 to 38 fold less than parent with M7 having no affinity. Transfer studies indicate that metabolites may distribute to blood cells more readily than parent.
The PK data suggests bile as the primary excretion pathway. When labeled YM087 was given to animals, the majority of radioactivity was excreted primarily in the feces through bile within 24 hours in rat and dogs. After an IV administration, the cumulative biliary and urinary excretions were 77 and 13% at 72 hrs in rats. Nearly 80% of the drug is excreted with in 24 hrs. The excretion profile of conivaptan in dogs was similar to rats.

2.6.4.2 Methods of Analysis

Plasma concentrations of conivaptan were determined by HPLC. [redacted] Plasma concentrations of metabolites M1, M2, M4 in rats and dogs were determined in conjunction with parent using [redacted] Methods were validated for specificity, linearity, extraction recovery, accuracy, precision and stability in plasma.

2.6.5.2A Analytical methods and validation reports Test Article: Conivaptan Hydrochloride

Species/Strain	F344 Rat	F344 Rat	F344 Rat	F344 Rat	F344 Rat	F344 Rat
Sample	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma
Analyte	YM087[a]	YM087[a]	YM087[a]	YM-95931 (M1)	YM-95461 (M2)	YM-152721 (M4)
Assay	HPLC	[redacted]				
Validation data						
Limit of quantification (ng/mL)	[redacted]					
Sample volume (mL)						
Concentration range (ng/mL)						
Extraction recovery (%)						
1-day accuracy (%)						
3-day accuracy (%)						
1-day precision (%)						
3-day precision (%)						
Stable period						
Temperature for storage						
Study number	R087-ME-003	R087-ME-008	R087-ME-061	R087-ME-061	R087-ME-061	R087-ME-061

Additional Information:
Analytical methods for TK studies in mouse [R087-TX-034], rat [R087-TX-031, 032, 033], rabbit [R087-TX-099] and dog [R087-TX-032, 033] plasma were validated but are not shown.

2.6.5.2B Analytical methods and validation reports Test Article: Conivaptan Hydrochloride

Species/Strain	Beagle Dog	Beagle Dog	Beagle Dog	Beagle Dog	Beagle Dog	Beagle Dog	Beagle Dog
Sample	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma
Analyte	YM087[a]	YM087[a]	YM087[a]	YM087[a]	YM-95931 (M1)	YM-95461 (M2)	YM-152721 (M4)
Assay	HPLC	[redacted] HPLC	[redacted]				
Validation data							
Limit of quantification (ng/mL)	[redacted]						
Sample volume (mL)							
Concentration range (ng/mL)							
Extraction recovery (%)							
1-day accuracy (%)							
3-day accuracy (%)							
1-day precision (%)							
3-day precision (%)							
Stable period							
Temperature for storage							
Study number	R087-ME-004	R087-TX-031	R087-ME-008	R087-ME-061	R087-ME-061	R087-ME-061	R087-ME-061

Additional Information:
Analytical methods for TK studies in mouse [R087-TX-034], rat [R087-TX-031, 032, 033], rabbit [R087-TX-099] and dog [R087-TX-032, 033] plasma were validated but are not shown.

a – Conivaptan hydrochloride; b – Not examined

2.6.4.3 Absorption

Since only the intravenous formulation of YM087 is being developed, the absorption of the oral formulation will be mentioned briefly. The oral formulation absorption occurs primarily in the jejunum (51%) followed by duodenum (43.5%) and ileum (36%). Less than 15% of the dose was absorbed from stomach. Food decreased or delayed absorption by approximately 3 fold. Oral bioavailability of the oral formulation was about 20% in rats and dogs. Results with oral administration are consistent with IV dosing in rats and dogs; nonlinear PK. Absolute bioavailability was 20% in rat, 15% in dogs at 1 and 0.1 mg/kg, respectively and increased with increasing dose suggesting saturation of 1st pass metabolism.

2.6.4.4 Distribution

Whole-body autoradiography of intravenous YM087 in Male Rats

In whole-body autoradiography studies, rats were sacrificed at 5 minutes after IV administration of C^{14}- YM087 (in glycerin) at 30 minutes, 1, 4, or 24 hours after administration of the dose. Radioactivity was widely distributed to all tissues except the central nervous system, with high concentrations particularly in the liver and renal cortex (5 x plasma) and adrenal cortex. In IV and oral studies tissue concentrations declined rapidly except adrenal cortex and testes. The high drug concentrations in adrenal gland correlate with adrenal cortical hypertrophy and hyperplasia. 24 hours post-dose, radioactivity was detected in the adrenal cortex, liver, and kidneys, but the other tissues contained little or no radioactivity. Metabolite levels differed in the adrenal cortex M2 > M4 > parent > M1.

2.6.5.7A PK: Tissue distribution after a single dose (iv) Test Article: Conivaptan Hydrochloride

Species/Strain	F344 Rat (albino)				
Number of animals/Gender (M/F)	3M/each time point				
Feeding condition	Non-fasted				
Vehicle/Formulation	Solution[a]				
Method of administration	Intravenous				
Dose (mg/kg)	1				
Radionuclide/Assay	[redacted]				
Specific activity					
Sampling time	5 and 30 min, 1, 4 and 24 hr				
	Concentration (µg equivalents/g or mL)				
Tissues/organs	5 min	30 min	1 hr	4 hr	24 hr
Plasma	[redacted]				
Whole blood					
Brain					
Lung					
Heart					
Liver					
Kidney					
Adrenal					
Testis					
Eye					
Study number	R087-ME-049				

Additional Information:

Spleen, pancreas, muscle, stomach, small intestine wall, large intestine wall, skin, fat, hypophysis, submandibular gland, thymus, thyroid, bone marrow and thoracic aorta were examined but are not shown. These results, which were obtained with [aminobenzoyl-^{14}C] conivaptan hydrochloride, were similar to those obtained with [imidazole-^{14}C] conivaptan hydrochloride [R087-ME-018].

a – The dosing solution contained [redacted] glycerin and [redacted] lactic acid.; ND = Not detected

After intravenous administration of C^{14}-conivaptan in glycerin to pigmented Lister Hooded rats, the highest drug concentrations were found in liver, lung, adrenal gland and kidney. The concentrations in adrenal gland and kidneys were 18 and 8 fold less than plasma concentrations. YM087 concentrations in the eye were nearly 3 x blood levels at 1-hr post dose.

2.6.5.7B PK: Tissue distribution after a single dose (iv) Test Article: Conivaptan Hydrochloride

Species/Strain	Lister Hooded Rat (pigmented)				
Number of animals/Gender (M/F)	1M/each time point				
Feeding condition	Non-fasted				
Vehicle/Formulation	Solution[a]				
Method of administration	Intravenous				
Dose (mg/kg)	1				
Radionuclide/Assay	[redacted]				
Specific activity					
Sampling time	1, 24, 168, 240 and 360 hr				
	Concentration (µg equivalents/g)				
Tissues/organs	1 hr	24 hr	168 hr	240 hr	360 hr
Plasma	[redacted]				
Whole blood					
Lung					
Heart					
Liver					
Kidney					
Adrenal					
Testis					
Eye					
Study number	R087-ME-045				

Additional Information:
Skin (non-pigmented), skin (pigmented), thymus, thyroid and bone marrow were examined but are not shown. This study was performed only with [aminobenzoyl-^{14}C] conivaptan hydrochloride.

a – The dosing solution contained [redacted] glycerin and [redacted] lactic acid.; ND = Not detected

Distribution in Pregnant Female Rats

To investigate the transfer of radioactivity to fetuses and breast milk, YM087 was administered by both oral and IV administration in pregnant and lactating Sprague-Dawley rats on Day 14 of pregnancy.

Whole-body autoradiograms of longitudinal sections were obtained from rats sacrificed at 1, 4, or 24 hours after dose administration on Day 19 of pregnancy. Radioactivity concentrations at 1 and 4 hours after dosing were higher in the amnion, mammary gland, and placenta compared with blood. 24-hours after dosing substantial concentrations of radioactivity were observed only in the contents of the large intestine of dams. Since no notable concentration were detected in fetus, thus the transfer of YM087 and its metabolites into the fetus is likely to be very low during the perinatal period.

2.6.5.9B PK: Study in pregnant or nursing animals (po) Test Article: Conivaptan Hydrochloride

Placental transfer

Species/Strain	SD Rat
Gestation day/Number of animals	14 days gestation/3 animals at each time point
Feeding condition	Fasted
Vehicle/Formulation	Solution[a]
Method of administration	Gavage
Dose (mg/kg)	3
Radionuclide/Assay	[redacted]
Specific activity	
Sampling time	1, 4 and 24 hr

	Concentration (µg equivalents/g or mL)		
Tissues/organs	1 hr	4 hr	24 hr
Maternal plasma	[redacted]		
Mammary gland			
Ovary			
Uterus			
Amniotic fluid			
Placenta			
Fetus			
Study number	R087		

Additional Information:
Maternal whole blood, brain, lung, heart, liver, kidney, spleen, and pancreas were examined but are not shown. This study was performed only with [imidazole-^{14}C] conivaptan hydrochloride.

a – The dosing solution contained 10% PEG 200 in 0.5 mM phosphoric acid.

2.6.5.9C PK: Study in pregnant or nursing animals (iv) Test Article: Conivaptan Hydrochloride

Excretion into milk

Species/Strain	SD Rat
Lactating date/Number of animals	14 days after parturition/3 animals at each time point
Feeding condition	Non-fasted
Vehicle/Formulation	Solution[a]
Method of administration	Intravenous
Dose (mg/kg)	1
Radionuclide/Assay	[redacted]
Specific activity	
Sampling time	1, 4 and 24 hr

	Concentration (µg equivalents/g or mL)		
Tissues/organs	1 hr	4 hr	24 hr
Maternal milk	[redacted]		
Maternal plasma			
Neonatal plasma			
Neonatal milk lump in stomach			
Neonatal brain			
Neonatal lung			
Neonatal heart			
Neonatal liver			
Neonatal kidney			
Study number	R087-ME-022		

Additional Information:
Maternal whole blood and neonatal blood were examined but are not shown. This study was performed only with [imidazole-^{14}C] conivaptan hydrochloride.
a – The dosing solution contained [redacted] glycerin and [redacted] lactic acid.; ND = Not detected

Tissue Radioequivalent Concentrations in Reproduction and Lactation Tissues

At the time of maximum plasma radioactivity concentration in pregnant rats, tissue radioactivity concentration was 2- to 3-fold higher in placenta and mammary gland. Fetus and amniotic fluid concentrations were 5% to 10% of plasma radioactivity concentrations suggesting only small amounts of YM087 are transferred to the fetus. Concentrations in the fetuses 24 hours after oral dosing were 32% of the maximum fetal values and 39% after IV dosing. The fetal/plasma concentration ratio increased over time after the oral and IV dose, suggesting that clearance of radioactivity from the fetus is slower than from plasma, and, therefore, accumulation may

Tissue and Plasma Radioactivity Concentrations in Pregnant and Lactating Rats

Time	Oral (3 mg/kg [^{14}C]YM087)			IV (1 mg/kg [^{14}C]YM087)		
	1 Hour	4 Hours	24 Hours	1 Hour	4 Hours	24 Hours
Plasma Concentration	0.603 ± 0.022	0.578 ± 0.084	0.031 ± 0.004	0.257 ± 0.050	0.104 ± 0.022	0.011 ± 0.003
Mammary Gland	1.957 ± 0.274	1.201 ± 1.084	0.032 ± 0.006	0.545 ± 0.035	0.191 ± 0.042	0.008 ± 0.001
Ovary	0.656 ± 0.083	0.630 ± 0.194	0.035 ± 0.005	0.329 ± 0.068	0.122 ± 0.022	0.010 ± 0.001
Uterus	0.577 ± 0.037	0.887 ± 0.122	0.079 ± 0.024	0.348 ± 0.060	0.233 ± 0.068	0.022 ± 0.006
Amniotic Fluid	0.020 ± 0.002	0.043 ± 0.012	0.015 ± 0.005	0.015 ± 0.002	0.020 ± 0.010	0.005 ± 0.001
Placenta	0.928 ± 0.114	1.919 ± 0.052	0.525 ± 0.197	0.562 ± 0.122	0.745 ± 0.327	0.125 ± 0.024
Fetus	0.028 ± 0.006	0.050 ± 0.013	0.016 ± 0.002	0.012 ± 0.004	0.013 ± 0.001	0.005 ± 0.001

Data expressed as mean ±SD of 3 rats
Concentration = Microgram equivalent of YM087/g or mL.

occur. However, the accumulated concentrations are very low and could not be detected by autoradiography after Day 19.

Milk Secretion

A single oral (3 mg/kg) or IV (1 mg/kg) dose of C^{14}-YM087, was administered to dams housed with their neonates on Day 14 after parturition. Breast milk and blood were collected at 1, 4, or 24 hours. Blood was also collected from neonates at these times. Concentrations of C^{14}-YM087 were determined in maternal breast milk, blood, and plasma and in neonate blood, plasma, and tissue.

The radioactivity concentrations in milk reached a maximum 4 hours after PO administration or 1 hour after IV administration and were 2- to 3-fold greater than plasma radioactivity. Concentrations rapidly decreased reaching less than 2% of maximum value at 24 hours after administration. Tissue radioactivity concentrations of neonates reached a maximum 4 hours after oral or IV administration.

Mean (±SD) Tissue Concentrations of Radioactivity After Administration of [^{14}C]YM087 to Female Rats (n = 3) on Day 14 After Parturition

Route/Dose	Oral (3 mg/kg [^{14}C]YM087)			IV (1 mg/kg [^{14}C]YM087)		
Time	1 Hour	4 Hours	24 Hours	1 Hour	4 Hours	24 Hours
Maternal						
Milk	0.564 ± 0.019	0.626 ± 0.318	0.014 ± 0.002	0.461 ± 0.072	0.282 ± 0.082	0.005 ± 0.001
Blood	0.296 ± 0.119	0.206 ± 0.107	0.016 ± 0.002	0.185 ± 0.051	0.089 ± 0.011	0.006 ± 0.002
Plasma	0.267 ± 0.092	0.211 ± 0.107	0.013 ± 0.002	0.166 ± 0.040	0.082 ± 0.010	0.005 ± 0.001
Neonate						
Blood	ND	ND	ND	ND	0.002 ± 0.002	ND
Plasma	ND	0.014 ± 0.016	ND	ND	0.003 ± 0.000	0.002 ± 0.002
Brain	ND	ND	ND		ND	ND
Lung	ND	0.008 ± 0.008	ND	ND	0.009 ± 0.004	0.003 ± 0.001
Heart	ND	0.007 ± 0.008	ND	ND	0.006 ± 0.002	0.002 ± 0.001
Liver	ND	0.043 ± 0.043	0.039 ± 0.003	ND	0.039 ± 0.021	0.017 ± 0.004
Kidney	ND	0.014 ± 0.015	0.013 ± 0.001	ND	0.018 ± 0.005	0.004 ± 0.002

Neonate tissue and plasma concentrations determined from one neonate per dam
ND = Not detected.
Plasma concentration = Microgram equivalents of YM087/g or mL.

Neonate plasma concentrations were 14 to 26 times lower than that of dams at this time point. Relative to plasma, tissue radioactivity concentrations in the neonate were 15 fold higher in the liver and 2- to 6-fold higher in the heart and kidney after the IV dose. No radioactivity was detected in the brain. The dissipation of radioactivity from the tissue of neonates in the IV study appeared to be slower than that in maternal tissue- however these observations were not confirmed by the oral dose study.

Protein binding

Protein binding was similar and high in all species.

Study system		*In vitro*		
Target entity, Test system and method		Plasma, Equilibrium dialysis		
Assay		[redacted]		
Analyte		YM087[a]		
Parameter	**Nominal concentration (ng/mL)**	**Species/Strain**		
		F344 Rat	**Beagle Dog**	**Human**
% Bound	[redacted]	[redacted]		[redacted]
Study number		R087-ME-023		

Additional Information: None

***In vitro* transfer ratio into blood cells (T) and blood cell-to-plasma partition coefficient (Kp)**

Parameters	**Nominal concentration (ng/mL)**	**Species/Strain**		
		F344 Rat	Beagle Dog	Human
T (%)	18.6	40.2	28.2	16.7
	186.4	35.7	26.8	18.4
	1863.9	37.2	32.0	21.6
Kp	18.6	0.87	0.40	0.24
	186.4	0.72	0.38	0.27
	1863.9	0.78	0.48	0.33
Study number		R087-ME-043		

Additional Information:

The *in vivo* transfer ratios of radioactivity into blood cells in rats were approximately 40% – 70% after single intravenous and oral doses [R087-ME-049, 050]. Transfer ratios increased over time after drug administration, indicating that metabolite(s) more readily distributed into blood cells in rats.

Conivaptan binding to purified human albumin, alpha-1acid glycoprotein, high density proteins and immunoglobulin G are shown in table below which accounts for the majority of plasma protein binding of conivaptan.

Table 2.7.2-3: Conivaptan protein binding to purified human plasma proteins (087-ME-023)

Protein	**Protein Concentration (mg/mL)**	**Protein Binding* (%)**
[redacted]	[redacted]	98.30 ± 0.29
		99.18 ± 0.23
[redacted]		93.18 ± 2.29
		62.84 ± 4.48

* Data are presented as means ± SD (N = 3).

2.6.4.5 Metabolism

Conivaptan is metabolized primarily by CYP3A4 in mice, rats, dogs and humans. Conivaptan having IC_{50} =0.5 μM for CYP3A4 suggests it inhibits CYP3A4 activity by occupying the enzyme. Mechanism based studies indicate that when human microsomes are pre-incubated with conivaptan greater inhibition of CYP3A4 metabolism occurs that without preincubation however the inhibition occurs only under conditions where can be biotransformed (i.e. conivaptan is not direct 3A4 inhibitor). Furthermore spectral analysis reveals that mechanism based inhibition is not through the heme group which implies that the interaction occurs at the amino acids of the active site.
Conivaptan is likely to interact with other drugs that are metabolized by CYP3A4. In fact the potential drug interaction had convinced [redacted] in favor of intravenous formulation for a maximum duration of 4 days.

Table 2.7.2-4: IC_{50} values of conivaptan for major human CYP isozymes (087-ME-033)

CYP Isozyme	IC_{50} (μM)*
CYP1A2	198.3 ± 37.1
CYP2C9	13.3 ± 6.9
CYP2C19	19.2 ± 3.6
CYP2D6	12.6 ± 8.8
CYP3A4	0.47 ± 0.39

IC_{50} = concentration required to produce 50% inhibition.
* Data are presented as means ± SD (N = 4).

Two major metabolites, M1 and M2 were identified in liver microsomes derived from mice, rats, dogs and humans. The results of mass balance studies in rats suggested that radioactivity was mainly excreted into bile after both intravenous and oral administration of C^{14}-conivaptan hydrochloride.
In rat bile, eight metabolites have been identified: M1, M2, M4, M5 (*N*-hydroxyimidazole derivative of M2), M6 (*O*-glucuronide of M2), M7 (carboxylic acid compound derived from hydrolysis of conivaptan at the 6-position of the imidazobenzazepine, YM-175043), M8 (mono-hydroxylated conivaptan at the benzene ring of the benzazepine skeleton, EE-1) and M9 (mono-hydroxylated compound of M2 at benzene ring bound to the benzanilide, OE-1). M1, M2, M4 and M7 metabolites present in human are also have been found in rat and dog plasma, suggesting that rat and dog are appropriate species for pharmacology and toxicology studies of conivaptan.
The affinity of the metabolites found in plasma (i.e. M1, M2, M4 and M7) to rat arginine vasopressin V_{1A} and V_2 receptors were evaluated. M1 metabolites had similar affinity as the parent compound. M2 affinity was [redacted] and M4 was [redacted] relative to parent to V_{1A} and V_2 receptors, respectively. M7 exhibited no affinity to rat V_{1A} and V_2 receptors. These metabolites at concentrations up to 10 μM, demonstrate no effect on battery of different receptors (peptide, steroid or neurotransmitter receptors).
The pharmacokinetics of M1, M2 and M4 were characterized in rats and dogs following intravenous administration of conivaptan hydrochloride. Values of Cmax and AUC of these metabolites were much lower than those of unchanged drug (less than 6% of unchanged drug), suggesting that metabolites are unlikely to contribute to the pharmacological action of conivaptan *in vivo*.

2.6.5.12 PK: Metabolic profiles in tissues (iv) Test Article: Conivaptan Hydrochloride

Species/Strain	F344 Rat (albino)	Lister Hooded Rat (pigmented)
Number of animals/Gender (M/F)	17M	6M
Feeding condition	Non-fasted	Non-fasted
Vehicle/Formulation	Solution[a]	Solution[a]
Method of administration	Intravenous	Intravenous
Dose (mg/kg) – ^{14}C-conivaptan hydrochloride	1	1
Radionuclide/Assay	[redacted]	
Specific activity		
Sampling time	24 hr	24 hr
Extraction solvent	MeOH containing 10% 1N HCl	MeOH containing 10% 1N HCl

Species/Strain	Tissues	Composition (%) Parent	M1	M2	M4	M7	Study number
F344 Rat	Adrenal	8.51	4.61	12.88	9.93	ND	R087-ME-075
Lister Hooded Rat	Eye	86.05	ND	ND	ND	ND	R087-ME-065

Additional Information:
Since quantitative tissue distribution studies indicated slow elimination of radioactivity from adrenals of albino rats and eyes of pigmented rats, metabolic fingerprinting was performed to determine the composition of conivaptan-related material in each tissue.
Extraction recoveries of radioactivity were 36.5% in adrenals and 79.7% in eyes.
All results were obtained with [aminobenzoyl-^{14}C] conivaptan hydrochloride.
a – The dosing solution contained [redacted] glycerin and [redacted] lactic acid.: ND = Not detected

2.6.5.14A PK: Metabolite PK after a single dose (iv) Test Article: Conivaptan Hydrochloride

Species/Strain	F344 Rat			
Number of animals/Gender (M/F)	3M	3M	3M	3M
Feeding condition	Non-fasted	Non-fasted	Non-fasted	Non-fasted
Vehicle/Formulation	Solution[a]	Solution[a]	Solution[a]	Solution[a]
Method of administration	Intravenous	Intravenous	Intravenous	Intravenous
Dose (mg/kg) – conivaptan hydrochloride	10	10	10	10
Sample	Plasma	Plasma	Plasma	Plasma
Analyte	YM087[b]	M1	M2	M4
Assay	[redacted]			
PK parameters				
t_{max} (hr)	–[c]	1.0	0.5	1.0
C_{max} (ng/mL)	4587[d]	51.5	120	4.2
CL_{tot} (L/hr/kg)	0.8	–[c]	–[c]	–[c]
V_{dss} (L/kg)	2.7	–[c]	–[c]	–[c]
AUC (ng·hr/mL)	11673	259	605	18
(Time for calculation – hr)	(0-inf)	(0-inf)	(0-inf)	(0-inf)
$t_{1/2}$ (hr)	2.2	2.5	2.9	2.3
(Time for calculation – hr)	(0.1-24)	(1-10)	(0.5-10)	(1-8)
Study number	R087-ME-062			

Additional Information: None

a – The dosing solution contained 30% PG and 10% EtOH.; b – Conivaptan (free base); c – Not calculated; d – C_0

2.6.5.14B PK: Metabolite PK after a single dose (iv) Test Article: Conivaptan Hydrochloride

Species/Strain	Beagle Dog			
Number of animals/Gender (M/F)	4M	4M	4M	4M
Feeding condition	Non-fasted	Non-fasted	Non-fasted	Non-fasted
Vehicle/Formulation	Solution[a]	Solution[a]	Solution[a]	Solution[a]
Method of administration	Intravenous	Intravenous	Intravenous	Intravenous
Dose (mg/kg) – conivaptan hydrochloride	5	5	5	5
Sample	Plasma	Plasma	Plasma	Plasma
Analyte	YM087[b]	M1	M2	M4
Assay				
PK parameters				
t_{max} (hr)	–[c]	1.6	0.25	0.9
C_{max} (ng/mL)	4820[d]	37.6	72.7	1.3
CL_{tot} (L/hr/kg)	0.2	–[c]	–[c]	–[c]
V_{dss} (L/kg)	1.4	–[c]	–[c]	–[c]
AUC (ng·hr/mL)	28331	413	685	11[e]
(Time for calculation – hr)	(0-inf)	(0-inf)	(0-inf)	(0-inf)
$t_{1/2}$ (hr)	6.6	7.1	14.9	5.8[e]
(Time for calculation – hr)	(0.5-24)[f]	(1-24)[f]	(8-24)	(1-8)[f]
Study number	R087-ME-062			

Additional Information: None

a – The dosing solution contained 30% PG and 10% EtOH.; b – Conivaptan (free base); c – Not calculated; d – C_0; e – Mean of three dogs; f – Total time range; times varied for individual animals.

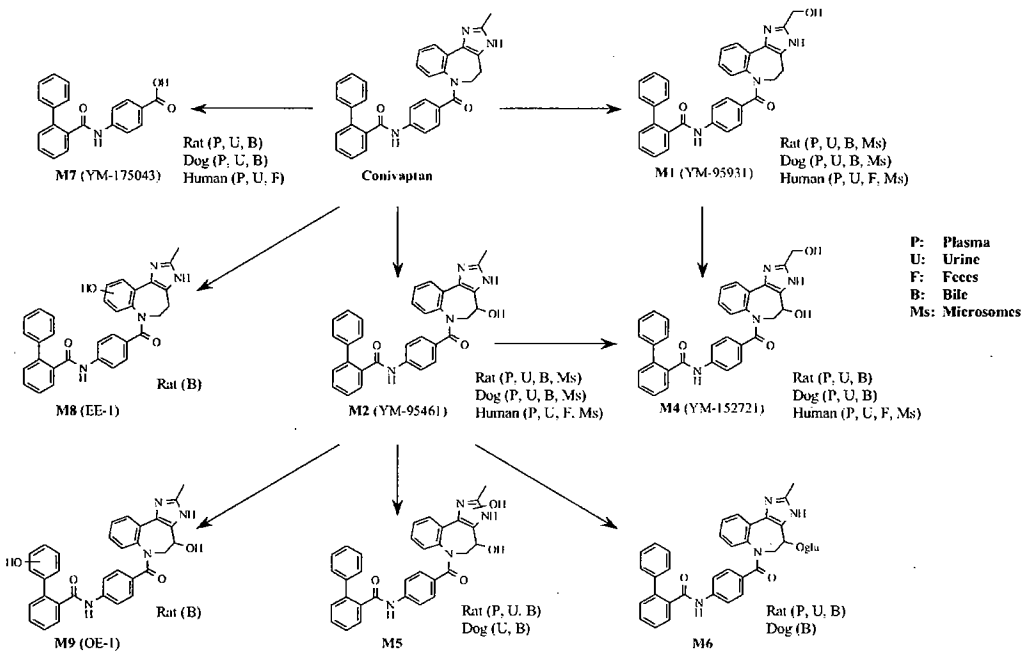
2.6.5.14C PK: Metabolite PK after a single dose (iv infusion)
Test Article: Conivaptan Hydrochloride

Species/Strain	Beagle Dog			
Number of animals/Gender (M/F)	4M	4M	4M	4M
Feeding condition	Non-fasted	Non-fasted	Non-fasted	Non-fasted
Vehicle/Formulation	Solution[a]	Solution[a]	Solution[a]	Solution[a]
Method of administration	Intravenous infusion (24 hr)	Intravenous infusion (24 hr)	Intravenous infusion (24 hr)	Intravenous infusion (24 hr)
Dose (mg/kg/24 hr) – conivaptan hydrochloride	5	5	5	5
Sample	Plasma	Plasma	Plasma	Plasma
Analyte	YM087[b]	M1	M2	M4
Assay				
PK parameters				
t_{max} (hr)	24	24.1	24.1	NA
C_{max} (ng/mL)	1257	8.9	12.8	NA
C_{ss} (ng/mL)	1122	–[c]	–[c]	NA
CL_{tot} (L/hr/kg)	0.2	–[c]	–[c]	NA
V_{dss} (L/kg)	2.0	–[c]	–[c]	NA
AUC (ng·hr/mL)	25088	175	375	NA
(Time for calculation – hr)	(0-inf)	(0-inf)	(0-inf)	NA
$t_{1/2}$ (hr)	6.1	5.1	9.5	NA
(Time for calculation – hr)	(30-48)[d]	(24-48)[d]	(24.1-48)[d]	NA
Study number	R087-ME-062			

Additional Information:
Plasma concentrations of M4 were less than LOQ at any time point.

a – The dosing solution contained 0.6% PG and 0.2% EtOH.; b – Conivaptan (free base); c – Not calculated; d – Total time range; times varied for individual animals. NA = Not applicable

PK: Metabolic pathways ***Test Article: Conivaptan Hydrochloride***



2.6.4.6 Excretion

Excretion profile of C^{14}-conivaptan and metabolites were similar in rat and dog. After IV and oral C^{14}-conivaptan, majority of radioactivity was excreted in feces (>88%; 2-5% urinary excretion).

Table 2.6.4- 25: Urinary and biliary excretion of radioactivity after single-dose, intravenous (1 mg/kg) and oral (3 mg/kg) administration of ^{14}C-conivaptan hydrochloride to rats [R087-ME-049, 050]

Time (hr)	Excretion of radioactivity (% of dose)					
	Intravenous			Oral		
	Urine	Bile	Total	Urine	Bile	Total
0 – 6	7.5 ± 8.9	43.0 ± 27.4	50.5 ± 25.3	1.5 ± 0.3	33.7 ± 1.3	35.2 ± 1.1
0 - 24	11.3 ± 9.8	68.6 ± 15.2	79.9 ± 10.9	3.5 ± 0.7	55.5 ± 3.3	59.1 ± 3.4
0 - 48	12.5 ± 9.4	74.7 ± 12.4	87.2 ± 4.6	4.1 ± 0.9	59.7 ± 3.0	63.8 ± 3.2
0 - 72	12.8 ± 9.4	76.0 ± 12.3	88.7 ± 4.0	4.6 ± 0.9	61.8 ± 3.1	66.3 ± 3.2

Data are expressed as the mean ± SD of four rats.

Table 2.6.4- 26: Urinary and biliary excretion of radioactivity after single-dose, intravenous (0.3 mg/kg) and oral (0.3 mg/kg) administration of ^{14}C-conivaptan hydrochloride to dogs [R087-ME-019]

Time (hr)	Excretion of radioactivity (% of dose)					
	Intravenous			Oral		
	Urine	Bile	Total[1)]	Urine	Bile	Total[1)]
0 – 6	1.22 ± 0.17	51.5 ± 4.7	52.7 ± 4.5	0.91 ± 0.27	42.4 ± 1.8	43.3 ± 1.5
0 - 24	2.69 ± 0.37	75.2 ± 4.0	77.9 ± 3.9	2.15 ± 0.32	59.7 ± 4.7	61.8 ± 4.5
0 - 48	3.16 ± 0.66	78.5 ± 4.3	81.6 ± 4.1	2.38 ± 0.30	62.4 ± 5.0	64.7 ± 4.9

Data are expressed as the mean ± SD of three dogs.

1) The values were calculated from reported individual data of urinary and fecal excretion.

2.6.5.18 PK: Enterohepatic circulation ***Test Article: Conivaptan Hydrochloride***

Species/Strain	F344 Rat			F344 Rat		
Number of animals/Gender (M/F)	4M			4M		
Feeding condition	Non-fasted			Fasted		
Vehicle/Formulation	Bile[a]			Bile[b]		
Method of administration	Intraduodenal			Intraduodenal		
Analyte	[redacted]					
Assay						
Excretion route / **Time**	**Bile**	**Urine**	**Total**	**Bile**	**Urine**	**Total**
0 – 6 hr	[redacted]					
0 – 24 hr						
0 – 48 hr						
Study number	R087-ME-049			R087-ME-050		

Additional Information:
The reabsorption rates obtained with [aminobenzoyl-^{14}C] conivaptan hydrochloride were lower than those with [imidazole-^{14}C] conivaptan hydrochloride for both intravenous and oral doses (estimated to be more than 20%) [R087-ME-017, 018].
a – Bile collected from one bile duct-cannulated rat which received intravenous (1 mg/kg) dose of [aminobenzoyl-^{14}C] conivaptan hydrochloride.; b – Bile collected from one bile duct-cannulated rat which received oral (3 mg/kg) dose of [aminobenzoyl-^{14}C] conivaptan hydrochloride.; c – Total radioactivity, ^{14}C

2.6.5.16A PK: Excretion (iv) ***Test Article: Conivaptan Hydrochloride***

Species/Strain	F344 Rat			Beagle Dog			Human		
Number of animals/Gender (M/F)	4M			3M			4M		
Feeding condition	Non-fasted			Fasted			Fasted		
Vehicle/Formulation	Solution[a]			Solution[a]			Solution[b]		
Method of administration	Intravenous			Intravenous			Intravenous infusion (5 min)		
Dose (mg/kg) – ^{14}C-conivaptan hydrochloride	1			0.3			10 mg		
Analyte	[redacted]								
Assay									
Excretion route / **Time**	**Urine**	**Feces**	**Total**	**Urine**	**Feces**	**Total[d]**	**Urine**	**Feces**	**Total**
0 – 6 hr	3.3	—[e]	—[e]	0.8	—[e]	—[e]	5.0	—[e]	—[e]
0 – 24 hr	4.5	79.6	84.2	1.9	55.6	57.5	10.1	13.2	23.3
0 – 48 hr	4.7	91.8	96.5	2.3	86.4	88.7	11.5	55.2	66.7
0 – 72 hr	4.8	92.8	97.6	2.5	88.9	91.3	11.9	74.5	86.4
0 – 96 hr	—[e]	—[e]	—[e]	2.5	89.4	91.9	12.1	75.9	88.0
0 – 120 hr	—[e]	—[e]	—[e]	2.6	90.1	92.7	12.2	77.3	89.4
0 – 144 hr	—[e]	—[e]	—[e]	2.6	90.2	92.9	12.3	78.1	90.4
Total (0 – t) (Rat, Dog: t=168 hr; Human: t=168-336 hr)	4.8	93.7	98.6	2.7	90.4	93.1	12.3	79.9	92.1
Study number	R087-ME-049			R087-ME-019			R087-CL-061		

Additional Information:
Results in rats, which were obtained with [aminobenzoyl-^{14}C] conivaptan hydrochloride, were similar to those obtained with [imidazole-^{14}C] conivaptan hydrochloride [R087-ME-018].
a – The dosing solution contained [redacted] glycerin and [redacted] lactic acid.; b – Phase I formulation for intravenous dose;
c –Total radioactivity, ^{14}C; d – Total recovery was calculated based on individual urinary and fecal recoveries in the report.;
e – Not examined

Mass Balance Studies

The excretion of conivaptan was studied in 8-week-old male F344 rats after an oral (3 mg/kg) or intravenous (1 mg/kg) administration of C^{14}-YM087. Urine and feces were collected up to 168 hrs. Following both routes of administration, the cumulative excretion of radioactivity relative to the administered radioactive dose was 6% in urine and greater than 93% in feces, suggesting complete recovery of the radioactivity. The majority of radioactivity was excreted within 24 hours.

2.6.5.18 PK: Enterohepatic circulation *Test Article: Conivaptan Hydrochloride*

Species/Strain	F344 Rat			F344 Rat		
Number of animals/Gender (M/F)	4M			4M		
Feeding condition	Non-fasted			Fasted		
Vehicle/Formulation	Bile[a]			Bile[b]		
Method of administration	Intraduodenal			Intraduodenal		
Analyte						
Assay						
Excretion route Time	Bile	Urine	Total	Bile	Urine	Total
0 – 6 hr	3.7	1.4	5.0	4.7	0.7	5.4
0 – 24 hr	5.9	2.3	8.2	7.0	2.5	9.5
0 – 48 hr	7.3	3.7	10.9	8.8	3.4	12.3
Study number	R087-ME-049			R087-ME-050		

Additional Information:
The reabsorption rates obtained with [aminobenzoyl-^{14}C] conivaptan hydrochloride were lower than those with [imidazole-^{14}C] conivaptan hydrochloride for both intravenous and oral doses (estimated to be more than 20%) [R087-ME-017, 018].
a – Bile collected from one bile duct-cannulated rat which received intravenous (1 mg/kg) dose of [aminobenzoyl-^{14}C] conivaptan hydrochloride.; b – Bile collected from one bile duct-cannulated rat which received oral (3 mg/kg) dose of [aminobenzoyl-^{14}C] conivaptan hydrochloride.; c – Total radioactivity, ^{14}C

2.6.4.7 Pharmacokinetic drug interactions

The effect of conivaptan on hepatic drug metabolizing enzymes has been evaluated in male F344 rats after repeated oral administration of conivaptan hydrochloride. Rats were administered daily with 0 (control), 3 and 10 mg/kg of conivaptan for 7 days. Phenobarbital, a hepatic enzyme induced was given for 7 days (100 mg/kg/day po) was used as a positive control. Rats were sacrificed one day after the last dose. In a similar study, rats treated with 10 mg/kg of conivaptan were also sacrificed at 7 and 28 days post-dose. After sacrifice, the following hepatic parameters were measured: liver weight to body weight ratio; protein and cytochrome P450 content; 7-ethoxyresorufin O-deethylase activity; testosterone 2α/2β-hydroxylases activity; testosterone 6β-hydroxylase activity; testosterone 7α-hydroxylase activity; testosterone l6α-hydroxylase activity; testosterone 16β-hydroxylase activity; testosterone 17β-dehydrogenase activity; lauric acid 11-hydroxylase activity; lauric acid l2-hydroxylase activity; and debrisoquine 4-hydroxylase activity.

Phenobarbital produced marked increases in the majority of hepatic parameters, especially in the activities of 7-ethoxyresorufin O-deethylase and testosterone 6β-hydroxylase (>5 fold the control levels). At a dose of 3 mg/kg of conivaptan hydrochloride, hepatic parameters were largely unchanged. At a dose of 10 mg/kg of conivaptan hydrochloride, testosterone 6β-hydroxylase activity (a marker for CYP3A) was significantly increased on Day 1 after the final dose by 1.8 x compared to the negative control. This increase in CYP3A4 marker activity, however, was less than 20% of that produced by phenobarbital (11.6-fold) and had markedly declined after 7 days of drug withdrawal. Complete resolution was seen at 28 days post-dose. Plasma conivaptan concentrations decreased by 15% to 63% in rat toxicity studies with continuous intravenous infusion of 10 to 100 mg/kg/day for 1 week in toxicology study. However, consistent decreases in plasma concentrations were not observed after repeated doses suggesting a lack of appreciable enzyme induction of 3 to 100 mg/kg/day for 13 weeks. According to the sponsor, these findings suggest that conivaptan at the recommended human dose (IV of 20 mg bolus + 40 mg/day infusion for 4 days) may not be a significant inducer of CYP3A4. Whether the acute IV administration of conivaptan in clinical setting will significantly affect CYP3A4 enzymes and is yet to be determined.

2.6.5.15 PK: Induction/Inhibition of drug-metabolizing enzymes (po)

Test Article: Conivaptan Hydrochloride

Type of study	Enzyme induction study in F344 rats				
Method	Rats were administered by repeated oral gavage for 7 days, at dose levels of 0, 3 and 10 mg/kg/day. Phenobarbital (100 mg/kg/day p.o. for 7 days) was used as a positive control drug. Animals treated with 10 mg/kg/day were sacrificed 1 day, 7 days and 28 days after the last dose, and those treated with 3 mg/kg/day and phenobarbital were sacrificed 1 day after the last dose. The following hepatic parameters were measured.				
Tabulated results	**Ratio to the value of the dose vehicle control**				
Day after the final dose	1	1	1	7	28
Compound	PB[a]	YM087[b]	YM087[b]	YM087[b]	YM087[b]
Dose (mg/kg/day)	100	3	10	10	10
Parameters					
Relative liver weight	1.4	1.1	1.0	1.0	1.0
Microsomal protein concentration	1.3	0.9	1.0	1.0	1.0
Cytochrome P450 concentration	2.3	1.0	1.0	1.0	1.0
7-Ethoxyresorufin O-deethylase activity	5.4	1.0	1.1	0.9	1.0
Testosterone 2α/2β-hydroxylase activity	0.6	1.0	0.8	0.8	1.1
Testosterone 6β-hydroxylase activity	11.6	1.1	1.8	1.2	1.0
Testosterone 16α-hydroxylase activity	0.9	1.0	0.8	0.8	1.0
Testosterone 17β-dehydrogenase activity	0.9	1.0	0.9	0.9	1.1
Lauric acid 11-hydroxylase activity	1.8	1.0	1.1	1.0	1.0
Lauric acid 12-hydroxylase activity	0.9	1.0	1.0	1.0	1.1
Debrisoquine 4-hydroxylase activity	0.9	1.0	1.1	0.9	1.0
Study number	R087-ME-037				
Additional Information: None					
a – Phenobarbital; b – Conivaptan hydrochloride					

Human Drug-Interaction Studies

Summary of Conivaptan Pharmacokinetic Parameter Values Following Administration of 10-mg Conivaptan Tablets Alone (Reference) and During 200-mg q12h Ketoconazole Dosing (Test): Protocol 1025-38

Parameter	Least-Squares Mean Values		Ratio	90% Confidence Interval
	Conivaptan 10-mg Tablets Alone (Reference)	Conivaptan 10-mg Tablets With Ketoconazole (Test)		
Cmax, ng/mL	51.4	204	392	335 to 458
tmax, hr	0.96	1.50	157	Not Applicable
AUC(0-tlqc), µg·hr/mL	0.141	1.55	1100	938 to 1290
AUC(0-∞), µg·hr/mL	0.146	1.58	1090	938 to 1270
t½, hr	2.80	9.17	327	Not Applicable
CL/F, mL/min	1220	110	9.07	Not Applicable

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference)

90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean

2.6.4.8 Other Pharmacokinetic Studies

Not applicable

Human PK

Studies have shown that YM087 is metabolized primarily by liver and intestinal Cyp3A4. Therefore in humans, plasma concentrations of drugs metabolized by Cyp3A4 are likely to increase when co-administered with conivaptan. In the drug interaction studies, ketoconazole, a potent inhibitor of CYP3A4 increased YM087 AUC by 11 fold while YM087 administration increased simvastatin AUC by 20 fold.

In vitro studies suggest YM087 is metabolized by Cyp3A4 enzyme in jejunum microsomes. The intrinsic clearance of YM087 was 0.58 ml/min/mg, 75% of human liver microsome activity. Data appears to suggest that the intestinal metabolism may have contributed to the first-pass effect with oral administration of tablets in humans.

Due to lack of AUC data from SIADH patients, the larger AUC (3580 ng.h/ml vs. 3631 ng.h/ml) after IV study in healthy volunteers was used for exposure comparisons since the AUC in SIADH and patients with compromised liver and renal function is likely to be significantly higher. In the NDA submission, the sponsor has used a simulated linear PK modeling method to estimate AUC for IV dose formulation. Since conivaptan has a non-linear PK, a linear modeling used by the sponsor is incorrect. Furthermore, simulated AUC number even with correct assumptions is inappropriate in determining exposure multiples or safety margins. Conivaptan PK after 20 mg bolus and 40 mg IV for 3 days in healthy subjects is presented in table below. The total AUC divided per day is approximately 3580 ng.h/ml per day. The AUC_{0-24} of 3580 ng.h/ml was used in the exposure comparisons.

Table 2.7.2-15: Conivaptan and metabolite pharmacokinetic parameters in healthy male subjects (087-CL-074)

Analyte	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-inf} (ng•h/mL)	$t_{½,z}$ (h)	CL (L/h)
Conivaptan	619 ± 105	0.5 ± 0	10740 ± 4376	5.0 ± 1.4	15.2 ± 6.7
M1	2.93 ± 1.43	30.5 ± 33.1	141 ± 96.6	4.5 ± 0.6	NA
M2	17.32 ± 5.06	0.8 ± 0	634 ± 258	7.5 ± 2.2	NA
M4	0.48 ± 0.41	1.0 ± 0.1	10.24*	2.3*	NA

AUC_{0-inf} = area under the plasma concentration versus time curve from time zero to infinity; CL = total plasma clearance; C_{max} = maximum observed plasma concentration; NA = not available; $t_{½,z}$ = terminal phase elimination half-life; t_{max} = time at which C_{max} was observed.

Note: Data are presented as means ± SD (N = 5-8).

* Data available for a single subject only.

Conivaptan AUC after 20 mg bolus followed by 40 mg IV for 4 days in health subjects at steady state (AUC_{ss} 3631 ng.h/ml).

Table 9: Summary of Arithmetic Mean (SD) Steady-State Pharmacokinetic Parameters by Treatment Study No. 087-CL-083

Parameter	i.v. Conivaptan n=21	Oral Conivaptan[a] AM Dose n=20	Oral Conivaptan[b] PM Dose n=20	Oral Conivaptan[c] Sum of AM and PM n=20
C_{avg} (ng/mL)	151.31 (72.021)	123.17 (88.304)	73.06 (50.540)	98.11 (66.173)
AUC_{SS} (ng•hr/mL)	3631.43 (1728.49)	1478.09 (1059.65)	876.67 (606.474)	1177.38 (794.07)
CL or CL/F (L/hour)	12.92 (6.849)	40.56 (27.325)	80.85 (92.468)	49.17 (34.301)
Vd (L)	376.13 (251.273)	N/A	N/A	N/A
λ_z (Ke) ($hour^{-1}$)	0.0479 (0.0336)	N/A	N/A	N/A
t½ (hour)	21.64 (12.542)	N/A	N/A	N/A
F (AUCss Ratio)	1	0.3778	0.2349	0.3063

[a] C_{avg} and AUC_{SS} results for oral AM dose normalized to 40 mg

[b] C_{avg} and AUC_{SS} results for oral PM dose normalized to 40 mg

[c] Results for sum of AM and PM oral doses

F = Ratio of normalized oral AUCss/IV AUCss

2.6.4.9 Discussion and Conclusions

The initial goals of the sponsor were to develop conivaptan for chronic use [redacted] IV route.
acute intravenous formulation for treatment of hyponatremia in SIADH patients. Thus most of the pharmacokinetics and toxicokinetic data was originally collected from animal toxicology studies with oral formulation. Additional 4-WK studies were also performed with intravenous formulation (conivaptan in PG/EtOH) in rats and dogs. Conivaptan is rapidly and extensively absorbed following oral administration in rats and dogs. It is widely distributed into tissues, extensively metabolized, and predominantly excreted in feces following biliary excretion. In both animal and human studies, conivaptan demonstrated a nonlinear pharmacokinetic behavior; AUC values increased more than dose-proportionally. This phenomenon was probably due to inhibition /saturation of saturation of hepatic enzymes after dosing and inhibition/saturation of gastrointestinal microsomal enzymes after oral dosing. Conivaptan had similar metabolic profile rats, dogs and humans, supporting the use of rats and dogs for nonclinical safety evaluations.

Following an oral or IV dose, the increase in AUC was greater than dose proportional over a dose range of 0.3 to 3 mg/kg in rats and dogs. This indicates saturation of the first pass effect and nonlinear pharmacokinetics. The bioavailability of YM087 is approximately 20% in rats and dogs. Radiography studies showed radioactivity was widely distributed to all tissues except for central nervous system. Tissue concentrations relative to maximum plasma concentrations were 10- to 20-fold higher in the alimentary tract (oral dose only), liver, kidney, and adrenals, and 3- to 6-fold higher in lung, heart, spleen, pancreas, pituitary gland, submandibular gland, thyroid, and bone marrow. Radioactivity disappears fairly rapidly from most tissues accompanying decreasing plasma concentrations. After 24 hrs drug levels were detectable in liver, kidney and adrenal glands. Following IV administration, tissue concentrations rapidly declined except for adrenal gland and testes. The adrenal hypertrophy noted in toxicology studies was likely due to prolonged residence and higher concentrations in adrenal glands. Metabolic fingerprinting in adrenal glands showed that M2 was the most abundant followed by M4, parent and M1, respectively. These metabolites were also seen in dog plasma, bile and urine.

When the distribution of C^{14} conivaptan was examined in pregnant rats, high radioactivity was found in amnion, mammary gland, placenta relative to blood. In this study, there was no notable detectable C^{14}-YM087 in fetus after 24-hrs suggesting that drug may transfer to fetus but the transfer is likely to be very low. In reproduction and lactation study tissue analysis, the concentrations in the fetuses 24 hours after oral dosing declined to 32% of the fetal Cmax and 39% after IV dosing. The fetal/plasma concentration ratio increased over time after the oral and IV dose, suggesting that clearance of radioactivity from the fetus is slower than from plasma, and, therefore, accumulation may occur. In a single dose study (3 mg/kg po, 1 mg/kg IV) in dams with neonates, radioactivity has been found in maternal milk, blood and plasma and in neonate blood, plasma and tissue. In rat, YM087 transfers to breast milk after oral and IV doses. The transfer of YM087 and its metabolites to the rat fetus is very low during the period of organogenesis and during the perinatal period

Estimates of clearance and volume of distribution indicate that conivaptan is highly extracted drug. *In vitro* transfer studies demonstrate that the metabolites may distribute into blood cells more readily than parent drug. YM087 subject to enterohepatic recirculation in rat, consequently the pharmacokinetic behavior is different between low and high dosages.

YM087 had high and similar protein binding in rats, dogs and humans (99.1, 99.2 and 99.5%, respectively). YM087 binding to α-1acid glycoprotein, HDL and immunoglobulin were 99.2, 93.2 and 62.8%, respectively. Conivaptan is metabolized by CYP3A4. Several potential co-administered drugs (i.e. captopril, simvistatin, amlodipine) also are substrates for CYP3A4 enzyme which demonstrate a drug-drug interaction in human. Metabolic profile of conivaptan was similar across species examined (rats, dogs and humans). Two major metabolites, M1 and M2 were identified in liver microsomes derived from mice, rats, dogs and humans. The results of mass balance studies in rats suggested that radioactivity was mainly excreted into bile after both intravenous and oral administration of C^{14}-conivaptan hydrochloride. In rat bile, nearly 8 metabolites have been identified (M1, M2, M4, M5 (*N*-hydroxyimidazole derivative of M2), M6 (*O*-glucuronide of M2), M7, M8 and M9 (mono-hydroxylated compound of M2). M1, M2, M4 and M7 metabolites are present in human plasma and have been found in rat and dog plasma, suggesting that rat and dog are appropriate species for pharmacology and toxicology studies of conivaptan.
The affinity of metabolites M1, M2, M4 and M7 to V_{1A} and V_2 receptors has been evaluated in rats. M1 affinity is similar to parent product. M2 and M4 affinities were [redacted] fold less than parent with M7 having no affinity to V_{1A} and V_2 receptors. Since plasma levels of the metabolites are <6% of parent, they are unlikely to have a meaningful contribution to pharmacological activity.

The PK data suggests bile as the primary excretion pathway. When labeled YM087 was given to animals, the majority of radioactivity was excreted primarily in the feces through bile within 24 hours in rat and dogs. After an IV administration, the cumulative biliary and urinary excretions were 77 and 13% at 72 hrs in rats. Nearly 80% of the drug is excreted (60% bile to feces) with in 24 hrs. The excretion profile of conivaptan in dogs was similar to rats. However following single dose bolus IV and oral administration of C^{14}-conivaptan the $t^1/_2$ was shorter than plasma radioactivity, and the proportion of $AUC_{0-\infty}$ represented by parent was 34-53% this suggests that substantial fraction of plasma radioactivity was metabolites.

The sponsor had conducted several clinical studies using oral formulation in SIADH and CHF patients. There has been no IV pharmacokinetic clinical study in SIADH patients; however 2 studies in healthy volunteers had examined the PK for IV formulation PG/EtOH (20 mg IV bolus + 40 mg infusion for 4 days). In attempt to estimate the drug exposure from PK data from SIADH oral studies, a linear PK modeling method was used by the sponsor. Since conivaptan follows a non-linear model in animals and humans, a non-linear modeling is the most pertinent and appropriate. For the AUC comparisons in this review, the cumulative AUC form the 4 day IV study in healthy humans was divided by 4 to estimate the AUC for 24 hrs (3580 ng.h/ml). Since the AUC in SIADH or CHF and patients with liver cirrhosis or renal dysfunction is likely to be higher, the conservative higher AUC value in humans was selected for exposure comparisons.

2.6.4.10 Tables and figures to include comparative TK summary

PK: Pharmacokinetics after a single dose (iv) ***Test Article: Conivaptan Hydrochloride***

Species/Strain	F344 Rat		Beagle Dog		Human	
Number of animals/Gender (M/F)	3M	3M	3M	3M	4M	4M
Feeding condition	Non-fasted	Non-fasted	Fasted	Fasted	Fasted	Fasted
Vehicle/Formulation	Solution[a]	Solution[a]	Solution[a]	Solution[a]	Solution[b]	Solution[b]
Method of administration	Intravenous	Intravenous	Intravenous	Intravenous	Intravenous infusion (5min)	Intravenous infusion (5min)
Dose (mg/kg) – ^{14}C-conivaptan hydrochloride	1	1	0.3	0.3	10 mg	10 mg
Sample	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma
Analyte						
Assay	[redacted]					
PK parameters						
CL_{tot} (L/hr/kg)	0.8	2.5	–[e]	–[e]	–[e]	17.9 L/hr
V_{dss} (L/kg)	5.4	3.4	–[e]	–[e]	–[e]	50.2 L
AUC (ng or ng equivalents·hr/mL)	1099	378	2227	1178	3064[f]	547[f]
(Time for calculation – hr)	(0-inf)	(0-inf)	(0-inf)	(0-inf)	(0-inf)	(0-inf)
$t_{1/2}$ (hr)	8.3	1.1	8.6	4.1	23.0	5.0
(Time for calculation – hr)	(6-24)	(1-6)	(8-24)	(8-24)		
Study number	R087-ME-049		R087-ME-019		R087-CL-061	

Additional Information:
Results in rats, which were obtained with [aminobenzoyl-^{14}C] conivaptan hydrochloride, were similar to those obtained with [imidazole-^{14}C] conivaptan hydrochloride [R087-ME-018].

a – The dosing solution contained [redacted] glycerin and [redacted] lactic acid.; b – Phase I formulation for intravenous dose;
c – Total radioactivity, ^{14}C; d – Conivaptan (free base); e – Not calculated; f – The values presented as conivaptan hydrochloride in the original report [R087-CL-061] were converted to those of conivaptan free base.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

PK: Pharmacokinetics after a single dose (iv) Test Article: Conivaptan Hydrochloride

Species/Strain	F344 Rat			F344 Rat
Number of animals/Gender (M/F)	3M	3M	3M	3M
Feeding condition	Non-fasted	Non-fasted	Non-fasted	Non-fasted
Vehicle/Formulation	Solution[a]	Solution[a]	Solution[a]	Solution[b]
Method of administration	Intravenous	Intravenous	Intravenous	Intravenous
Dose (mg/kg) – conivaptan hydrochloride	0.3	1	3	10
Sample	Plasma	Plasma	Plasma	Plasma
Analyte	YM087[c]	YM087[c]	YM087[c]	YM087[c]
Assay	HPLC [redacted]	HPLC [redacted]	HPLC- [redacted]	[redacted]
PK parameters				
CL_{tot} (L/hr/kg)	3.3	2.7	1.5	0.8
V_{dss} (L/kg)	3.8	3.1	3.0	2.7
AUC (ng·hr/mL)	84	352	1877	11673
(Time for calculation – hr)	(0-inf)	(0-inf)	(0-inf)	(0-inf)
$t_{1/2}$ (hr)	0.9	1.0	1.8	2.2
(Time for calculation – hr)	(0.5-2)	(1-4)	(2-8)	(0.1-24)
Study number	R087-ME-010			R087-ME-062

Additional Information:
Plasma concentration profiles exhibited a biphasic decline following single bolus intravenous doses.

a – The dosing solution contained [redacted]glycerin and [redacted] lactic acid.; b – The dosing solution contained 30% PG and 10% EtOH.;
c – Conivaptan (free base)

2.6.5.3C PK: Pharmacokinetics after a single dose (iv) Test Article: Conivaptan Hydrochloride

Species/Strain	Beagle Dog				Beagle Dog
Number of animals/Gender (M/F)	4M	4M	4M	4M	4M
Feeding condition	Non-fasted	Non-fasted	Non-fasted	Non-fasted	Non-fasted
Vehicle/Formulation	Solution[a]	Solution[a]	Solution[a]	Solution[a]	Solution[b]
Method of administration	Intravenous	Intravenous	Intravenous	Intravenous	Intravenous
Dose (mg/kg) – conivaptan hydrochloride	0.03	0.1	0.3	1	5
Sample	Plasma	Plasma	Plasma	Plasma	Plasma
Analyte	YM087[c]	YM087[c]	YM087[c]	YM087[c]	YM087[c]
Assay	HPLC [redacted]	HPLC- [redacted]	HPLC- [redacted]	HPLC [redacted]	[redacted]
PK parameters					
CL_{tot} (L/hr/kg)	0.6	0.5	0.5	0.4	0.2
V_{dss} (L/kg)	1.5	1.3	1.5	1.6	1.4
AUC (ng·hr/mL)	48	203	566	2300	28331
(Time for calculation – hr)	(0-inf)	(0-inf)	(0-inf)	(0-inf)	(0-inf)
$t_{1/2}$ (hr)	1.9	2.1	2.3	2.7	6.6
(Time for calculation – hr)	(0.5-4)[d]	(1-10)[d]	(1-10)[d]	(6-24)[d]	(0.5-24)[d]
Study number	R087-ME-013				R087-ME-062

Additional Information:
Plasma concentration profiles exhibited a biphasic decline following single bolus intravenous doses.

a – The dosing solution contained [redacted]glycerin and [redacted] lactic acid.; b – The dosing solution contained 30% PG and 10% EtOH.;
c – Conivaptan (free base); d – Total time range; times varied for individual animals.

PK: Pharmacokinetics after repeated doses (iv & po)

Species/Strain	Beagle Dog			Beagle Dog		
Number of animals/Gender (M/F)	6M	6M	6M	6M	6M	6M
Feeding condition	Non-fasted	Non-fasted	Non-fasted	Fasted	Fasted	Fasted
Vehicle/Formulation	Solution[a]	Solution[a]	Solution[a]	Solution[b]	Solution[b]	Solution[b]
Method of administration	Intravenous	Intravenous	Intravenous	Gavage	Gavage	Gavage
Dose (mg/kg/day) – conivaptan hydrochloride	0.1	0.1	0.1	0.3	0.3	0.3
Sample	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma
Sampling day	1	8	15	1	8	15
Analyte	YM087[c]	YM087[c]	YM087[c]	YM087[c]	YM087[c]	YM087[c]
Assay	[redacted]					
PK parameters						
t_{max} **(hr)**	—[d]	—[d]	—[d]	1.0	0.9	1.2
C_{max} **(ng/mL)**	—[d]	—[d]	—[d]	82	64	61
CL_{tot} **(L/hr/kg)**	0.5	0.6	0.6	—[d]	—[d]	—[d]
V_{dss} **(L/kg)**	1.2	1.4	1.6	—[d]	—[d]	—[d]
AUC (ng·hr/mL)	216	190	179	363	288	292
(Time for calculation – hr)	(0-inf)	(0-inf)	(0-inf)	(0-inf)	(0-inf)	(0-inf)
$t_{1/2}$ **(hr)**	2.1	2.2	2.3	2.0	1.9	2.0
(Time for calculation – hr)	(0.5-10)[e]	(0.5-10)[e]	(0.5-10)[e]	(2-10)[e]	(1-10)[e]	(2-10)[e]
Study number	R087-ME-014			R087-ME-012		

Additional Information:
Plasma concentrations of the parent compound slightly decreased after repeated intravenous and oral dosing to dogs.

a – The dosing solution contained [redacted] glycerin and [redacted] lactic acid.; b – The dosing solution contained 10% PEG-200 in 0.5 mM phosphoric acid.; c – Conivaptan (free base); d – Not calculated; e – Total time range; times varied for individual animals.

Table 2.6.4- 20: Pharmacokinetic parameters of unchanged drug and its metabolites, M1, M2 and M4, after single-dose bolus intravenous administration of 10 mg/kg of conivaptan hydrochloride to rats [R087-ME-062]

Analyte	C_{max} (ng/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (ng·hr/mL)
Unchanged				
M1				
M2				
M4				

Table 2.6.4- 21: Pharmacokinetic parameters of unchanged drug and its metabolites, M1, M2 and M4, after single-dose bolus intravenous administration of 5 mg/kg of conivaptan hydrochloride to dogs [R087-ME-062]

Analyte	C_{max} (ng/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (ng·hr/mL)
Unchanged	4820 ± 824[1)]	-	6.6 ± 0.5	28331 ± 4607
M1	37.6 ± 5.9	1.63 ± 1.60	7.1 ± 1.4	413 ± 109
M2	72.7 ± 25.5	0.25 ± 0.00	14.9 ± 3.0	685 ± 145
M4	1.32 ± 0.53	0.88 ± 0.25	5.8 ± 3.9[2)]	11 ± 3[2)]

Each parameter was calculated from individual dog plasma concentration, time data and expressed as mean ± SD of four dogs.
1) C_0
2) Mean ± SD of three dogs.

Table 2.6.4- 22: Pharmacokinetic parameters of unchanged drug and its metabolites, M1, M2 and M4, during and after 24-hour continuous intravenous infusion of 5 mg/kg of conivaptan hydrochloride to dogs [R087-ME-062]

Analyte	C_{max} (ng/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (ng·hr/mL)
Unchanged	1257 ± 147	24.00 ± 0.00	6.1 ± 1.1	25088 ± 2912
M1	8.88 ± 1.59	24.13 ± 0.14	5.1 ± 1.9	175 ± 20
M2	12.8 ± 2.4	24.13 ± 0.14	9.5 ± 2.9	375 ± 74
M4[1)]	-	-	-	-

Each parameter was calculated from individual dog plasma concentration, time data and expressed as mean ± SD of four dogs.
1) Plasma concentrations of M4 were less than LOQ at all time points.
- : Not applicable

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology Summary

The toxicology of conivaptan HCl was evaluated in oral, bolus IV and continuous IV studies. Two formulations were developed for IV administration. The first was a glycerin formulation consisting of glycerin and less than lactic acid. This formulation was used for some toxicology studies but was not considered optimal for commercial use. The clinical formulation consists of propylene glycol ethanol (PG/EtOH) and less than 0.06% lactic acid and is the same formulation used for 4-week rat and dog toxicology studies. The clinical dose is a 20 mg bolus IV on day 1 followed by up to 3 days of IV infusion at 40 mg in SIADH patients. Clinical exposure data is not available in this patient population with this dosing regimen. However based on an averaging of a 20 mg bolus followed by a 40 mg IV infusion in healthy volunteers an AUC=3580 ng h/ml per day is being used. Since SIADH patients may have underlying renal/liver impairment the actual exposures may be much greater, hence the safety margins calculated from animal data may be underestimated.

Acute Dose Toxicity

The lethal dose of conivaptan in rats after single oral dose was >2000 mg/kg. Signs of acute toxicity included: hypoactivity, lacrimation, piloerection, urine staining, hunched posture and ataxia from 3 hr. post dose. In single bolus intravenous studies with the PEG/EtOH formulation females given 100 mg/kg experienced tremors and died shortly postdose. Ataxia was observed at 30 mg/kg. Controls receiving vehicle also experienced convulsions, recumbency and irregular respiration. Therefore some of the effects may be attributed to vehicle which are further exacerbated by conivaptan. The FDA Inactive ingredient guide lists propylene glycol in approved products at concentrations above 30% for IV use. which may be resulting in the convulsions particularly since other studies using this formulation acutely and with repeated dosing did not exhibit convulsions.

In dogs single dose oral administration of 100, 300, 1000 mg/kg did not cause mortality. Vomiting was frequently seen. Feces containing test material was observed in all dogs except for males given 100 mg/kg. Following a single bolus IV dose in an escalation study (5, 10, 30 mg/kg) of 30 mg/kg with PG/EtOH, the male dog experienced prone position, vomiting, ataxia and red urine. Hemolysis, dehydration, red cranial fluid retention, renal tubular casts, renal medullary microcalculi and GI congestion were observed at necropsy. The female showed similar clinical signs but recovered within 24 h post dose. At 10 mg/kg the male exhibited slight ataxia and decreased water consumption, weight and food. Water consumption increased in all treated animals but returned to predose levels by day 10.

Repeat Dose Toxicity

Repeat dose toxicity of conivaptan was evaluated by oral, bolus IV and continuous IV infusion administration in rats and dogs. Conivaptan administered to rats by oral gavage at 0.3, 1, 3, 10,

30, 100 mg/kg/day for 13 weeks and 1, 3, 10, 100 mg/kg for 26 weeks. Using the PG/EtOH formulation rats were given bolus IV doses of 0.5, 1.25 and 2.5 for 4 weeks and by continuous IV infusion at 10, 30, 100 mg/kg/day for 4 weeks. Dogs were dosed orally at 1, 3, 10, 30 mg/kg for 13 weeks and 1, 3, 10, 20 mg/kg for 52 weeks. Dogs received the bolus IV dosing using the PG/EtOH formulation at 2, 5, 10 mg/kg conivaptan for 4 weeks and 2, 10, 20 mg/kg for 4 weeks by continuous IV infusion.

Conivaptan was administered intravenously as a bolus and continuous infusion dose. In a 4-week bolus IV toxicity study with the PG/EtOH formulation [R087-TX-066] in rats at 2.5, 10 and 25 mg/kg at 20 ml/kg severe injection site lesions (tail vein) occurred by day 10 in groups given ≥10 mg/kg resulting in study termination. Mortality was observed in these groups beginning week 1. Convulsions and tremors were noted in high dose males by day 3. Toxicokinetics have not been provided. In a 4-week IV toxicity study in rats with the PG/EtOH formulation [R087-TX-067] with doses of 0.5, 1.25 and 2.5 mg/kg given by infusion at 1 ml/min at a 10 ml/kg dose concentration a dose related increase in water intake and increased urine output with an associated decrease in urine specific gravity was observed in males given 1.25 and females given 2.5 mg/kg/day. RBC, hemoglobin, and hematocrit decreased in HD males, higher BUN in males at 0.5 mg/kg/day and both genders at 1.25 mg/kg/day was observed. An increased incidence/severity of vascular/perivascular necrosis and thrombus formation in males and proliferation of the vascular intima for males and females is observed with treatment. Minimal adrenal cortical hypertrophy is observed in high dose males. The NOAEL of 1.25 mg/kg/day (AUC_{0-24}=1249 M; 1339 F ng h/ml) was established in this study based on injection site findings this represents less than clinical therapeutic exposure based on AUC.

In a 4-week bolus IV toxicity study in with the PG/EtOH formulation [R087-TX-072] in dogs at 2, 5, 10 mg/kg a dose volume of 4 ml/kg and 10 ml/min were used. Local injection site damage (inflammation/edema) resulted in termination of the high dose group by day 16. Thrombus formation was observed at ≥5 mg/kg/day. One high dose female was found dead on day 3, the cause of death was undetermined although necropsy was performed. One mid dose female had tremors, ataxia, hypoactivity and dehydration by the end of week 1. The NOAEL =2 mg/kg/day was established (AUC_{0-24}=13517 M; 10141 F ng h/ml) since one female at 5 mg/kg showed tremors, ataxia and hypoactivity. In a 4-week IV dog toxicity study [R087-TX-074] using 2, 10, 20 mg/kg with the PG/EtOH formulation given by infusion at 2 ml/kg/h significant deterioration consisting of dehydration and jaundice were observed in 2/3 high dose males. Significant decreases in RBC, PCV and hemoglobin was observed in HD males. Liver findings including: cytoplasmic alteration, sinusoidal dilatation, Kupffer cell hypertrophy, centrilobular degeneration, pigmentation and extramedullary hematopoiesis were observed at high dose. Minimal to slight renal tubular degeneration and fibrosis and minimal renal tubular regeneration kidney edema and seminiferous tubule degeneration were observed in doses ≥10 mg/kg. The kidney findings are attributed to the marked aquaresis, although the renal findings were not observed at all doses although the aquaresis was. The sponsor suggests that this type of renal finding is observed with various classes of diuretics based on literature. A NOAEL=2 mg/kg in males and 10 mg/kg in females was established based on histopathology (AUC_{0-24} =12,120 ng h/ml in males and 120,168 ng h/ml in females). This dose provides a 3 and 30 fold safety margin in males and females respectively for the therapeutic human dose based on AUC. Renal

tubular degeneration fibrosis and renal edema were observed at 20 mg/kg IV infusion in a one week dog study.

Bolus intravenous dosing resulted in significant toxicity including morbidity/mortality. This is likely a result of the rapid dehydration and potential hypernatremia resulting from achievement of a rapid Cmax than with continuous intravenous infusion. The local injection site inflammation was severe enough to prevent repeated dosing much beyond 7-10 days. Continuous infusion of conivaptan in rat and dog proved to be less toxic and NOAELs were obtained. The toxicokinetic data allowed bridging to the oral chronic toxicity studies where exposures at rat and dog NOAELs were consistent between IV and oral administration.

In dogs bone marrow findings (multifocal necrosis, decreased erythroblastic islands, myeloid hyperplasia, hypocellularity and fibrosis) were observed in the 2, 13 and 52 week oral studies and in the 4 week bolus and continuous IV infusion studies. Associated hematologic changes in PBL such as decreased erythrocytes, leukocytes and platelet counts were observed. In oral chronic toxicity studies one male had these bone marrow and hematology findings which had and $AUC_{0\text{-}24}$=164 μg h/ml. At similar exposures (173 μg h/ml) in a 4 week continuous IV infusion study similar bone marrow findings were observed. These exposures in dog are 50-fold higher than human therapeutic exposure (AUC=3.6 μg h/ml) and these findings were not observed at shorter durations of exposure in dogs. The bone marrow findings appear to be reversible as demonstrated following 6 weeks recovery in a 13 week oral toxicity study. Colony forming unit assays in rat and dog bone marrow cells indicated that conivaptan at ≥ 5 μg /ml was cytotoxic on hemopoietic precursor cells.

Liver changes were observed in both rat and dog. Bile duct hyperplasia, sinusoidal dilatation, hepatocyte hypertrophy and inflammatory infiltration were observed in the 2 and 13 week oral toxicity study and in the 1 and 4 week IV infusion studies along with increased liver enzyme levels and weight. In some severe cases in dogs, jaundice and increased total bilirubin were noted. In oral toxicity studies the lowest exposure resulting in liver findings was 207 μg h/ml. Similarly the lowest exposure resulting in liver changes (slight sinusoidal dilatation) with continuous IV infusion was 173 μg h/ml. The NOAELs for hepatocyte necrosis and liver enzyme elevations were 24 and 15 μg h/ml respectively corresponding to 4X clinical exposure based on AUC. In a 1-week continuous IV infusion study slight hepatocellular hypertrophy and minimal to severe hepatocyte necrosis was noted at 100 mg/kg in rats (60 μg h/ml; 15X clinical exposure). The lowest exposure at which these findings appear is 60 μg h/ml in females. However liver enzymes (ALT, AST) are elevated in males given ≥ 30 mg/kg which corresponds to 24 μg h/ml or 6X clinical exposure. In a 4 week IV infusion study at the same dose levels, only increased AST was noted in females at 30 mg/kg. Increased liver weight was noted in 13 and 26 week rat oral toxicity studies without enzyme elevation or histopathology.

The sponsor attributes the prolonged diestrus, decreased uterine weight and increased adrenal weight and adrenocortical hypertrophy/hyperplasia observed in oral, bolus and continuous IV infusion (100 mg/kg) rat studies to effects of conivaptan on steroidogenesis rather than direct organ toxicity. However tissue distribution studies demonstrate that the adrenal gland is exposed to significant conivaptan levels along with liver and kidneys. This might suggest direct adrenal effects rather than the proposed indirect effect on steroidogenesis. Oral administration of conivaptan to female rats at ≥ 10 mg/kg increased plasma AVP and progesterone but did not

affect prolactin, FSH, LH or estradiol-17β. The presence of prolonged diestrus was confirmed in rat fertility studies as evidenced by a decreased fertility index, increased pre/post implantation losses at 100 mg/kg. Mechanistic studies identified that the increased progesterone and AVP levels in rats following a single oral dose of 100 mg/kg without increasing gonadotropic or other sex steroid hormones (ACTH and progesterone increased and corticosteroids were suppressed). Mechanistic studies confirm that conivaptan increases progesterone levels and decreases corticosteroids via inhibition of 21-hydroxylase which converts progesterone to 11-deoxycorticosterone. The source of the increased progesterone was demonstrated to be of an adrenal source because OVX rats showed increased plasma progesterone but changes were not observed in adrenalectomized rats. Furthermore conivaptan strongly inhibited 21-hydroxylase (but not 11β-hydroxylase) in rat adrenocortical cells. Negative feedback mechanisms result in secretion of ACTH from the pituitary when plasma corticosterone decreases ultimately resulting in activation of steroidogenesis in the adrenal cortex. This feedback mechanism is implicated in stimulating progesterone release from the adrenal cortex. The sponsor believes the ACTH stimulation of the adrenal cortex is responsible for the adrenal hypertrophy although accumulation of conivaptan in the adrenals is observed in tissue distribution studies. Effects of conivaptan on estrous and plasma progesterone were compared in Brattleboro rats (congenital inability to synthesize AVP) and Long-Evans rats (wild type). Prolonged diestrus and elevated progesterone were observed in both strains following conivaptan treatment but the Cmax for progesterone was 5 times higher in Long-Evans 6 hr. post dose than in the AVP deficient Brattleboro strain. This suggests that AVP is at least partially involved in the increased progesterone effect observed in conivaptan treated rats.

Vascular irritation/injection site changes occurred in rats and dogs. These changes were severe enough to terminate a rat 4 week IV infusion and dog bolus IV study early. Some of the irritation is attributed to the PG/EtOH however there is a dose responsive exacerbation by conivaptan.

Chronic Toxicity

Two 6 month oral gavage rat toxicity studies were performed. Study [T087-TX-045] used doses of 1, 3, 10, 100 mg/kg/day and study [R087-TX-046] used 10 and 100 mg/kg/day doses but in males only to investigate the mortality and pneumonia observed in the prior study. Mortality was observed at ≥ 10 mg/kg/day in both genders. Many of these rats exhibit decreased body weight, hunched posture, rough haircoat, cold, hypoactivity, incoordination, labored/audible respiration before sacrifice, evidence of pneumonia. Dilation of the esophagus and granulomatous inflammation of the lung occasionally containing foreign material is observed at ≥3 mg/kg/day. Lymphocyte depletion of the thymus, mesenteric lymph node, spleen and hypocellularity of the bone marrow in addition to adrenocortical hypertrophy/plasia, atrophy of prostate/seminal vesicles, immature epididymal sperm and estrus disruption were observed at 10 and 100 mg/kg/day. A NOAEL=1 mg/kg/day (AUC_{0-24}=86 ng h /ml in males and 117 ng h /ml in females; less than therapeutic exposure). In the initial 26 week oral gavage study rats were fed a powdered diet whereas in the second study in males only a pellet diet was used and the pneumonia was not observed suggested a possible relationship to diet. Mortality, decreased body weight, granulomatous lung inflammation and lymphatic atrophy were not observed in the second 26 week oral gavage study at doses up to 100 mg/kg/day. In the second study a number of consistent findings are observed including an increase in platelet counts, albumin and plasma proteins attributed to the hemoconcentration resulting from diuresis.

Adrenocortical hypertrophy and hyperplasia with increased weight was observed at 100 mg/kg/day. This is attributed to elevated AVP and ACTH. Renal basophilic tubules and protein casts in the collecting ducts were considered a drug related acceleration of an age related rat lesion. A NOAEL could not be established based on the body weight, renal and adrenal changes at 100 mg/kg/day and increased adrenal weight at 10 mg/kg/day (AUC_{0-24}=6012 ng h/ml males; 2X therapeutic exposure) exposures in this second study are similar to those observed in the first.

In an oral dog toxicity study [RR745-02781] doses of 1, 3, 10, 20 mg/kg were given by gelatin capsule for one year. Most significant findings occurred at 20 mg/kg/day including: pale mucous membranes, hypoactivity, lower body weight and food consumption. The pale mucous membranes were associated with anemia and bone marrow findings of necrosis and hematopoietic cell hyperplasia. Plasma globin and albumin along with GOT were elevated. Two males with anemia had epididymal vasculitis. It doesn't appear that other vascular beds associated with vasculitis were examined e.g. mesenteric. A NOAEL=10 mg/kg/day was established providing an AUC_{0-24}=75,092 in males and 111,683 ng h/ml in females which provides exposures 25X greater than therapeutic exposure.

The table below indicates the sponsor's interpretation of NOAEL values from various oral and IV toxicology studies and the safety margins relative to the clinical dose. Note that the sponsor's clinical dose used for these calculations is 40 mg/day with an AUC=13.78 µg h/ml

Table 2.4-1: Ratios of Systemic Exposures (AUC_{0-24}) in Laboratory Animals to Those in Humans

Animal Species	Dosing Route	Sampling time	Daily dose levels (mg/kg)		Exposure ratio (AUC_{0-24})* Male	Female
Repeat-Dose Toxicity						
Rat	po	13 weeks	1	NOAEL in males	<1	-
			3	NOAEL in females	-	<1
			3	LOAEL in males	<1	-
			10	LOAEL in females	-	<1
			100	HD	3.58	4.94
		26 weeks	1	NOAEL	<1	<1
			3	LOAEL	<1	<1
			100	HD	2.25	2.61
			100	HD in the additional study	3.29	-
	iv bolus	4 weeks	1.25	NOAEL	<1	<1
			2.5	HD and LOAEL	<1	<1
	iv infusion	4 weeks	10	NOAEL	<1	<1
			30	LOAEL	<1	1.95
			100	HD	<1	<1
Dog	po	13 weeks	10	NOAEL	2.98	2.68
			30	HD and LOAEL	8.27	9.65
		52 weeks	10	NOAEL	5.45	8.10
			20	HD and LOAEL	7.05	6.37
	iv bolus	4-weeks	2	NOAEL	<1	<1
			5	LOAEL	3.78	2.87
			10	HD	15.32	7.26
	iv infusion	4 weeks	10	NOAEL	9.97	8.72
			20	HD and LOAEL	38.14	21.38
Pregnant Animals						
Rat	po	GD17	1	NOAEL for dams	-	<1
			100	No teratogenicity	-	2.84
	iv	GD7	2.5	No teratogenicity	-	<1
Rabbit	po	GD18	6	No teratogenicity	-	<1
	iv	GD18	3	NOAEL for dams	-	<1
			12	No teratogenicity	-	1.99

* Exposure ratio relative to the human exposure (13.78 µg·hr/mL) at the RHD (40 mg/day) [R087-CL-027]. Data at the final determination in each animal study were used.
- No data exists. NOAEL: No observed adverse effect level.
LOAEL: Lowest observed adverse effect level. HD: Highest dose. GD: Gestation day.

which differs from the AUC=3.58 μg h/ml used in this review which is based on an average obtained from a 20 mg IV bolus + 40 mg/day infusion in healthy volunteers as PK is unavailable for SIADH patients with this dosing regimen.

Toxicology Summary by Pivotal Studies

1-Week IV studies
Administration of IV bolus conivaptan at 0, 3, 10 and 30 mg/kg/d to rats for 1 week produced notable injection site lesions. Discoloration, vascular necrosis, perivascular necrosis, thrombosis, hemorrhage, edema and inflammation were among the notable findings in all rats at all injection sites, however, the severity appeared to be greater in conivaptan treated groups. Male rats and to lesser extend female rats treated with 30 mg/kg/d IV also had slight to moderately severe renal tubular degeneration. Renal tubular findings at 10 and 3 mg/kg/d IV conivaptan were similar to controls. The NOAEL was 3 mg/kg/d (0.3 x human dose based on AUC_{0-24}). At 30 mg/kg/d, the exposure in rats was approximately 4 x recommended human dose. The IV study was repeated in rats using continuous IV drug delivery via a catheter (10, 30 and 100 mg/kg/d) for 1 week. As expected, conivaptan dose-dependently increased urine volume and water consumption in rats. A significant increase in AST (1.3X) and ALT (2X) was noted at 100 mg/kg/d. A significant increase in adrenal and liver weight was observed at 30 and 100 mg/kg/d after 1 week of conivaptan infusion in rats. Liver hepatocyte necrosis was noted in 4/5 rats at 100 mg/kg/d but not at 30 mg/kg/d. Hemorrhage at catheter exit and entry were noted in control as well as 100 mg/kg/d dose group. The apparent incidence of thromboemboli in the lungs, endocardial hyperplasia in the heart, and inflammation and thrombosis at the injection site were likely related to continuous infusion method used. However, the severity of local damage at the injection site appeared to be dose-dependently increased suggesting some exacerbated irritation resulting from drug infusion.

In the 1-Week IV dog dose ranging study (2, 5 and 10 mg/kg/d, 3.6, 12 and 49 x human dose based on AUC_{0-24}), one male at 10 mg/kg/d was found dead on evening of Day 2. The animal had convulsion, labored breathing and erythema of the whole body earlier. Clinical pathology results appeared to suggest dehydration and stress-related (increased neutrophil and decreased lymphocytes). Other dogs had ataxia, hypoactivity and salivation with no change in blood pressure or ECG. In the continuous infusion dose ranging study in dogs (2, 10 and 30 mg/kg/d), there were no deaths or changes in blood pressure or ECG, however, ALT, AST and total bilirubin levels were increased at 30 mg/kg/d. Although the duration of the study was short, an increase in liver weight was observed at 30 mg/kg/d along with hyperplasia of bile duct and some inflammatory changes in the portal area of the liver. Infusion site vessel wall necrosis and proliferative thrombosis was observed at both 10 and 30 mg/kg/d (25-39x and 191-200 x human dose based on AUC_{0-24}, respectively). In the 9-Day continuous infusion study, conivaptan in PG/EtOH was infused at 2, 10 and 30 mg/kg/d (2.9, 29 and 196 x clinical dose based on AUC_{0-24}). Dogs in the 30 mg/kg/d dose group (n=3/sex) appeared thin, dehydrated with excessive urination and water intake as noted in previous studies. Bile duct hyperplasia and inflammation of portal area in the liver were noted in the 30 mg/kg/d treated dogs. Although injection site changes were observed in control as well as treated animals, the vessel wall necrosis and proliferative thrombosis were most common in the 10 and 30 mg/kg/d dose treated dogs. The exposure at 10 and 30 mg/kg/d in dogs were approximately 29 and 191 fold greater than clinical

dose suggesting that injection site findings severity will be relatively limited in humans (redness and slight swelling as noted in clinical studies).

4-Week IV studies
Fischer 344 rats were treated with IV conivaptan in PG/EtOH for 4 weeks (2.5, 10 and 25 mg/kg/d). All rats at treated with 25 mg/kg/d, were sacrificed during week 1 due to tail discoloration and IV dosing difficulty. One female at 10 mg/kg/d died during week 1 and 5 males and 1 female were sacrificed during wk 2. Due to injection site lesions, the whole study was terminated on Day 14. Common to most 10 and 25 mg/kg/d doses were convulsion characterized by tonic hind limb extension, dehydration and swollen ventral abdomen and ocular discharge. The abdominal distension was likely due to large water intake. Since the study was terminated early, another IV study at lower doses of conivaptan in PG/EtOH (0.5, 1.25 and 2.5 mg/kg/d, 0.1, 0.4 and 1 x human AUC_{0-24}) was performed in F344 rats. As expected there were no drug-related deaths at these lower doses. The decrease in body weight gains at 1.25 and 2.5 mg/kg/d dose at WK2 were likely due to drug-related increase in water consumption (leading to decrease in BW) and aquaresis. Although the water intake had increased, pharmacological studies suggest that conivaptan can lead to significant dehydration in animals even when there is ad lib access to water. Animals appear to respond to water loss but the net water/volume loss may be more severe than water intake (negative water balance). Even though the largest dose 2.5 mg/kg/d provided equal exposure to clinical IV dose, there was a significant dose-related increase in urine output (~14 x, 23 x and 30 x at 0.5, 1.25 and 2.5 mg/kg/d, respectively). Injection site lesions were seen in control but more pronounced in treated animals. Vascular/perivascular necrosis, proliferation of vascular intima and thrombus were more frequent in males and females treated with 2.5 mg/kg/d. Adrenal cortex hypertrophy noted in 7/10 males at 2.5 mg/kg/d was not observed in females. The NOAEL was 1.25 mg/kg/d (0.4 x clinical dose based on AUC_{0-24}) due to injection site lesions and drug related adrenal hyperplasia at 2.5 mg/kg/d. In a similar study in rat with IV glycerin formulation an increase in BUN was noted in female rats at 2.5 mg/kg/d. There were no notable injection site histological findings due to very poor drug exposure. At 1.0 and 2.5 mg/kg/d IV glycerin doses, the exposure was approximately 1/4 of the IV PG/EtOH formulation.

In an attempt to infuse conivaptan PG/EtOH continuously to F344 rats (n=10/sex/dose) catheters were implanted for infusion of 10, 30 and 100 mg/kg/d doses, however within 2 weeks most of the high dose rat catheters were occluded and drug delivery was interrupted and animals terminated. Animals with blocked catheters were sacrificed (n=26). The inconsistent drug delivery was evident in the AUC data. Female rats in the mid and high dose groups had significantly lower exposure than corresponding males. The occlusions appeared to be dose-related suggesting drug was inducing inflammation and fibrosis at the catheter exit site and blocking the patency of the catheter and adjacent vessel. Consistent with previous studies, significant increase in adrenal weight was observed however only significant in females at 30 mg/kg/d. In some animals fibrosis and inflammation had spread to thymus, heart and pericardial sac or trachea. Pulmonary emboli were noted in 1 animal in control, mid and high dose group. Granulomatous inflammation of the lung was also observed in 2 females at 30 mg/kg/d and 3male and 5 females at 100 mg/kg/d suggesting that in addition to route, drug is contributing to findings noted in other organs (heart, lung and thymus). The 10 mg/kg/d dose was considered NOAEL (1.4 to 2.6 x clinical dose based on AUC_{0-24}).

Dogs (n=3/sex/dose) were also injected with bolus doses of conivaptan in PG/EtOH (2, 5 and 10 mg/kg/d, approximately 3.3, 12.8 and 43 x clinical dose based on AUC_{0-24}) for 4 weeks. One female dog in the 10 mg/kg/d was found dead on Day 3. Cause of death was not determined. Dogs at 10 mg/kg/d were euthanized on Day 16 due to injection site thickening and inability to administer IV. Animals that were treated with conivaptan frequency appeared thin, dehydrated and hypoactive especially at 5 mg/kg/d. Cardiac parameters measured before and after treatment found not notable findings. No significant changes in organ weights were noted. During histopathology examination injection site thickening of the cephalic and saphenous veins and edema were noted in the dogs treated with 10 mg/kg/d. Focal necrosis in bone marrow in 1 HD dog that died early correlated with slight lymphoid depletion in the thymus and decrease in the RBC, Hb and hematocrit. There were no specific drug-related liver or renal findings. The 2 mg/kg/day was considered NOAEL (2.8-3.8 x clinical dose based on AUC_{0-24}).

In the 4-WK continuous infusion study in dogs (n=3/sex/dose), conivaptan in PG/EtOH was infused via an implanted catheter at dosage levels of 2, 10 and 20 mg/kg/d (2.9, 29 and 196 x clinical dose based on AUC_{0-24}). There were no deaths, however, 2 dogs at 20 mg/kg/d appeared thin, dehydrated and jaundice on Day 22. As expected, significant increase in uresis and water intake was noted in a dose-dependent manner. ECG measurement found no notable drug-related changes at exposure levels nearly 200 x clinical dose at steady state AUC. Significant decrease in RBC and PCV and hemoglobin was observed in males at 20 mg/kg/d. Clinical chemistry parameters in 20 mg/kg/d treated males were significantly altered (lower glucose, albumin and high triglyceride and ALP). The liver hypertrophy was noted in 2/3 male and 1/3 female treated with 20 mg/kg/d. Associated with liver hypertrophy were microscopic findings such as sinusoidal dilatation, kupffer cell hypertrophy, centrilobular degeneration in the 20 mg/kg/d treated dogs. Mottled lung in all 3 males at 20 mg/kg/d and dark area in lungs of 10 (MD) and 20 mg/kg/d (HD) females were noted at gross necropsy. Minimal to slight renal tubular degeneration (1/3) and fibrosis (2/3) in HD males and minimal renal tubular regeneration (1 MD and HD males and 1 HD female) were noted. Inflammation and fibrosis was noted at catheter entry and exit point in most animals. Three of the HD males and 1 HD female had minimal to slight degeneration/necrosis of sternal bone marrow. Overall the incidence of histopath findings were dose related (HD males > HD females> MD males). Since 20 mg/kg/d (HD) were nearly 200 x greater than clinical dose, the drug-related toxicological clinical chemistry changes are not unexpected. The 2 mg/kg/d was considered NOAEL in males (3.4 fold) and 10 mg/kg/d in females (36 x clinical dose based on AUC_{0-24}) due to wide spread histopath findings (renal, lung and liver) in dogs infused with 20 mg/kg/d.

13-Week Oral Gavage Rat Studies

In the first 13-WK oral gavage study, F344 rats were treated with 3, 10, 30 and 100 mg/kg/d of conivaptan (0.15, 1.4, 4.9 and 16.4 x clinical dose). Significant decrease in BW at 100 mg/kg/d treated males. Water consumption increased in dose-dependent manner. Urine excretion at 3, 10, 30 and 100 mg/kg/d increased by 3.5, 8, 14 and 23 fold relative to control, respectively. Adrenal wt increased by approximately 22, 34 and 55% at 10, 30 and 100 mg/kg/d male and female rats. Significant increase in liver wet was observed at 30 and 100 mg/kg/d. The 3 mg/kg/day was considered NOAEL in female rats (0.15 x clinical dose based on AUC_{0-24}). To determine the NOAEL in male rats, a 13-WK study at lower doses (0.3 and 1 mg/kg/d) was performed in male rats only. The 1 mg/kg/d dose increased water intake with no other notable findings. The NOAEL dose was considered to be 1 mg/kg/d (<0.02 x clinical dose).

26-Week Oral Gavage Rat studies
All doses of YM087 (1, 3, 10 and100 mg/kg/d, 0.03, 0.23, 1.7 and 9.3 x clinical dose based on AUC_{0-24} of 3580 ng.h/ml) increased urine volume and decreased urine electrolytes. The highest dose (100 mg/kg/d) increased the 24-h urine volume by 22-27 fold relative to control. Estrus disruption was noted by vaginal smears at doses ≥ 10 mg/kg/day. Several females remained in diestrus during week 24 and never went into estrus during this 3 week period. Reproductive studies have shown that conivaptan administration can increase plasma progesterone by nearly 20 fold at 100 mg/kg/d. Relative organ weight changes correspond to the observed histopathology: dilated esophagus ≥ 3 mg/kg/day; granulomatous / pyogranulomatous inflammation of lungs (both lobes more pronounced Left) ≥ 3 mg/kg/day; thymic lymphocytic depletion in males at 100 mg/kg/day, adrenocortical hypertrophy/-plasia ≥10 mg/kg/day, decreased splenic extramedullar hematopoiesis ≥10 mg/kg/day, atrophy of prostate at 100 mg/kg/day and tubular epithelial regeneration of kidney at 100 mg/kg/day. The multiple histopath findings were present in all groups regardless of treatment supports a compromised health status of the rats. However, moribund/early deaths consisted of drug treated groups. This would explain why the findings were present in all groups without morbidity in the controls. The sponsor suggests that the pulmonary effects are attributed to aspiration of powdered food used in this study accompanied by reduced water consumption and dehydration (see study repeat study R087-TX-046) however this is inconsistent with the dose responsive morbidity (The sponsor NOAEL=1 mg/kg/day). In a recent adverse report in clinic, a patient with CHF taking conivaptan had developed pulmonary insufficiency and aspirated food to the lung. It is hypothesized that conivaptan induced dehydration may contribute to food aspiration into the lungs. To re-evaluate some of the confounding pulmonary histopathology findings, the sponsor repeated the study in male rats with two doses of YM087 (10 and 100 mg/kg/d) plus a control group. The histopath analysis was carried out only in control and HD animals. Platelet counts, albumin, and plasma protein were slightly increased to a comparable extent to the previous 26 week study. The 13 week study shows plasma protein and albumin increased (107%, 111% respectively). The change in protein is attributed to hemoconcentration resulting from diuresis by the sponsor.

Adrenocortical hypertrophy and hyperplasia with increased adrenal weight occurred at 100 mg/kg/day. The sponsor attributes this to elevated AVP and ACTH as reported in literature for Sprague-Dawley female rats. Renal basophilic tubules and protein casts in the collecting tubules were observed at 100 mg/kg/day and were considered possible early lesions of chronic nephropathy in aging rats according to the sponsor. However, since these findings were enhanced in drug treated groups compared to control the sponsor acknowledges that drug treatment might accelerate nephropathy in aging rats.

52-Week Oral Gavage Dog study
Male and female beagles (4 /sex/dose) were treated with 0, 1, 3, 10 and 20 mg/kg/d YM087 (0.86, 2.9, 26, and 26 fold clinical dose based on AUC of 3580 ng.h/ml). The most important findings were limited to males given 20 mg/kg/day. Clinical observations of pale mucous membranes and hypoactivity were seen in two of four males given 20 mg/kg/day. Periodic slightly lower body weights, body weight gains, and food consumption were observed in these same two males given 20 mg/kg/day. Pale mucous membrane and hypoactivity finding appear primarily due to lower red cell mass (anemia). Histopathologic findings in the bone marrow

(necrosis and hematopoietic cell hyperplasia) were evident in one of three males with hematological findings (decreased red blood cell count, hemoglobin concentration, and hematocrit). Epididymal vasculitis was observed in 2/4 dogs with systemic exposure greater than 85,910 ng.hr/ml (20 mg/kg/d group).
Other clinical pathology findings observed in association with the findings described above (pale mucous membranes, anemia, body weight loss, low food consumption) were increased plasma globulin and decreased plasma albumin and elevated GOT in two of the animals. The two males (2/4) that had anemia also had histopathologic evidence of epididymal vasculitis. The cause of this vasculitis is unknown, but because these two animals had other adverse test material-related findings and because a similar vasculitis was not observed in controls or at lower test material treatment levels, a test material relationship to this finding cannot be ruled out. At Week 52, the Cmax value of one male with bone arrow necrosis was 9,820 ng/ml. The Cmax values of the two males with vasculitis were 5,560 and 8,510 ng/ml suggesting that high plasma concentration of the drug was responsible for the toxicological effects in the two males. Estrous cycle in females didn't appear to be affected by the drug. This probably reflects infrequent species related cycling rather than lack of drug effect, since the drug was clearly disrupting estrous cycle in an animal model with frequent estrous cycling (rodents).

With NOAEL of 10 mg/kg/d, the dog exposure was approximately 26 fold greater than clinical dose of 20 mg IV bolus followed by 40 mg IV infusion for 4 days (AUC 3580 ng.h/ml). Since the AUC data was collected from healthy volunteers, it is estimated that the AUC in SIADH subjects may increase due to other existing complications (liver cirrhosis and impaired renal function). The TK data in rats and dogs suggests nonlinear kinetics of YM087 in plasma with repeated treatments.

2.6.6.2 Single-dose toxicity

Oral studies:
For oral studies, conivaptan was suspended in 0.5% methylcellulose and administered by oral gavage to rats. In fasted Fischer F344 rats, oral doses up to 2000 mg/kg did not produce death. Clinical signs included hypoactivity, lacrimation, and soiled coat around urogenital organs. Significant decrease in body weight at high dose was due to pharmacological effect of YM087 on body water loss.

In fasted dogs, oral doses up to 1000 mg/kg had effects similar to that observed in rats: decrease in food consumption, transient decrease in BW, significant increase in water consumption related to severe urinary excretion. There were no deaths, however clinical symptoms such as emesis were noted with in 24-hr. There was no change in ECG. The 1000 mg/kg PO was considered the MTD.

Intravenous studies:
In rats, YM087 was prepared in propylene glycol/ethanol (PG/EtOH) and administered to F344 rats at doses of 10, 30 and 100 mg/kg (20 ml/kg) over 60 seconds. In one study, two females given 100 mg/kg had tremor, and died shortly after the dosing. At 30 mg/kg, ataxia was observed within 1 hour after dosing. Body weights at 10 and 30 mg/kg were decreased. Aquaretic effect of the drug was compensated by dose-dependent increased in water intake. In another study controls as well as treated rats exhibited convulsions, recumbency, irregular respiration, and red oral discharge suggesting that vehicle may have played a roll. Since findings were more severe (ataxia, hypoactivity and weight loss) in YM087 treated animals, the effects were attributed to vehicle and exacerbated by drug. In treated animals, water consumption increased, and correspondingly urine volume increased and specific gravity decreased. There were appeared to be no treatment-related histopath findings in any of the organs (liver, muscle and kidney) after single IV doses of conivaptan.

The sponsor also performed IV studies in rats using glycerin as the placebo at doses of 2.5, 5 and 10 mg/kg at 0.6 ml/min. There were no deaths at doses up to 10 mg/kg. Food consumption decreased and water consumption increase dose-dependently. Urine output increased with in 30 min IV administration.

In dogs, YM087 was prepared in PG/EtOH intravenous formulation and administered at 2, 5, 10 and 30 mg/kg (4 ml/kg over 10 min). There were no deaths; however one animal was sacrificed due to clinical signs (red-colored vomit, severe ataxia, hunched posture, and red urine). Clinical signs were noted at 30 mg/kg (ataxia, yellow vomit, red urine). BW decreased which was due to severe body water loss. Water consumption and urine volume increased in a dose-proportional manner. Increased hemolysis, increase in RBC, BUN and creatinine in blood and hematuria, urobilinogen in urine was noted at 30 mg/kg in males primarily. Histopathological examination found red fluid accumulation in the cranial cavity, renal tubular casts and lymphocytic depletion of thymus in males at 30 mg/kg. Microcalculi in the renal medulla and GI congestion were observed in male and females.
In additional dog studies, the intravenous conivaptan hydrochloride PG/EtOH formulation was also administered to dogs at 2 and 5 mg/kg (10 ml/kg). There were no deaths. There was no

effect on heart rate, ECG or body weight. Increase in water intake and urine volume and decrease in urine osmolality was observed in a dose-dependent manner. Occult blood was noted in urine at 5 mg/kg.

Single-dose intravenous toxicity study in dogs - toxicokinetics [R087-TX-004]

Dose (mg/kg)	2		5	
Number of Animals	M: 1	F: 1	M: 1	F: 1
C_{max} (ng/mL)	[redacted]			
AUC_{0-24} (ng·hr/mL)				

From Study No. R087-TX-109, Determination of YM087 in Dog Plasma Using High-Performance Liquid Chromatography High Sensitivity from "Single Intravenous Dose Study with YM087 in Beagle Dogs" (Yamanouchi Proj. No. 395204).

2.6.6.3 Repeat-dose toxicity

Title: 1-Week Repeat-Dose Intravenous Toxicity Study in Rats with PG/EtOH Formulation (Dose-Range Finding Study)

Study no: R087-TX-065 (20030728)
Conducting laboratory and location: [redacted]
Study completion Date: Jan 13, 1999
Methods:

Conivaptan was injected into tail vein of 12 to 13 WK old F344 rats (5/sex/group) for 7 days at doses of 3, 10 and 30 mg/kg/d (6 ml/kg at 1 ml/min). For IV administration, YM087 was prepared in Propylene glycol and ethanol. Since this was a dose-ranging study, only specific key points were noted.

Results (highlights of the study findings):

Clinical signs: Clinical signs such as convulsion, ataxia, tremor, hypoactivity and discolored urine were observed immediately to 30 minutes after dosing in control and 30 mg/kg groups. Until 3 hours after the dosing, two males at 30 mg/kg still showed hypoactivity. At 10 mg/kg, hypoactivity was also observed in males immediately after dosing and discolored urine was noted in 1 male.

Mortality: Due to high incidence of injection site lesions, rats treated with 30 mg/kg/d were sacrificed on Day 6.

Body weight: BW of HD animals was not determined. The BW of MD animals were decreased by 5% in males and 3.2% in females.

Water intake: Water intake increased in a dose-dependent manner. Food intake of MD rats was reduced by 12 to 20% relative to controls.

Urinalysis: Significant dose-related increase in urine output due to pharmacological effect of YM087.

Organ Weight: There were no organ weight changes.

Histopathology:

- Discoloration of the tail, vascular necrosis, perivascular necrosis, thrombosis, hemorrhage, edema and inflammation at the injection site were obvious in all groups including control animals. However, the extent and severity of the local effect increased with YM087 dose.

- Slight to moderately severe renal tubular degeneration was observed in HD males. Similar but less severe findings were also noted in HD females (3/5). Renal tubular findings in MD rats were similar to controls that received PG/EtOH (see table)

Histopath findings after 1 WK of intravenous YM087 administration in rats:

7-DAY INTRAVENOUS TOXICITY STUDY WITH YM087 (CI-1025) IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=1,2,3,4;WEEKS=ALL
DEATH=ALL;FIND=ALL;SUBSET=T

ORGAN/TISSUE EXAMINED		SEX:	MALE				FEMALE			
		GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
		NUMBER:	5	5	5	5	5	5	5	5
** TOP OF LIST **										
KIDNEY (KD)	NUMBER EXAMINED:		5	0	5	5	5	0	5	5
--LAMINATED BODIES	->		0	0	0	1	0	0	0	0
	1>		5	0	5	4	5	0	5	5
	TL>		5	0	5	5	5	0	5	5
	MN>		1.0	0.0	1.0	0.8	1.0	0.0	1.0	1.0
--DEGENERATION, TUBULAR	->		0	0	1	0	5	0	5	2
	1>		5	0	4	0	0	0	0	1
	2>		0	0	0	2	0	0	0	1
	3>		0	0	0	1	0	0	0	1
	4>		0	0	0	2	0	0	0	0
	TL>		5	0	5	5	5	0	5	5
	MN>		1.0	0.0	0.8	3.0	0.0	0.0	0.0	1.2
--HYALINE DROPLETS, TUBULAR EPITHELIUM	->		4	0	5	5	5	0	5	5
	1>		1	0	0	0	0	0	0	0
	TL>		5	0	5	5	5	0	5	5
	MN>		0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
INJECTION SITE (IS)	NUMBER EXAMINED:		5	1	5	5	5	0	5	5
	NOT REMARKABLE:		0	1	0	0	0	0	0	0
--VASCULITIS			2	0	4	0	3	0	2	3
--NECROSIS, VASCULAR			4	0	5	5	5	0	4	5
--INFLAMMATION, PERIVASCULAR			4	0	5	5	5	0	5	5
--NECROSIS, PERIVASCULAR			4	0	5	5	2	0	4	5
--HEMORRHAGE			4	0	5	5	4	0	5	5
--EDEMA			2	0	5	5	3	0	5	5
--NECROSIS, EPIDERMAL			1	0	2	5	0	0	1	5
--EPIDERMITIS			2	0	3	1	0	0	1	5
--THROMBOSIS			1	0	5	4	2	0	3	5

1-week repeat-dose intravenous toxicity study in rats – toxicokinetics [R087-TX-065]

Daily Dose (mg/kg)	3		10		30	
Number of Animals	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5
Toxicokinetics: Concentration 5 minutes postdose						
Day 1 (ng/mL)	1488	1536	4718	4634	14220	14080
Day 7 (ng/mL)	1266	1089.8	3800	4068	NA	NA

NA = Not applicable.

Key Findings:

- All animals at 30 mg/kg were sacrificed on Day 6 because of severe local damage at the injection site at the tail. There were no deaths at 3, or 10 mg/kg.
- Water consumption was increased at all dose levels which correlated with increase in urine volume, decrease in urine specific gravity at all doses.
- There were no clear treatment-related changes in hematology or blood chemistry.
- Injection site lesions were dose-dependent but also noted in controls

- Slight to moderately severe renal tubular degeneration in HD males and to a lesser degree in HD females (3/5). Renal tubular findings in MD rats were similar to controls that received PG/EtOH
- The NOAEL of YM087 in 7-day IV study was 3 mg/kg/d in rats.
- Plasma values represent free base conivaptan. The plasma concentrations increased in dose proportional manner.

Title: 1-Week continuous intravenous Infusion Toxicity Study in Rats with PG/EtOH Dose-Ranging Study)

Study no: R087-TX-068 (20030728)
Conducting laboratory and location: [redacted]
Study completion Date: Jan 13, 1999

Methods: Toxicity of the conivaptan PG/EtOH formulation after continuous intravenous infusion was evaluated in F344 rats. Conivaptan PG/EtOH formulation was continuously administered by intravenous infusion via a catheter implanted into jugular vein to 12- to 13-week-old F344 rats (5 animals/sex/group) for 7 days at doses of 10, 30, and 100 mg/kg at a dose rate of 2 ml/kg/hr. The PG/EtOH-based placebo vehicle was administered to 5 rats/sex in the control group. Additional 5 animals/sex/group were used for TK.

Results:

1-week continuous intravenous infusion toxicity study in rats – blood chemistry [R087-TX-068]

Daily Dose (mg/kg)	0		10		30		100	
Number of Animals	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5
AST (IU/L)	125	146	131	165	140*	147	165*	136
ALT (IU/L)	52	52	62	72	65*	62	103*	58

Dunnett's test: * - P<0.05

1-week continuous intravenous infusion toxicity study in rats – organ weight [R087-TX-068]

Daily Dose (mg/kg)		0		10		30		100	
Number of Animals		M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5
Adrenal:	Absolute (g)	0.0563	0.0604	0.0668	0.0632	0.0748*	0.0692	0.0892*	0.0801*
	Relative (%)	0.0246	0.0408	0.0317*	0.0447	0.0368*	0.0497*	0.0441*	0.0575*
Liver:	Absolute (g)	6.7530	4.1713	6.0578	4.2885	6.1994	4.6310	11.0042*	7.2534*
	Relative (%)	2.9358	2.8107	2.8787	3.0375	3.0374	3.3290*	5.4469*	5.1826*

Dunnett's test: * - P<0.05

1-week continuous intravenous infusion toxicity study in rats – histopathology [R087-TX-068]

Daily Dose (mg/kg)	0		10		30		100	
Number of Animals	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5
Liver:								
Panlobular hepatocellular hypertrophy	0	0	0	0	0	0	5	5
Hepatocyte necrosis	0	0	0	1	0	0	4	4
Catheter exit:								
Inflammation	4	5	0	0	1	1	3	5
Epithelial hyperplasia	2	3	0	0	0	1	0	3
Catheter entrance:								
Hemorrhage (exit and tip)	1	0	0	0	1	0	2	2
Catheter Tip:								
Endophlebitis	4	4	0	0	1	0	5	4
Thrombosis	4	3	0	0	1	0	4	4

Key findings:

- There were no deaths or changes of clinical signs.
- Body weights in males at 30 and 100 mg/kg were lower than that in controls. Both males and females at 100 mg/kg showed reduced food consumption.
- Water consumption was increased in all dose groups.
- Hematological parameters were not affected.
- Total protein, albumin and globulin increased in both sexes at 100 mg/kg, and triglyceride decreased in males at 10 mg/kg or more and in females at 30 mg/kg or more. Chloride increased in both sexes at 30, and 100 mg/kg. AST and ALT levels increased in males at 30, and 100 mg/kg.
- Urinalysis showed increased urine volume and decreased specific gravity in all dose groups.
- Mean absolute liver weight increased in both sexes at 100 mg/kg and relative liver weight also increased in females at 30 mg/kg.
- Slight to sever pan lobular hepatocellular hypertrophy and hepatocyte necrosis
- Thromboemboli in the lung, endocardial hyperplasia in the heart, and inflammation and thrombosis at the injection site were noted. The severity of local damage at the injection site was dose-dependently increased.
- Steady state concentrations (Css) increased with increasing dose and tended to be higher in males than in females.
- Plasma conivaptan concentrations were lower on Day 7 than on Day 1 in both sexes, suggesting enhance metabolism or increased clearance with repeated drug administration.
- Based on this study, the sponsor decided to use 100 mg/kg/d as the maximum dose in 4-WK rat study.

1-week continuous intravenous infusion toxicity study in rats – toxicokinetics [R087-TX-068]

Daily Dose (mg/kg)		10		30		100	
Number of Animals		M: 5	F: 5	M: 5	F: 5	M: 5	F: 5
C_{ss} (ng/mL):	Day 1	493	261	1560	1214	6846	6728
	Day 7	421	204	1003	643	2940	2501
AUC_{0-24} (ng·hr/mL)*:	Day 1	11832	6264	37440	29136	164304	161472
	Day 7	10104	4896	24072	15432	70560	60024

* $AUC_{0-24} = C_{ss} \times 24$.

Title: 3-Day Repeat Dose Intravenous Toxicity Study in Rats with Glycerin Formulation (Dose-Range-Findings Study for Glycerin formulation)

Note: This study used the old intravenous formulation with glycerin, thus brief summary is presented.

Study no: R087-TX-114
Conducting laboratory and location: [redacted]
Methods: Toxicity of the conivaptan glycerin formulation was evaluated in F344 rats. Conivaptan in glycerin was administered intravenously via the caudal vein to 8-week-old F344 rats (3 animals/sex/group) for 3 days at doses of 0.625, 1.25, and 2.5 mg/kg at a dose volume of 5 ml/kg. Undiluted glycerin vehicle (0.5 mg/ml) was dosed to animals at 2.5 mg/kg. Animals at 0.625 and 1.25 mg/kg received diluted formulation at concentrations of 0.125 and 0.25 mg/ml, respectively. The dose rate was approximately 0.7 to 1.4 ml/min.

Key Findings:

- There were no deaths.
- Hypoactivity was noted in the 2.5 mg/kg/d dose group
- Water intake increased in all groups
- The sponsor selected 2.5 mg/kg/d YM087 with glycerin formulation as the top rat IV dose

Title: 1-Week Repeat-Dose Intravenous Toxicity Study in Dogs with PG/EtOH Formulation (Dose-Ranging Study)

Study no: R087-TX-071

Conducting laboratory and location: [redacted]
Methods: Toxicity of the conivaptan hydrochloride PG/EtOH formulation was evaluated in dogs for 8 days. Conivaptan was administered intravenously to 9 to 12 month old beagle dogs (3/sex/dose) at 2, 5 and 10 mg/kg/d. The dose volume was 4 ml/kg and a dose rate was 10 ml/min in this study.

PK Parameters in dogs after IV administration of YM087 in PG/EtOH

1-week intravenous toxicity study in dogs – toxicokinetics [R087-TX-071]

Daily Dose (mg/kg)		2		5		10	
Number of Animals		M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
C_{max} (ng/mL):	Day 1	1087	1600	2963	3487	7690	7113
	Day 7	1217	1680	3993	4083	13450	10493
AUC_{0-24} (ng·hr/mL):	Day 1	11934	15465	34697	42897	140644	106549
	Day 7	11510	14410	45023	45901	193251	157796

Key Findings:

- One male at the highest dose of 10 mg/kg was found dead the evening of Day 2. This animal had convulsion, labored breathing, injected sclera and erythema of the whole body earlier. Results of clinical pathology indicated hemoconcentration related to

dehydration and stress leukogram (increased neutrophils and decreased lymphocytes). No other deaths occurred.

- Clinical signs such as ataxia, hypoactivity, vomitus, discharge and salivation were observed in some animals including controls.
- There were no clear changes in body weight. Food consumption decreased in males at 10 mg/kg and in females at $\geqslant$5 mg/kg. Water consumption increased in all dose groups.
- There were no drug related effects on ophthalmology, blood pressure, ECG, hematology or blood chemistry.
- Urinalysis showed increased urine volume, and decreased osmolality and specific gravity at all doses.
- Gross pathology or histopathology did not show any treatment-related effects. The severity and incidence of the changes at the injection site was comparable between the control and dose groups.
- No significant difference in male and female dog TK parameters

Title: 1-Week continuous intravenous Infusion Toxicity Study in Dogs with PG/EtOH formulation (Dose-Range-Finding Study)

Study no: R087-TX-073

Conducting laboratory and location: [redacted]

Methods: Conivaptan PG/EtOH formulation was continuously administered by intravenous infusion via a catheter implanted into jugular vein to 9 to 12-month old beagle dogs (3/sex/dose) at doses of 2, 10 and 30 mg/kg/d at the rate of 2ml/kg/h.

Key Results:

- No deaths
- Food consumption decreased at 30 mg/kg/d dose level
- Water consumption increased at all doses
- No ECG, blood pressure or ophthalmic findings at any dose level
- ALT, AST, ALP, GGT and total bilirubin increased at 30 mg/kg/d
- Urine volume increased and osmolality decreased at all dose levels

1-week continuous intravenous infusion toxicity study in dogs – blood chemistry [R087-TX-073]

Daily Dose (mg/kg)	0		2		10		30	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Blood Chemistry								
ALP (U/L):								
Pretreatment (Day -13)	63	54	59	67	50	42	50	53
Day 7	61	51	57	73	49	64	137	263
Total cholesterol (mg/dL):								
Pretreatment (Day -13)	142	167	136	182	132	154	130	161
Day 7	150	172	122	171	152	178	209	201
AST (U/dL):								
Pretreatment (Day -13)	29	30	31	27	34	28	32	28
Day 7	30	26	25	31	24	25	76	112
ALT (U/L):								
Pretreatment (Day -13)	27	29	28	25	34	26	32	24
Day 7	26	28	37	24	37	28	362*	276
GGT (U/L):								
Pretreatment (Day -13)	3	4	2	4	3	3	2	3
Day 7	3	4	4	4	4	2	13 *	19

ANOVA: * - P<0.05.

- Relative liver weight increased in HD dogs.
- Bile duct hyperplasia with inflammatory changes in the portal area in HD dogs
- Infusion site vessel wall necrosis and proliferative thrombosis were observed at 10 and 30 mg/kg/d.
- Increase in plasma conivaptan levels was more than dose proportional
- No difference in PK of male and female dogs

1-week continuous intravenous infusion toxicity study in dogs – toxicokinetics [R087-TX-073]

Daily Dose (mg/kg) Number of Animals		2 M: 3	F: 3	10 M: 3	F: 3	30 M: 3	F: 3
C_{ss} (ng/mL):	Day 1	160	230	882	983	3810	3697
	Day 7	606	541	5887	4960	28100	26533
	Day 9	553	327	4940	3707	29867	28533
AUC_{0-24} (ng·hr/mL)*:	Day 1	3840	5520	21168	23592	91440	88728
	Day 7	14544	12984	141288	119040	674400	636792
	Day 9	13272	7848	118560	88968	716808	684792

* $AUC_{0-24} = C_{ss} \times 24$.

1-week continuous intravenous infusion toxicity study in dogs – organ weight and histopathology [R087-TX-073]

Daily Dose (mg/kg) Number of Animals	0 M: 3	F: 3	2 M: 3	F: 3	10 M: 3	F: 3	30 M: 3	F: 3
Organ Weight								
Liver/gallbladder: Absolute (g)	228	207	221	198	257	200	242	241
Relative(%)	3.0	2.7	2.8	2.7	3.2	3.2*	3.5	3.3*
Histopathology of the Liver[a]								
Hypertrophy/ hyperplasia, bile ductule epithelium	0	0	0	0	0	0	3	2
Necrosis with acute inflammation, peribiliary	0	0	0	0	0	1	1	0
Cytoplasmic clearing/vacuolization, periportal	0	0	0	0	0	0	1	3
Cytoplasmic increase, hepatocellular	0	0	0	0	0	0	1	0
Leukocytosis	0	0	0	0	0	0	1	0
Inflammation, chronic-active, portal	0	0	0	0	0	1	3	2

ANOVA: * - $P<0.05$. a – Number of animals showed sings.

Title: 4-Week Repeat-Dose Intravenous Toxicity Study in Rats with PG/EtOH formulation

Note: In this study F344 rats were treated with conivaptan PG/EtOH formulation but at significantly higher doses (0, 2.5, 10 and 25 mg/kg/d at volume of 20 ml/kg bolus). Due to severe injection site lesion, the study was terminated on Day 14. Brief summary of the data is provided for reference. Due to early termination histopathology was not performed.

Study # R087-TX-066
Key Study Findings:

- Convulsions or convulsions and tremors were noted in some HD males on Day3
- All animals at 25 mg/kg/day were sacrificed during Week 1 due to tail discoloration and difficulty in dosing. One female given 10 mg/kg/day died during Week 1, and five males and one female given 10 mg/kg/day were sacrificed during Week 2
- Other clinical signs noted in some animals given 10 or 25 mg/kg/day included convulsions characterized by tonic hind limb extension, dehydration or hunched appearance, swollen ventral abdomen, limb tremors, red genital and ocular discharge, few feces, and cold to touch. These clinical signs were considered test material-related.
- At WK 2, mean body weight of males given 10 mg/kg/day was slightly lower (5.7%) than that of the control males.
- There was a marked dose-related increase in water consumption across all groups
- Drug-related macroscopic findings in urinary bladder for several males and females given 25 mg/kg/day and injection site findings for all animals given 25 mg/kg/day and for most animals given 10 mg/kg/day.
- The injection sites were diffusely red, dark, or having red focal areas. Three females given 25 mg/kg/day and one male given 10 mg/kg/day had red focal areas on the thymus.
- Microscopic evaluations were not done so the histopathologic correlates to these test material-related macroscopic findings are not known.
- Animals were terminated on Day 14 because of the dose-related increase in the difficulty to administer drug via tail vein in rats at 10 and 25 mg/kg/day.

Title: 4-Week Repeat-Dose Intravenous Toxicity Study in Rats at Lower doses with PG/EtOH formulation

Study no: R087-TX-067 (: 6359-177)
Conducting laboratory and location: (
Date of study initiation: Initiated on Feb 02, 99, Completed on Aug 09, 1999, Final Report May 30, 03
GLP compliance: yes
QA report: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: CRO120298, unlabeled,
Formulation/vehicle: 5% dextrose used to dilute liquid YM087 in PG/EtOH
Methods (unique aspects):

Group	Number of Animals Male	Female	Dose Level[a] (mg/kg/day)	Dose Concentration[a] (mg/mL)
1 (Control)[b]	10	10	0	0
2 (Low)	10	10	0.5	0.05
3 (Mid)	10	10	1.25	0.125
4 (High)	10	10	2.5	0.25

a The dose volume was 10 mL/kg.
b The control group received the control material at the same placebo concentration and volume as the high-dose group.

Dosing:

Species/strain: Fischer F344 rats,
Number/sex/group or time point (main study): 10
Satellite groups used for toxicokinetics: none
Age: 42-48 days
Weight: 151-169 g females and 248 to 271 g males
Doses in administered units: 0, 0.5, 1.25 and 2.5 mg/kg/day injected iv
Route, form, volume, and infusion rate: IV, suspended in PG/EtOH, 10 ml/kg and at 1 ml/min

Observations and times:

Clinical signs: 2X daily
Body weights: weekly
Food consumption: weekly
Water consumption: First 2 days of each week
Ophthalmoscopy: pre-dose and Day 28
Hematology: Day 29
Clinical chemistry: Day 29
Urinalysis: Urine was collected from nonfasted animals for 8 hr on Day 29. Following the 8 hrs, animals were fasted and urine was collected into containers in ice for 16 hrs. Blood samples were collected after urine samples.

Gross pathology: at necropsy on Day 30
Organs weighed: standard list of organ were weighted at the end of the study
Histopathology: Standard list of tissues in control and HD dose group plus adrenal gland and injection sites at LD and MD groups.
Toxicokinetics: One ml of blood was collected from jugular vein of all animals at 5 and 30 min and 2, 4 and 24 hr post dose on Day 26.

Results:

Clinical signs:
There were no deaths. There were no specific clinical signs except for injection site findings (red or blue tail skin color, scab and sore spots on the tail). Prominent biological effect of the drug highlighted by significant dose-related increase in urine volume was seen at all doses in rats.

Body weight, Food and water intake:

- Mean BWs were similar across all groups at the end of the study.
- BW gains were decreased by 57.1% and 64.3% at WK2 in MD and HD males, respectively
- Significant decrease in food intake in males at 2.5 mg/kg/d (-88%)

4-week repeat-dose intravenous toxicity study in rats – body weight, and food and water consumption [R087-TX-067]

Daily Dose (mg/kg)		0		0.5		1.25		2.5	
Number of Animals		M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Body Weights (g):									
	Week 1	260	163	259	161	260	163	261	162
	Week 2	269	168	267	167	264	166	266	169
	Week 3	283	172	279	173	272	171	275	174
	Week 4	288	171	285	176	281	173	282	177
	Week 5	294	174	290	177	284	176	283	179
Food Consumption (g/week):									
	Week 1	127	93	125	86	115	81	112 *	85
	Week 2	134	98	135	95	126	99	125	103
	Week 3	127	94	129	93	119	91	128	95
	Week 4	136	97	138	100	132	101	135	108 *
Water Consumption (mL/day):									
	Week 1	40	37	111 *	106 *	170 *	136 *	248 *	205 *
	Week 2	41	46	114 *	90 *	150 *	115 *	223 *	157 *
	Week 3	44	56	122 *	107 *	169 *	130 *	253 *	162 *
	Week 4	40	43	128 *	108 *	192 *	149 *	251 *	173 *

Dunnett's test: * - P<0.05

Ophthalmoscopy: No drug-related findings. (Corneal dystrophy was seen in all animals before and on day 28, it was not drug-related. Dystrophy has been reported in F344 strain of rats).

Hematology, Blood Chemistry and Urinalysis data are presented in the table:

- Significant decrease in RBC in females at MD and males at HD
- Packed cell volume appeared to lower with YM087 with no clear dose-response relationship

Blood Chemistry

- Slight but significant increase in BUN at ⩾0.5 mg/kg/d
- Drug related decrease in total protein in plasma
- The significance of changes in triglycerides, globulin and calcium is not clear

Urinalysis data:

- Dose-related increase in 8 hr urine output (~ 14X, 23 x and 30 x at 0.5, 1.25 and 2.5 mkd, respectively), consistent with the pharmacological effect of YM087.
- Dose-related decrease in urine specific gravity

4-week repeat-dose intravenous toxicity study in rats – hematology, blood chemistry and urinalysis [R087-TX-067]

Daily Dose (mg/kg)	0		0.5		1.25		2.5	
Number of Animals	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Hematology:								
RBC (10^6/μL)	8.31	7.07	8.10	6.86	8.09	6.80*	7.90*	7.07
Hemoglobin (g/dL)	14.6	13.6	14.3	13.3	14.5	13.3	14.1*	13.7
PCV (%)	44.1	40.4	42.8*	39.6	43.6	39.3	42.8*	40.6
Blood Chemistry:								
BUN (mg/dL)	16	18	19*	19	20*	20*	21*	20*
Total protein (g/dL)	7.4	7.2	7.0*	6.7*	7.0*	6.7*	6.9*	6.7*
Albumin (g/dL)	4.9	4.8	4.7*	4.5*	4.8	4.6*	4.6*	4.6*
Globulin (g/dL)	2.5	2.4	2.3*	2.2*	2.2*	2.1*	2.2*	2.1*
Triglyceride (mg/dL)	113	34	95	38	65*	34	58*	34
Calcium (mg/dL)	10.9	10.7	10.8	10.6	10.7	10.5	10.7	10.4*
Sodium (mmol/L)	143	143	142*	141*	141*	140*	141*	140*
Urinalysis: Week 5								
8 hr - Volume (mL)	2.4	1.2	35.8*	25.4*	58.9*	39.6*	76.2*	50.9*
16 hr - Volume (mL)	6.0	6.8	1.5*	1.8*	4.1	1.3*	6.8	5.5
24 hr - Volume (mL)	8.4	8.0	37.3*	27.2*	62.9*	41.0*	83.0*	56.3*
Specific gravity	1.035	1.030	1.040	1.036	1.024*	1.024	1.014*	1.017*
pH	7.3	7.2	6.8	6.6*	6.8*	7.2	7.2	7.0

Dunnett's test: * - P<0.05

Organ Weights:

- Significant increase in abs adrenal weight in MD (17%) and HD males (20%). The slight increase in female rats was not statistically different (MD: 14%, HD: 6.3%).

4-week repeat-dose intravenous toxicity study in rats – organ weight [R087-TX-067]

Daily Dose (mg/kg)		0		0.5		1.25		2.5	
Number of Animals		M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Adrenal:	Absolute (g)	0.0569	0.0615	0.0564	0.0584	0.0667*	0.0701	0.0683*	0.0654
	Relative (%)	0.0213	0.0394	0.0214	0.0369	0.0262*	0.0452	0.0268*	0.0411
Thymus:	Absolute (g)	0.2179	0.2092	0.1886	0.1992	0.1804*	0.2070	0.1711*	0.2026
	Relative (%)	0.0812	0.1340	0.0716	0.1255	0.0710	0.1331	0.0667	0.1270

Dunnett's test: * - P<0.05

Gross Pathology: No visible macroscopic findings were reported

Histopathology:

- Injection site lesion was seen in most animals including controls suggesting possible vehicle effect in addition to YM087 (7/10 in males, 5/10 in females) given *2.5* mg/kg/day.
- Adrenal cortex of males (7/10), but not females, given *2.5* mg/kg/day.
- Vascular/perivascular necrosis (7/10 males), proliferation of the vascular intima (6/10 males and 5/10 females and thrombus formation (6/10) in HD rats
- Increased incidence of cortical cell hypertrophy in the inner zones of the adrenal cortex in HD males
- No other notable histopath findings was observed at lowered doses
- Increased incidence and severity of the injection site finding suggest in addition to the route of delivery, vehicle, YM087 was a significant contributory factor.

4-week repeat-dose intravenous toxicity study in rats – histopathology [R087-TX-067]

Daily Dose (mg/kg)	0		0.5		1.25		2.5	
Number of Animals	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Injection site:								
Exudate, epidermal surface	1	1	0	1	1	4	0	1
Hemorrhage	6	4	6	7	6	5	7	6
Inflammation, chronic, perivascular	2	0	1	2	1	2	0	0
Inflammation, chronic-active, perivascular	8	10	6	7	7	6	10	9
Inflammation, chronic, subcutaneous	1	0	0	0	0	0	0	0
Necrosis, vascular / perivascular	4	4	1	5	3	6	7	5
Proliferation, vascular intima	2	2	0	1	3	1	6	5
Thrombus	1	3	1	2	2	2	6	1
Ulceration, epidermal	1	0	1	0	0	0	0	0
Vasculitis	6	6	9	5	7	6	8	8
Adrenal, Cortex:								
Hypertrophy, cortical cell, inner cortex	1	0	1	0	1	0	7	0

Toxicokinetic Parameters:

- There were no gender differences in PK
- Cmax and AUC increased was nearly dose-proportional

4-week repeat-dose intravenous toxicity study in rats – toxicokinetics [R087-TX-067]

Daily Dose (mg/kg)	0.5		1.25		2.5	
Number of Animals	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
C_{max} (ng/mL)	232	181	545	593	1190	1015
$AUC_{0\text{-}24}$ (ng·hr/mL)	373	482	1249	1339	4143	3192

Human Exposure Multiples:

Species	NOAEL, mg/kg/day	AUC, ng.h/ml	Ratio of Animal to Human AUC
Rats,	1.25	1339	0.4
		3580 ng.h/ml/day	

Key Study Findings:

- All animals survived to the scheduled sacrifice with no notable clinical signs
- No change in BW at the end of the study, although a 27 to 37% decrease in BW was noted initially
- Significant dose-related increase in water intake correlated with increase in urine output
- Increase in urine volume was associated with decrease in urine specific gravity for males given 1.25 and males and females given 2.5 mg/kg/day
- Injection site (an increased incidence and severity of vascular/perivascular necrosis and thrombus formation for males, and a slightly increased incidence and severity of proliferation of the vascular intima for both sexes).
- Drug-related increase in incidence of cortical cell hypertrophy (minimal) in the inner zones of the adrenal cortex in males at 2.5 mg/kg/day
- Exposure to YM087 increased as the dose of the test material was increased from 0.5 to 2.5 mg/kg/day
- NOAEL was 1.25 mg/kg/d due to histological findings at injection site primarily in males and to some extent in females. The NOAEL dose was approximately 0.4 x clinical dose based on AUC.

Study Title: 4-Week Repeat-Dose Intravenous Toxicity Study in Rats with Glycerin Formulation

Note: This study used the old intravenous formulation with glycerin. Since the IV formulation has changes from glycerin to PG/EtOH, only a brief summary of the study is presented for reference purposes.

Study No: R086-TX-007 ([redacted] 6478-129)
Conducting laboratory and location: [redacted]
Date of study initiation: Nov 16, 94 (Completed July 1996)
GLP compliance: Yes
QA- Report: Yes (x) No ()
METHODS: Previous studies had identified injection site lesions including control rats. The sponsor had initially used glycerin formulation before switching to intravenous conivaptan PG/EtOH formulation. The present study was performed with glycerin at doses 0.1, 0.3, 1 and 2.5 mg/kg/d for 4 WKs administered via caudal tail vein to F344 rats (10/sex/dose). The dose volume was 5 ml/kg at a rate of 0.6 to 0.1 ml/min. Additional rats (21/sex/dose) were used for PK evaluation. The drug was dissolved in lactic acid (0.1 mg/ml) and glycerin (26 mg/ml) in sterile water.

Dosing: 0, 0.1, 0.3, 1.0 and 2.50 mg/kg/day, IV
species/strain: F344 rats
age: 5 to 6 WK old
weight: 8.8 to 12 kg
satellite groups used for toxicokinetics or recovery: none
Drug, lot#, radiolabel, and % purity: WT0871A, nonlabled, [redacted]
Formulation/vehicle:
OBSERVATIONS AND TIMES:

Clinical signs:	Twice a day
Body weights:	Weekly
Food consumption:	Daily
Water consumption:	Daily from Day –6, to Day 4 and 2 consecutive days in Wk2 &4
Ophthalmoscopy:	Before and during Wk 2 and 4
EKG:	Before and during Wk 2 and 4
Hematology:	Standard hematology pre-dose and during WK 2 and 4
Clinical chemistry:	Standard clinical chemistry, pre-dose and during Wk 2 and 4
Urinalysis:	16-hr urinalysis pre-dose and during WK 2 and 4. 8-hr urine volume was measured pre-dose and during WK2 and 4
Gross pathology:	All animals fasted overnight and necropsied on Day 30 or 31
Organ weights:	Standard list or organs
Histopathology:	All were evaluated. Kidney and liver issue was also collected for electron microscopy. See the addendum for list (page 14)
Toxicokinetics:	TK data was collected on Day 1 and during WK 4 at 0.5, 2, 4 and 24 hrs postdose.
Statistical Analyses:	Standard statistical analysis were done using SAS program. Levene's test was used to test homogeneity of variance. P was less than 5%.

RESULTS:
Clinical signs: There were no treatment-related mortalities. No effect on estrous cycle was noted in the 4 WK intravenous rat study.

Body weights: No change in BW
Food consumption: No notable change in food intake
Water Consumption: YM087 treatment increased water consumption in a dose-dependent manner in both males and females.
Ophthalmology: No ophthalmic findings.
Hematology: RBC, hemoglobin concentration and hematocrit value decreased in males at 2.5 mg/kg.
Clinical chemistry:

- Glucose levels were higher in females ≥ at 0.3 mg/kg or more,
- Increased BUN and lower cholesterol levels in females at 2.5 mg/kg.
- Plasma sodium decreased in males at 0.3 mg/kg and in both sexes at 1.0 m/kg,
- Plasma chloride level was lower in males at 2.5 mg/kg and in females at 1.0 and 2.5 mg/kg.

Urinalysis:

- Dose-dependent increase in 8-hr urine volume.
- Urine samples collected from 8 to 24 hrs, Na, K, Cl excretion was less than controls

Organ Weights:

- Absolute and relative adrenal weight increased in females at 1 mg/kg/d and in both sexes at 2.5 mg/kg/d. Increase in adrenal weight was also noted with PG/EtOH formulation in rats.

Gross pathology:

- There were no notable macroscopic findings except for reddening and thickening at the injection sites which was noted in both control and treated animals.

Histopathology:

- No major drug related histopathological findings. The drug exposure in the 2 mg/kg/d treated dogs was similar to dogs treated 2 or 3 mg/kg/d by oral gavage. The lack of effect was likely due to low drug exposures in dogs.

Toxicokinetics:

- Plasma concentration increased with dose
- Drug exposure was dose-proportional

4-week repeat-dose intravenous toxicity study in rats – toxicokinetics [R087-TX-007]

Daily Dose (mg/kg)		0.1		0.3		1.0		2.5	
Number of Animals		M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
C_{max} (ng/mL):	Day 1	15.7	13.8	29.7	49.4	185	178	466	471
	Week 5	15.9	18.6	60.6	53.6	213	155	554	477
AUC_{0-24} (ng·hr/mL):	Day 1	17.0	22.4	35.9	63.3	199	265	731	941
	Week 5	21.7	24.0	75.7	72.8	339	270	1097	879

Human Exposure Multiples:

Rats	NOAEL, mg/kg	AUC, ng.h/ml	Ratio of animal to human AUC
4-WK Rat, intravenous via tail vein	0.3	75.8	0.02
Human dose, 20 bolus + 40 mg IV for 4 days		3580 ng.h/ml/day	

KEY STUDY FINDINGS:

- NOAEL dose was 0.3 mg/kg/d (0.02 x clinical dose, based on AUC)
- No effect on estrous cycle was noted.

Study Title: 4-Week Continuous Intravenous Infusion Toxicity Study with YM087 in Rats with PG/EtOH formulation

Note: Pk data values were converted to and expressed as conivaptan base molecule to simplify data comparisons across species and formulations.

Study No: R087-TX-069 (20030728)
page # 1-434
Conducting laboratory and location: [redacted]
Date of study initiation: Sept 21, 1998 (completed in March 12, 1999)
GLP compliance: Yes
QA- Report: Yes (x) No ()
METHODS: F344 rats (10/sex/dose) were randomized catheterized and continuously infused with conivaptan PG/EtOH. Two weeks before the study right jugular vein of the rats were catheterized for continuous drug infusion. The drug solution was provided by the sponsor in liquid form in PG/EtOH. The solutions for infusion were diluted in 5% dextrose. Controls received PG/EtOH without drug diluted with 5% dextrose. Animals were infusion right after surgery with saline at a rate of 1 ml/kg/hr until initiation of drug treatment. Saline was used to maintain catheter patency. Drug was infused at a rate of 2 ml/kg/h for 4 WKs via a syringe pump. Animals were housed individually and fed ad lib. Drug solution concentration were within the +10% range.

Group	No. of Animals Male	Female	Dose Level (mg/kg/day)	Dose Concentration (mg/mL)
1 (Control)[a]	10	10	0	0
2 (Low)	10	10	10	0.21
3 (Mid)	10	10	30	0.62
4 (High)	10	10	100	2.1

a The control group received the control material at the same placebo concentration as the high-dose group.

Dosing: 0 (C), 10 (LD), 30 (MD) and 100 (HD) mg/kg/day, continuous intravenous infusion
species/strain: CDF® (F344) [redacted]BR rats
age: 88 to 94 days
weight: 209-272 g males and 145 to 161 g females
satellite groups used for toxicokinetics or recovery: none
Drug, lot#, radiolabel, and % purity: CRO120298, nonlabled, [redacted]
Formulation/vehicle: [redacted]PG and [redacted] EtOH diluted with 5% dextrose
OBSERVATIONS AND TIMES:

Clinical signs: Twice a day
Body weights: Weekly
Food consumption: Weekly
Water consumption: First 2 days of each week
Ophthalmoscopy: Before and during WK 4
EKG: Not done
Hematology: Standard hematology, during Day 31
Clinical chemistry: Standard clinical chemistry, Day 31
Urinalysis: 16-hr urinalysis, Day 30, after over an over night fast
Gross pathology: All scheduled necropsy animals were fasted overnight and necropsied on Day 3

Organ weights: Standard organ list
Histopathology: All were evaluated
Toxicokinetics: TK data was collected on Day 16 from HD animals and Day 25 on the surviving animals from non-catheterize jugular vein.
Statistics: Levene's test for homogeneity, ANOVA test + Dunnett's t-test

RESULTS:
Clinical signs:

- Rats appeared thin, dehydrated, hypoactive or hunched appearance with audible irregular or labored breathing. Since most of the occlusions occurred in treated animals in dose-related manner, drug irritation and dehydrations were likely the contributing cause of catheter occlusions.
- Total of 41 rats had infusion interruption for greater than 1 hr on a given day. The interruptions occurred in 1 control, 17 MD and 17 HD rats. (none of the HD rats received the drug for full 4 WKs; in the MD group, 1 rat received at least 90% of it's intended dose for the 30-day infusion period, 9 received at least 80%, 5 received at least 70%, and 2 received less than 50% of their intended dose. The latter two animals were sacrificed by Day 16)
- Total of 36 rats did not complete the study (1 control, 5 LD, 10 MD and 20 HD). Of these animals, 1C, 5 LD, 6 MD and 14 HD (4 M, 10 F) were sacrificed early because of infusion line occlusion.

4-week continuous intravenous infusion toxicity study mortality,

Daily Dose (mg/kg)	0		10		30		100	
Number of Animals	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Noteworthy Findings:								
Died	0	0	0	0	2	1[a]	1	0
Sacrificed Moribund	0	0	2	0	0	1	5	0
Sacrificed because dosing prevented due to catheter complications	1	0	0	3	4	2	4	10
Clinical Observation:								
Thinness	1	0	0	0	1	1	6	5
Hypoactivity	0	0	0	0	0	0	3	1

Body weights:

- Final BW in LD and MD males and females were similar to control, however, BW gains in LD and MD were lower at some time points (see table)

4-week continuous intravenous infusion toxicity study body weight,

Daily Dose (mg/kg)	0		10		30		100	
Number of Animals	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Body Weight (g):								
Week 1	229 (N=10)	152 (N=10)	230 (N=10)	152 (N=10)	229 (N=10)	155 (N=9)	240 (N=9)	151 (N=10)
Week 3	255 (N=9)	163 (N=10)	236 (N=9)	162 (N=9)	239 (N=10)	168 (N=8)	191* (N=5)	152* (N=7)
Week 5	270 (N=9)	173 (N=10)	253 (N=8)	171 (N=7)	267 (N=4)	168 (N=7)	-	-
Body Weight gain (g)								
Week 1-2	13	11	-9*	6	-3*	2*	-28*	1*
Week 3-4	9	10	11	1*	4	0*	9	4
Week 4-5	7	0	8	7	10	0	NA	NA

Food consumption:

- Food consumption in the HD was significantly lower than control during WK 1
- Food intake at LD and MD were higher than control during WK2 & 4

Daily Dose (mg/kg)	0		10		30		100	
Number of Animals	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Food Consumption (g):								
Week 1	102	86	91*	87	93	75	50*	64*
	(N=9)	(N=10)	(N=9)	(N=9)	(N=10)	(N=8)	(N=7)	(N=9)
Week 3	100	83	130*	102*	127*	91	133	68
	(N=9)	(N=10)	(N=9)	(N=7)	(N=7)	(N=8)	(N=1)	(N=1)
Week 4	101	79	127*	100*	129*	88	-	-
	(N=9)	(N=10)	(N=8)	(N=7)	(N=4)	(N=7)		
Water Consumption (g):								
Week 1	31	29	468*	345*	416*	410*	259*	322*
	(N=10)	(N=10)	(N=9)	(N=7)	(N=7)	(N=8)	(N=5)	(N=6)
Week 2	33	29	432*	315*	446*	335*	412*	250*
	(N=9)	(N=10)	(N=9)	(N=9)	(N=9)	(N=9)	(N=6)	(N=10)
Week 3	32	33	332*	235*	277*	238*	289*	268*
	(N=9)	(N=10)	(N=9)	(N=8)	(N=6)	(N=8)	(N=2)	(N=6)
Week 4	29	29	280*	210*	283*	217*	314*	235*
	(N=9)	(N=10)	(N=9)	(N=7)	(N=7)	(N=8)	(N=1)	(N=1)

N = Number of animals. NA = Not applicable. Dunnett's test: * - P<0.05 a - Accidental death

Water Consumption: Dose-dependent increase in water consumption in both male and female conivaptan treated rats.

Ophthalmology: No ophthalmic findings.

Hematology: No Notable change

Clinical chemistry:

- Slight decrease in creatinine at 10 and 30 mg/kg/d in both sexes
- Slight decrease in total protein, calcium, triglycerides in females at 30 mg/kg/d
- Slight increase in AST in at 30 mg/kg/d and ALT at 10 mg/kg/d in females

Table 2.6.6-32: 4-week continuous intravenous infusion toxicity study in rats – blood chemistry [R087-TX-069]

Daily Dose (mg/kg)	0		10		30		100	
Number of Animals	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Number Examined	9	10	8	7	4	6	0	0
Creatinine (mg/dL)	0.8	0.8	0.7*	0.7*	0.7	0.7*	NA	NA
Total protein (g/dL)	7.2	7.2	6.8	6.9	7.1	6.6*	NA	NA
Albumin (g/dL)	4.4	4.7	4.4	4.5	4.4	4.2	NA	NA
Globulin (g/dL)	2.8	2.5	2.4	2.4	2.7	2.4	NA	NA
Triglyceride (mg/dL)	71	36	38*	28	38	32	NA	NA
AST (IU/L)	97	100	104	112	110	131*	NA	NA
ALT (IU/L)	45	39	53	48*	50	44	NA	NA
Calcium (mg/dL)	10.7	10.8	10.4	10.4*	10.6	10.2*	NA	NA

NA = Not applicable. Dunnett's test: * - P<0.05.

Urinalysis:

- Significant increase in urine output (3 fold) at LD and MD. The increase correlated to water intake, an expected pharmacological effect of conivaptan.

Organ Weights:

- There was statistically significant increase in adrenal weight in females at 30 mg/kg/d.

Table 2.6.6-34: 4-week continuous intravenous infusion toxicity study in rats – organ weight [R087-TX-069]

Daily Dose (mg/kg)		0		10		30		100	
Number of Animals		M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Number Examined		9	10	8	7	4	6	0	0
Adrenal:	Absolute (g)	0.0546	0.0514	0.0543	0.0554	0.0548	0.0585*	NA	NA
	Relative (%)	0.0225	0.0332	0.0242	0.0372	0.0237	0.0403*	NA	NA

NA = Not applicable. Dunnett's test: * - P<0.05.

Gross pathology:

- There were no notable macroscopic findings except for reddening and thickening of the skein at the infusion sites.

Histopathology:

- No notable microscopic findings at 100 mg/kg/d sacrificed early except for catheter related sites and thymus (fibrosis 4/10 F, 1/10 M)
- Catheter related lesions: catheter entrance and end site thickening, inflammation, fibrosis and edema at catheter site in both control and drug treated rats
- In some animals inflammation and fibrosis spread included thymus, heart and pericardial sac/ or trachea
- Pulmonary thrombi in 1 C male, 1 MD female and 1 HD female
- Granulomatous inflammation of the lungs in 2 MD females, 3 M and 5 F in the HD

4-WEEK CONTINUOUS INTRAVENOUS INFUSION TOXICITY STUDY WITH YM087 (CI-1025) IN RATS

		--- NUMBER-OF-ANIMALS -							
TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=ALL;FIND=ALL;SUBSET=ALL	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	10	10	10	10	10	10	10	10
CATHETER EXIT (IS0)	NUMBER EXAMINED:	10	3	6	10	10	3	5	10
	NOT REMARKABLE:	2	0	1	0	1	0	1	0
--EDEMA		6	3	0	4	3	1	2	5
--FIBROSIS		7	3	5	8	8	3	4	10
--FOREIGN BODY, HAIR SHAFT		1	0	1	1	2	0	0	0
--HEMORRHAGE		1	2	0	1	0	2	1	4
--INFLAMMATION, ACUTE		2	1	2	0	1	1	1	1
--INFLAMMATION, CHRONIC		0	0	0	0	0	0	0	2
--INFLAMMATION, CHRONIC-ACTIVE		2	0	2	2	4	1	2	4
--INFLAMMATION, GRANULOMATOUS		0	0	0	3	2	0	0	2
--MINERALIZATION		0	0	0	1	1	0	0	1
CATHETER ENTRANC (IS1)	NUMBER EXAMINED:	10	2	9	10	10	3	6	10
	NOT REMARKABLE:	0	0	0	1	0	0	0	0
--BACTERIAL COLONIES		0	0	0	0	0	0	1	1
--EDEMA		0	1	1	1	1	1	1	2
--FIBROSIS		9	2	9	8	10	2	5	9
--FOREIGN BODY, HAIR SHAFT		1	0	1	1	0	0	0	1
--HEMORRHAGE		1	1	1	2	0	1	0	2
--INFLAMMATION, ACUTE		1	0	0	0	0	0	0	1
--INFLAMMATION, CHRONIC		1	0	0	3	0	0	1	0
--INFLAMMATION, CHRONIC-ACTIVE		1	0	2	2	1	1	0	1
--INFLAMMATION, GRANULOMATOUS		3	0	2	2	4	0	3	1
--MINERALIZATION		4	0	4	3	5	1	4	0
--THROMBUS		0	0	2	1	1	1	1	6
CATHETER TIP (IS2)	NUMBER EXAMINED:	10	4	9	10	10	4	10	10
	NOT REMARKABLE:	1	0	0	0	0	0	0	0
--BACTERIAL COLONIES		2	1	1	0	0	0	1	0
--EDEMA		0	0	1	2	0	0	1	4
--FIBROSIS		4	2	7	8	2	3	8	9
--HEMORRHAGE		1	0	1	4	1	0	0	0
--INFLAMMATION, ACUTE		2	0	1	1	1	0	0	0
--INFLAMMATION, CHRONIC		0	0	1	3	0	0	1	3
--INFLAMMATION, CHRONIC-ACTIVE		0	0	2	3	0	1	2	1
--INFLAMMATION, GRANULOMATOUS		0	0	2	0	0	0	0	1
--MINERALIZATION		0	0	0	0	0	0	3	0
--THROMBUS		6	4	7	7	8	4	9	10

Toxicokinetics:

- Mean steady state plasma concentrations increased with dose up to 30 mg/kg/d
- Plasma concentrations were lower at 100 mg/kg/d possibly to drug deliver via catheter and catheter patency. These animals were sacrificed early due to catheter occlusions.
- NOAEL was 10 mg/kg/d, (1.4 to 2.6 x human exposure based on AUC)

Table 2.6.6-35: 4-week continuous intravenous infusion toxicity study in rats – toxicokinetics [R087-TX-069]

Daily Dose (mg/kg)	10		30		100	
No of Animals	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Day 16:						
Number of Animals					2	6
C_{ss} (ng/mL)	NA	NA	NA	NA	273	372
AUC_{0-24} (ng·hr/mL)*	NA	NA	NA	NA	6552	8928
Day 25:						
Number of Animals	9	7	5	7	1	1
C_{ss} (ng/mL)	387	206	483	1122	56.9	315
AUC_{0-24} (ng·hr/mL)*	9288	4944	11592	26928	1366	7560
Unscheduled:						
Number of Animals	2	3	4	3	7	4
C_{ss} (ng/mL)	593	135	347	304	1585	212
AUC_{0-24} (ng·hr/mL)*	14232	3240	8328	7296	38040	5088

* $AUC_{0-24} = C_{ss} \times 24$. NA = Not applicable.

Human Exposure Multiples:

Toxicology Study	NOAEL, mg/kg	AUC, ng.h/ml	Ratio of animal to human AUC
4-WK Rat, Continuous infusion	10	M: 9288, F:4944	M: 2.6, F: 1.4
Human dose, 20 bolus + 40 mg IV for 4 days		3580 ng.h/ml/day	

Key Findings:

- F344 rats (10/sex/group) were continuously infused with 0, 10, 30 and 100 mg/kg/d conivaptan PG/EtOH for 4 WKs
- Common dose-related clinical signs: thin, dehydration and hypoactivity
- Catheter occlusion appeared to be more common in treated rats. All HD rats were sacrificed on Day 16 primarily due to frequent catheter occlusion
- 41 animals had interrupted infusions greater than 1 hr on a given day (1 C, 17 MD and 17 HD rats
- Total of 36 rats did not complete the study (1 control, 5 LD, 10 MD and 20 HD).
- Total of 26 sacrificed/died early (1C, 5 LD, 6 MD and 4 HD male & 10 HD female were sacrifice while 2 MD males, 1 MD female and 1 HD male died due to drug).
- Several animals did not complete the study to catheter occlusion (1 C male, 3 LD female, 4 MD males, 2 MD female, 10 HD female which explains low mortality in HD females).
- Water intake and urine output increased in dose-dependent manner as expected
- No notable macroscopic or microscopic findings except for catheter infusion site inflammation, fibrosis, edema that may have also spread to other organs
- NOAEL was 10 mg/kg/d due to mortality at 30 mg/kg/d

Study Title: 4-Week Repeat-Dose Intravenous Toxicity Study in Dogs with Glycerin Formulation

Note: Since this study was performed with glycerin formulation, only brief summary and toxicokinetic data was reported.

Study No: R087-TX-008 (20030710)
Conducting laboratory and location: [redacted]
Date of study initiation: Nov 11, 1994
GLP compliance: Yes
QA- Report: Yes (x) No ()
METHODS: Dogs were randomized into 5 groups (3/sex/group) and injected via slow bolus solution of conivaptan. Drug was provided in glycerin solution and diluted to doses with 5% dextrose. Dose volume was 4 ml/kg.

Dosing: 0, 0.1, 0.3, 1 and 2 mg/kg/day, IV
species/strain: Dogs, beagle

Summary:
Intravenous administration of conivaptan up to 2 mg/kg/d did not cause any significant clinical signs, mortality. Except for significant increase in water consumption and urine volume, there were no significant changes in BW, food consumption, ECG, auditory examination, ophthalmology, hematology or blood chemistry. There were no treatment-related changes in gross pathology or histopathology. The NOAEL dose was estimated to be 2 mg/kg/d. Exposure at NOAEL dose was 4 to 6 fold greater than clinical IV dose based on AUC (3580 ng.h/ml).

Toxicokinetic parameters are shown in table below. Plasma conivaptan concentrations increased with increasing dose. There were no significant differences between male and female drug exposures.

Table 2.6.6-71: 4-week repeat-dose intravenous toxicity study in dogs – toxicokinetics [R087-TX-008]

Daily Dose (mg/kg)		0.1		0.3		1		2	
Number of Animals		M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
$C_{0.5hr}$ (ng/mL):	Day 1	72.2	62.6	192	178	771	736	1753	1167
	Week 4	87.6	60.8	230	219	861	796	2113	1463
AUC_{0-24} (ng·hr/mL):	Day 1	409	338	1246	1123	5586	6234	19189	10090
	Week 4	458	305	1643	1375	7042	5178	22126	13267

Study Title: 4-Week Intravenous Toxicology Study with YM087 in Dogs with PG/EtOH formulation

Note: In this study the HD dogs (10 mg/kg/d) were euthanized on Day 16 due to injection site lesions. The remaining dogs were maintained on treatment and necropsies on day 31.

Study No: R087-TX-072 (20030728)
page # 25-489
Conducting laboratory and location: [redacted]
Date of study initiation: Sept 8, 1998
GLP compliance: Yes
QA- Report: Yes (x) No ()
METHODS: Dogs were randomized into 4 groups (3/sex/group). The conivaptan PG/EtOH was prepared in 5% dextrose for daily by intravenous administration (4 ml/kg) at a rate of 10 ml/min for 4 WKs. Injection were via any peripheral via (cephalic, saphenous or jugular vein). However due to injection site lesions at 10 mg/kg/d, treatment for the HD dogs could not be continued for longer than 15 days. Therefore the HD dogs were sacrificed on Day 16. The ECG data for this study (R087-TX-072) and 4-WK continuous infusion (R087-TX-074) study were reported as study # R087-TX-075 is presented in this review.

	Dosage Level[a]	Concentration[a]	Number of Animals		Animal Numbers	
Group	mg/kg	mg/mL	Male	Female	Male	Female
1 (Control)	0	0	3	3	G35587-G35589	G35599-G35601
2 (Low)	2	0.5	3	3	G35590-G35592	G35602-G35604
3 (Mid)	5	1.25	3	3	G35593-G35595	G35605-G35607
4 (High)	10	2.5	3	3	G35596-G35598	G35608-G35610

[a] The dose volume was 4 mL/kg.

Dosing: 0, 2, 5 and 10 mg/kg/day, IV bolus 10 ml/min
species/strain: Dogs, beagle, [redacted]
age: 11 to 12 months
weight: 7.7 to 9.5 kg males and 5.7 to 7.3 kg females
satellite groups used for toxicokinetics or recovery: none
Drug, lot#, radiolabel, and % purity: CR0120298 in 30% PG and 10% EtOH, nonlabled, [redacted]
Formulation/vehicle: PG/EtOH and 5% dextrose
OBSERVATIONS AND TIMES:

Clinical signs:	Twice a day
Body weights:	Weekly
Food consumption:	Daily
Water consumption:	Daily
Ophthalmoscopy:	Before and on Day 15 (HD only) and 24
ECG:	Measured prior to treatment, 0.5 to 1 h prior to dosing on Day 15 for the HD and 3 to 3.5 hrs postdose on Day 24 for control, LD and MD group
Hematology:	Standard hematology after overnight fast, pre-dose and on Day 15 (HD only) and 23
Clinical chemistry:	Standard clinical chemistry after overnight fast, pre-dose and on Day 15 (HD only), 23 and during necropsy collected via jugular vein
Urinalysis:	Urinalysis pre-dose and on Day 15 (HD only) and 23
Gross pathology:	All animals fasted overnight and necropsied on Day 30 or 31
Organ weights:	Standard organ list

Histopathology: All were evaluated
Toxicokinetics: TK data was collected on Day 1, 15 and 25 at 10, 30 min and 2, 4 and 24 hrs post dose.

RESULTS:

Clinical signs:

- One HD female dog was found dead on the morning of Day 3. The cause of death was not determined by histopathology. The remaining HD dogs were sacrificed on Day 16 due to marked thickening at the injection sites (cephalic and saphenous veins) and inability to administer the drug. The thickening was likely due to drug-induced injury and fibrosis. Inflammation, swelling and was noted at injection site. Most had tremor, ataxia and vocalization post dose.
- MD dogs had frequent emesis and excessive salivation very early. One had swollen forelimb on day 15. One dog in the MD group also had difficulty acclimating to watering system, looked thin and dehydrated. Her clinical signs in the first two weeks included tremor, ataxia, and hypoactivity likely caused by dehydration.
- Control dogs had no symptoms; however LD dogs had emesis and excessive salivation. One dog had difficulty acclimating to watering system, looked thin and dehydrated.

Body weights:

- No significant change in terminal BW controls and conivaptan treated dogs
- BW (3%) and BW gain (-57%) of HD males decreased between Day 8-15 (perhaps due to water loss, dehydration). The HD animals were terminated early on Day 15 of the study.

4-week repeat-dose intravenous toxicity study in dogs – mortality [R087-TX-072]

Daily Dose (mg/kg)	0		2		5		10	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Died or Sacrificed Moribund	0	0	0	0	0	0	0	1
Body Weight (kg)								
Pretreatment	8.4	6.8	8.6	6.4	8.4	6.8	8.8	6.6
Week 1	8.2	6.6	8.5	6.0	8.3	6.6	8.6	6.3
Week 2	8.4	6.6	8.4	6.4	8.2	6.4	8.0	6.4
Week 3	8.5	6.6	8.6	6.5	8.4	6.8	NE	NE
Week 4	8.3	6.7	8.3	6.2	8.2	6.8	NE	NE

Food consumption:

- Significant increase in food intake in dogs treated with 2 mg/kg/d on day 14.
- The sporadic changes in food intake were not clearly dose-dependent. There was no significant difference in food intake on Day 30 among groups.

4-week repeat-dose intravenous toxicity study in dogs – food intake [R087-TX-072]

Daily Dose (mg/kg)	0		2		5		10	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Food Consumption (g/day)								
Day 1	219	227	157	58	143	95	108	119
Day 7	204	201	212	156	288	240	218	255
Day 14	218	144	339	262 *	303	169	116	65
Day 15	192	145	258	135	245	332	141	159
Day 21	236	194	267	203	253	343 *	NE	NE
Day 28	307	220	134 *	142	188	262	NE	NE
Day 30	83	81	116	58	101	148	NE	NE

NE = Not examined. ANOVA: * - P<0.05

Water Consumption:

- Water intake nearly double with conivaptan on day 1 relative to control. In HD animals water intake increased by nearly 4 to 6 fold relative to controls on Day 1 through Day 15. No statistical analysis was performed due to several missing data points.

4-week repeat-dose intravenous toxicity study in dogs – [R087-TX-072]

Daily Dose (mg/kg)	0		2		5		10	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Water Consumption (g/day)								
Day 1	898	766	2778	1492	2713	2472	2997	1906
Day 7	669	765	2440	944	1824	1967	1712	2722
Day 14	803	718	1299	914	1515	1035	809	2107
Day 15	772	530	1156	761	1465	1064	NE	4547
Day 21	945	1005	1076	1316	1348	952	NE	NE
Day 28	845	1641	733	600	887	900	NE	NE
Day 29	735	1587	1082	1427	1105	1196	NE	NE

NE = Not examined.

ECG evaluations:

ECG parameters were measured before and on Day 15 (10 mg/kg/d) or Day 24 (0 to 5 mg/kg/d) in dogs. Conivaptan had no notable effect on ECG parameters in 4-WK dog study. Conivaptan did not induce arrhythmias in dogs at up to 10 mg/kg/d IV bolus injection.

Ophthalmology: No ophthalmic findings.

Hematology:

- The overall hematological changes were not notable.
- HD dogs that were terminated early due to difficulty in drug administration had slight decrease in RBC, HD and PC (noted below).

4-week repeat-dose intravenous toxicity study in dogs – [R087-TX-072]

Daily Dose (mg/kg)	0		2		5		10	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Hematology								
WBC (10^3/μL):								
Pretreatment	7.2	8.6	7.5	6.8	6.9	8.5	7.0	8.5
Day 15	NE	NE	NE	NE	NE	NE	16.6	11.9
Day 23	6.7	7.9	8.1	7.9	10.3	9.7	NE	NE

Table 2.6.6-57: 4-week repeat-dose intravenous toxicity study in dogs - hematology in animal number G35598 [R087-TX-072]

	Day -7	Day -3	Day 15
RBC (10^6/μL)	6.71	6.83	5.73
Hb (g/dL)	15.2	15.3	13.0
PCV (%)	45.4	46.8	38.2

Clinical chemistry:

- Variation in ALP and globulin at different time intervals were likely due to plasma volume changes produced by aquaretic effect of conivaptan.

- Most notable changes in HD males on Day 15 are noted in table below.

4-week repeat-dose intravenous toxicity study in dogs – blood chemistry [R087-TX-072]

Daily Dose (mg/kg)	0		2		5		10	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Blood Chemistry								
ALP (U/L):								
Pretreatment	44	49	37	42	38	59	45	47
Day 15	NE	NE	NE	NE	NE	NE	97	81
Day 23	54	42	37	40	48	56	NE	NE
Globulin (g/dL):								
Pretreatment	1.8	2.0	2.1	1.7	2.0	1.7	2.0	2.1
Day 15	NE	NE	NE	NE	NE	NE	2.5	2.4
Day 23	1.7	1.7	1.8	1.6	2.1	1.7	NE	NE

Urinalysis:

- All treated animals had a dose-depend increase in urine volumes and decrease in urine osmolality.

4-week repeat-dose intravenous toxicity study in dogs – urinalysis [R087-TX-072]

Daily Dose (mg/kg)		0		2		5		10	
Number of Animals		M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Urinalysis									
Volume (mL):									
Day-8/-7	0-8 hr	68	128	101	137	10	139	165	55
	8-24 hr	41	46	65	165	31	44	69	75
Day-4/-3	0-8 hr	21	68	79	36	52	108	183	104
	8-24 hr	123	58	43	54	31	69	66	60
Day14/15	0-8 hr	NE	NE	NE	NE	NE	NE	334	409
	8-24 hr	NE	NE	NE	NE	NE	NE	275	757
Day22/23	0-8 hr	43	153	85	250	148	171	NE	NE
	8-24 hr	38	221	114	248	227 *	329	NE	NE
Osmolality (mOsm/kg):									
Day-8/-7	0-8 hr	1359	806	907	412	1574	1406	300	1080
	8-24 hr	1784	1695	1749	1252	1943	1616	1615	1797
Day-4/-3	0-8 hr	2263	1464	1638	1692	1712	905	743	647
	8-24 hr	1533	1690	2196	1946	2104	1637	1429	2004
Day14/15	0-8 hr	NE	NE	NE	NE	NE	NE	500	337
	8-24 hr	NE	NE	NE	NE	NE	NE	606	164
Day22/23	0-8 hr	1611	1001	633	299	501	481	NE	NE
	8-24 hr	2481	1635	754 *	529	435 *	532	NE	NE

NE = Not examined. ANOVA: * - P<0.05

Organ Weights:

- There were no significant change in organ weights, organ to body weight percentages

Gross pathology:

- No notable gross pathology was observed in MD (5 mg/kg/d) dogs, however in HD dogs, the injection site thickenings (cephalic and saphenous veins) and edema were serious enough that drug administration was stopped and animals sacrificed on Day16.
- Small thymus in 1 HD dogs correlated with lymphoid depletion noted in histopath.

Histopathology:

- Injection site findings were dose-related and most notable in the HD animals. IV injection site thrombus formation were very common in MD and HD dogs
- Although there were no gross findings in MD dogs, histological examination found thrombosis in 4/6 MD dogs.
- Focal necrosis in bone marrow of 1 HD males, slight lymphoid depletion in the thymus in 1 HD dog.
- There were no notable drug-related liver or renal findings

Table 2.6.6-59: 4-week repeat-dose intravenous toxicity study in dogs – histopathology [R087-TX-072]

Daily Dose (mg/kg)	0		2		5		10	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Bone marrow: necrosis	0	0	0	0	0	0	1	0
Injection site:								
Inflammation, chronic	2	2	2	3	0	3	0	2
Inflammation, chronic, active	0	1	1	0	3	0	3	2
Intimal thickening	0	0	0	0	1	0	0	1
Thrombus	0	0	0	0	2	2	3	1
Hemorrhage	1	2	3	3	2	2	3	2
Edema	0	0	0	0	1	0	1	2

Toxicokinetics:

- Plasma concentration increased with dose but AUCs were more than dose proportional (D1 vs. Wk4)
- Drug exposure in males was slightly greater than females measured on Day 1 or Wk 4.
- NOAEL dose was 2 mg/kg/d

Table 2.6.6-60: 4-week repeat-dose intravenous toxicity study in dogs – toxicokinetics [R087-TX-072]

Daily Dose (mg/kg)		2		5		10	
Number of Animals		M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
C_{max} (ng/mL):	Day 1	1440	1500	3727	3673	6783	8080
	Week 4 [a]	1467	1387	4320	3940	13633	9790
AUC_{0-24} (ng·hr/mL):	Day 1	13383	10520	48149	42433	102028	102077
	Week 4 [a]	13517	10141	52139	39555	211119	100109

a - Day 15 for animals at 10 mg/kg.

Human Exposure Multiples:

Toxicology Study	NOAEL, mg/kg	AUC, ng.h/ml	Ratio of animal to human AUC
4-WK dog, bolus IV	2	M: 13517, F:10141	M: 3.8, F: 2.8
Human dose, 20 bolus + 40 mg IV for 4 days		3580 ng.h/ml/day	

KEY STUDY FINDINGS:

- Dogs were treated repeated IV doses of conivaptan for 4 weeks
- Administration of 10 mg/kg/d was stopped in dogs on Day 16 due to difficulty in IV administration

- Thickening of injection site veins (inflammation, edema) was noted in a dose-related manner
- Thrombus at the injection site was noted in dogs $\geqslant$ 5 mg/kg/d
- Significant drug related increase in urine out put and water intake in IV treated dogs
- The NOAEL was 2 mg/kg/d for repeated IV conivaptan study in dogs

Study Title: 7-Day Continuous Intravenous Infusion Toxicity Study with YM087 in Dogs with PG/EtOH formulation

Note: Since this was a short study only the key study points are highlighted in the brief review (for reference only). There were no significant changes in ECG in dogs treated for 1 week with continuous IV administration of conivaptan. There were no deaths at doses up to 30 mg/kg/d iv.

Study No: R087-TX-073 (20030910)
page # 25-489
Conducting laboratory and location: [redacted]
Date of study initiation: June 9, 1998
GLP compliance: Yes
QA- Report: Yes (x) No ()

METHODS: Conivaptan PG/EtOH (0, 2, 10 and 30 mg/kg/d) prepared in 5% dextrose was administered by continuous infusion for 8 days via catheter in jugular vein to dogs (3/sex/group). Placebo controls received PG/EtOH. PK was determined on Day 1, 7 and 9. ECG was measured before treatment and on Day 9, day of necropsy for histopathological examination.

Results:

Clinical signs: There were no deaths at any dose level. Dogs treated with 30 mg/kg/d appeared thin, possibly due to dehydration. At 30 mg/kg/d BW and food intake decrease. As expected, the significant increase in water intake was associated with significant increase in urine out.

Clinical Chemistry: ALT, AST, ALP and GGT increased in dogs after 8 days of 30 mg/kg/d IV infusion

Histopathology:

- The increase in liver weight in females at 10 mg/kg/d
- Bile duct hyperplasia and inflammation in the portal area in liver at 30 mg/kg/d
- 1 MD female had localized subcapsular necrosis
- Although local injection site changes were noted in controls as well, the vessel wall necrosis and proliferative thrombosis were common at 10 and 30 mg/kg/d

Table 2.6.6-62: 1-week continuous intravenous infusion toxicity study in dogs – organ weight and histopathology [R087-TX-073]

Daily Dose (mg/kg)	0		2		10		30	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Organ Weight								
Liver/gallbladder: Absolute (g)	228	207	221	198	257	200	242	241
Relative(%)	3.0	2.7	2.8	2.7	3.2	3.2*	3.5	3.3*
Histopathology of the Liver[a]								
Hypertrophy/ hyperplasia, bile ductule epithelium	0	0	0	0	0	0	3	2
Necrosis with acute inflammation, peribiliary	0	0	0	0	0	1	1	0
Cytoplasmic clearing/vacuolization, periportal	0	0	0	0	0	0	1	3
Cytoplasmic increase, hepatocellular	0	0	0	0	0	0	1	0
Leukocytosis	0	0	0	0	0	0	1	0
Inflammation, chronic-active, portal	0	0	0	0	0	1	3	2

ANOVA: * - P<0.05. a – Number of animals showed sings.

PK parameters

Table 2.6.6-63: 1-week continuous intravenous infusion toxicity study in dogs – toxicokinetics [R087-TX-073]

Daily Dose (mg/kg)		2		10		30	
Number of Animals		M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
C_{ss} (ng/mL):	Day 1	160	230	882	983	3810	3697
	Day 7	606	541	5887	4960	28100	26533
	Day 9	553	327	4940	3707	29867	28533
AUC_{0-24} (ng·hr/mL)*:	Day 1	3840	5520	21168	23592	91440	88728
	Day 7	14544	12984	141288	119040	674400	636792
	Day 9	13272	7848	118560	88968	716808	684792

* $AUC_{0-24} = C_{ss} \times 24$.

Human Exposure Multiples:

Toxicology Study	NOAEL, mg/kg	AUC, ng.h/ml	Ratio of animal to human AUC
9-Day dog, continuous IV	2	M: 13272, F:7848	M: 3.7, F: 2.2
Human dose, 20 bolus + 40 mg IV for 4 days		3580 ng.h/ml/day	

Key findings:

- Dogs were treated with intravenous doses of 2, 10 and 30 mg/kg/d for 9 days
- Dogs treated with 30 mg/kg/d appeared thin due to dehydration
- At 30 mg/kg/d BW and food intake decrease. As expected, the significant increase in water intake was associated with significant increase in urine out
- ALT, AST, ALP and GGT increased in dogs after 8 days of 30 mg/kg/d IV infusion
- The increase in liver weight in females at 10 mg/kg/d
- Bile duct hyperplasia and inflammation in the portal area in liver at 30 mg/kg/d
- 1 MD female had localized subcapsular necrosis
- The NOAEL was 2 mg/kg/d due to vessel wall proliferative thrombosis at $\geqslant$10 mg/kg/d

Study Title: 4-Week Continuous Intravenous Infusion Toxicity Study with YM087 in Dogs with PG/EtOH formulation

Note:

Study No: R087-TX-074 (20030910, [redacted] #6359-165)
page # 1-365
Conducting laboratory and location: [redacted]
Date of study initiation: Sept 23,1998 (completed on March 8, 1999)
GLP compliance: Yes
QA- Report: Yes (x) No ()

METHODS: Dogs were randomized into 4 groups (3/sex/group). The conivaptan PG/EtOH was prepared in 5% dextrose for continuous intravenous administration at a rate of 2 ml/kg/h for min for 4 WKs. Dogs were anesthetized and subcutaneous vascular access port and jugular catheters were implanted 3 Wks before the study under thiopental and isoflurane anesthesia (maintenance). Drug solution was prepared daily and transferred into infusion bags and pumped by a batter operated infusion pump. Prior to start of the study, animals were infused with saline at a rate of 2 ml/kg/h for 7 days (24hrs /day). The drug solution was infused at the same rate. Infusion system was inspected twice daily. Formulation solution concentrations were within ±10% of the target.

	Dosage Level	Concentration	Number of Animals		Animal Numbers	
Group	mg/kg[a]	mg/mL[a]	Male	Female	Male	Female
1 (Control)	0	0	3	3	G35655-G35657	G35667-G35669
2 (Low)	2	0.042	3	3	G35658-G35660	G35670-G35672
3 (Mid)	10	0.208	3	3	G35661-G35663	G35673-G35675
4 (High)	20	0.417	3	3	G35664-G35666	G35676-G35678

[a] The dose volume was 2.0 mL/kg/hr. (The total dose was 48 ml/kg/24 hours.)

Dosing: 0, 2, 10 and 20 mg/kg/day, IV continuous infusion
species/strain: Dogs, beagle, [redacted]
age: 11 to 12 months
weight: 7.7 to 9.5 kg males and 5.7 to 7.3 kg females
satellite groups used for toxicokinetics or recovery: none
Drug, lot#, radiolabel, and % purity: CR0120298 in [redacted] PG and [redacted] EtOH, nonlabled,
Formulation/vehicle: PG/EtOH and 5% dextrose
OBSERVATIONS AND TIMES:

Clinical signs:	Twice a day
Body weights:	Weekly
Food consumption:	Daily
Water consumption:	Daily
Ophthalmoscopy:	Before and study termination (sacrifice)
ECG:	Measured prior to treatment and on study termination
Hematology:	Standard hematology after an overnight fast before treatment and on Day 28 via non-catheterized jugular vein (plus day of necropsy for blood smear)
Clinical chemistry:	Similar to above
Urinalysis:	Similar to above

Gross pathology:	All animals fasted overnight and necropsied on Day 30 or 31
Organ weights:	Standard organ list
Histopathology:	All were evaluated
Toxicokinetics:	Standard hematology on Day 2 and 28

RESULTS:

Clinical signs:

- All animals survived
- HD animals looked thin due to pharmacologically-induce dehydration, especially 2 HD males had significant health deterioration (thin, emesis, few feces, jaundice on Day 22, high body temp 103-105 F)

Table 2.6.6-64: 4- week continuous intravenous infusion toxicity study in dogs – clinical signs [R087-TX-074]

Daily Dose (mg/kg)	0		2		10		20	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Clinical Signs								
Thin appearance	0	1	0	0	0	0	3	2
Appears dehydrated	0	0	0	0	0	0	2	0
Yellow gums	0	0	0	0	0	0	2	0
Yellow skin/Entire body	0	0	0	0	0	0	2	0

Body weights:

- No significant change in terminal BW controls and conivaptan treated dogs likely due to small number of animals /group. The HD dogs weight less and appeared thin due to water loss.

4- week continuous intravenous infusion toxicity study in dogs – body weight [R087-TX-074]

Daily Dose (mg/kg)	0		2		10		20	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Body Weight (kg):								
Day 1	8.2	6.9	8.1	6.7	8.5	7.2	8.1	6.9
Day 8	8.1	6.9	8.2	6.7	8.6	7.2	8.1	6.8
Day 15	7.9	7.0	8.3	6.8	8.6	7.3	7.8	6.5
Day 22	8.2	6.6	8.1	7.0	8.4	7.3	7.4	6.7
Day 29	8.1	6.6	7.9	6.8	8.2	7.1	6.6	6.3

Food consumption:

- Significant decrease in food intake was noted at some days in LD, MD and HD dogs.
- Food intake measurement did not include supplemented food (half of can of [redacted]

4- week continuous intravenous infusion toxicity study in dogs – food consumption [R087-TX-074]

Daily Dose (mg/kg)	0		2		10		20	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Food Consumption (g):								
Day 1	212	237	133	245	170	171	207	86
Day 2	222	192	147	196	95	189	146	84
Day 3	255	179	197	180	172*	205	134*	73
Day 4	258	240	227	219	257	217	141	118
Day 5	272	222	255	263	265	255	193	158
Day 6	259	227	230	292	246	214	168*	115
Day 7	206	193	180	238	234	235	171	186
Day 14	276	176	253	255	307	251	98*	155
Day 21	209	178	183	187	157	158	56	163
Day 28	207	249	173	173	226	124	46*	144
Day 29	162	76	201	222	209	289	46	73

ANOVA: * - P<0.05.

Water Consumption:

- As expected the water intake was 2 to 4 fold greater than control on Day 1.

4- week continuous intravenous infusion toxicity study in dogs water consumption [R087-TX-074]

Daily Dose (mg/kg)	0		2		10		20	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Water Consumption (g):								
Day 1	740	338	1992	3170*	3272*	3036*	3051*	1901
Day 7	2131	327	1204	1321	1440	2474*	1146	1189
Day 14	902	284	690	986*	1161	1227*	339	755
Day 21	421	451	559	557	606	953	174	680
Day 28	306	578	459	869	716*	701	123	657
Day 29	492	277	426	357	426	916*	97	249

ANOVA: * - P<0.05

ECG evaluations: No change in ECG parameters. The sponsor did not say when the ECG and blood pressure parameters were measured. Since the drug was continuously infused, the trough and peak Cmax is not as critical as in daily oral gavage study.

Ophthalmology: yellow colored appearance in 2/3 HD male (jaundice appearance).

Hematology:

- Significant decrease in RBC, PCV and hemoglobin in HD males on WK4. Since the plasma volume was likely to be contracted, the PCV and hemoglobin levels should have been the opposite. Thus, the decrease in RBC, hemoglobin and PCV were likely a toxicological effect of the high dose in dogs (NOAEL was 10 mg/kg/d).

Table 2.6.6-65: 4- week continuous intravenous infusion toxicity study in dogs – hematology [R087-TX-074]

Daily Dose (mg/kg)	0		2		10		20	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
RBC (10^6/µL)								
Week –3	7.28	6.70	7.67	7.03	7.46	6.26*	7.15	6.23*
Week –1	7.12	5.85	7.01	6.62	7.13	6.06	6.54	6.21
Week 4	6.45	6.18	6.87	6.89	6.51	6.39	4.63*	5.80
Reticulocyte (% RBC)								
Week –3	0.6	0.2	0.4	0.1	0.2	0.2	0.6	0.1
Week –1	0.2	0.1	0.1	0.2	0.3	0.1	0.1	0.0
Week 4	0.2	0.5	0.4	0.3	0.3	0.4	0.3	0.9
Reticulocyte (10^6/µL)								
Week –3	0.05	0.01	0.04	0.01	0.02	0.01	0.04	0.01
Week –1	0.01	0.01	0.01	0.01	0.03	0.01	0.01	0.00
Week 4	0.01	0.03	0.03	0.02	0.02	0.02	0.01	0.05
Hemoglobin (g/dL)								
Week –3	16.6	15.4	17.6	16.3	17.5	14.6	16.4	14.0
Week –1	15.8	13.2	15.6	14.9	16.4	13.8	14.5	13.6
Week 4	14.5	14.0	15.4	15.5	14.9	14.6	10.1*	12.8
PCV (%)								
Week –3	50.8	47.2	53.7	49.4	53.3	44.6	50.3	43.7
Week –1	49.3	41.2	48.9	46.4	50.6	43.0	45.5	43.2
Week 4	43.4	42.7	46.2	46.7	44.7	43.9	30.7*	39.5
Platelets (10^3/µL)								
Week –3	282	384	261	321	272	377	262	329
Week –1	268	369	277	357	271	347	231	340
Week 4	298	375	248	328	321	317	147*	292

ANOVA: * - P<0.05.

Clinical chemistry:

- Slight increase in ALP (20%) in MD males and nearly 10fold increase in HD males
- HD males also had lower glucose, albumin and higher triglycerides suggesting deterioration of health with continuous infusion of 20 mg/kg/day in male dogs.

Table 2.6.6-66: 4- week continuous intravenous infusion toxicity study in dogs – blood chemistry [R087-TX-074]

Daily Dose (mg/kg)		0		2		10		20	
Number of Animals		M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Blood Chimistry									
Glucose (mg/dL)									
	Week -3	81	87	86	85	84	86	79	87
	Week -1	94	89	92	86	93	92	86	87
	Week 4	91	89	96	81	90	93	64*	85
Albumin (g/dL)									
	Week -3	3.7	3.5	3.9	3.8	3.9	3.7	3.6	3.5
	Week -1	3.6	3.6	3.7	3.7	3.9	3.8	3.6	3.8
	Week 4	3.5	3.6	3.5	3.6	3.4	3.6	1.9*	3.1
ALP (U/L)	Week -3	43	84	58	72	68	100	68	98
	Week -1	34	53	43	45	56	66	52	80
	Week 4	34	52	39	42	82*	61	672*	111*
AST (U/L)	Week -3	25	31	34	27	29	31	26	33
	Week -1	32	36	34	35	34	37	32	36
	Week 4	30	34	31	38	30	33	123	41
ALT (U/L)	Week -3	26	24	30	25	29	19	23	23
	Week -1	32	30	35	33	44	34	33	33
	Week 4	33	25	33	28	28	27	122	37
LDH (U/L)	Week -3	115	96	164	157	91	92	205	117
	Week -1	81	95	66	154	58	67	67	111
	Week 4	88	98	60	175	56	54	169*	84
Total bilirubin (mg/dL)									
	Week -3	0.2	0.2	0.1	0.2	0.2	0.1	0.1	0.1
	Week -1	0.2	0.1	0.1	0.1	0.2	0.2	0.2	0.1
	Week 4	0.2	0.1	0.1	0.3	0.2	0.2	4.8	0.2
GGT (U/L)	Week -3	5	7	7	6	6	7	5	5
	Week -1	4	6	5	5	5	6	5	5
	Week 4	4	4	4	4	4	5	11	4
Triglicerides (mg/dL):									
	Week -3	36	44	47	43	34	43	40	51
	Week -1	29	36	31	32	33	33	33	38
	Week 4	23	33	23	27	28	32	72*	32

ANOVA: * - P<0.05.

Urinalysis:

- All treated animals had a dose-depend increase in urine volumes and decrease in urine osmolality (likely due to volume dilution).

4- week continuous intravenous infusion toxicity study in dogs –urinalysis [R087-TX-074]

Daily Dose (mg/kg)		0		2		10		20	
Number of Animals		M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Urinalysis									
Volume (mL):									
	Week -3	81	427	103	34	457	38	146	99
	Week -1	193	190	278	96	383	213	242	358
	Week 4	250	87	281	419*	282	509*	218	164
Osmolality (mOsm/kg):									
	Week -3	1251	444	1580	1431	556	2744	1617	986
	Week -1	1288	1593	1073	1400	832	2106	1088	977
	Week 4	781	1604	612	887	974	415*	949	1005

ANOVA: * - P<0.05.

Organ Weights:

- Significant increase in absolute liver in HD males and relative liver wt in HD males and females was likely due to high drug exposure.-induced hypertrophy.
- Significant increased in lung wt in HD males
- Significant decrease in prostate wt in LD and HD males. The significance of lower prostate weight in treated rats relative to controls is not clear.

Table 2.6.6-67: 4-week continuous intravenous infusion toxicity study in dogs – organ weight [R087-TX-074]

Daily Dose (mg/kg)		0		2		10		20	
Number of Animals		M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Liver/gallbladder:	Absolute (g)	213	181	197	172	231	206	305*	242
	Relative (%)	2.7	2.8	2.5	2.5	2.8	2.8	4.6*	3.8*
Lung:	Absolute (g)	72.8	60.8	55.4	54.2	62.0	51.0	91.5*	69.7
	Relative (%)	0.91	0.96	0.71	0.80	0.75	0.70*	1.36*	1.10
Spleen:	Absolute (g)	30.0	26.7	24.6	23.5	26.2	24.2	81.1	30.1
	Relative (%)	0.38	0.42	0.32	0.35	0.32	0.34	1.22	0.48
Prostate:	Absolute (g)	6.56	NA	4.07*	NA	4.70	NA	2.55*	NA
	Relative (%)	0.082	NA	0.052*	NA	0.057	NA	0.037*	NA

NA = Not applicable. ANOVA: * - P<0.05.

Gross pathology:

- Enlarged liver (2/3 males, 1/3 females), spleen (3/3 males), kidneys (1 male) in HD dogs
- Small thymus in 1 HD male and 1 HD female
- Dark area appearance of lungs in MD and HD females
- Soft testis, small prostate and dark area in urinary bladder in 1 HD male
- Mottled lung in all 3 HD and pale appearance in 2 HD males
- There were no visible infusion catheter site (tip or end) findings

Histopathology:

- Incidence of histopath findings were primarily in HD males > HD females >MD males
- The increase in liver weight was associated with sinusoidal dilatation, kupffer cell hypertrophy, centrilobular degeneration primarily in HD males
- Minimal vascular inflammation in lungs in 1 HD male and female and
- Minimal to slight lung arterial emboli in 1 MD and 3 HD females and 1 HD male
- Slight to moderate pigmented gallbladder mucosa in 2 HD males
- Minimal to slight renal tubular degeneration (1/3) , fibrosis (2/3) HD male
- Minimal renal tubular regeneration in 1 MD and HD male and 1 HD female
- Lymphoid depletion of thymus, lymph node, peyer's patch and spleen in HD dogs
- Inflammation and fibrosis was noted in catheter entry and exit point in most animals
- Minimal to slight degeneration/necrosis of sternal bone marrow degeneration in 3 HD males and 1 HD female
- Minimal to slight degeneration of seminiferous tubules in 2 HD males
- The NOAEL was 2 mg/kg/d in males and 10 mg/kg/d in females due to widespread pathology findings at 20 mg/kg/day

Incidence of the most common histological findings in dogs treated with continuous infusion f 2, 10 and 20 mg/kg/d of conivaptan.

Table 2.6.6-68: 4-week continuous intravenous infusion toxicity study in dogs – histopathology [R087-TX-074]

Daily Dose (mg/kg)	0		2		10		20	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Kidney: Degeneration, renal tubule	0	0	0	0	0	0	2	0
Congestion	0	0	0	0	0	0	2	0
Fibrosis	0	0	0	0	0	0	2	0
Lung: Pneumonitis	1	2	1	0	2	2	3	3
Inflammation, vascular	0	0	0	0	0	0	1	2
Embolus, artery	0	0	0	0	1	1	0	3
Spleen: Hematopoiesis, extramedullary	0	0	0	0	0	0	3	0
Lymphoid depletion	0	0	0	0	0	0	2	0
Liver: Pigment	0	0	0	0	0	0	2	0
Dilation, sinusoidal	0	0	0	0	0	0	3	2
Hypertrophy, Kupffer cell	0	1	0	0	0	0	3	1
Cytoplasmic, alteration, hepatocyte	0	0	0	0	0	0	3	1
Hematopoiesis, extramedullary	0	0	0	0	0	0	3	0
Degeneration, centrilobular	0	0	0	0	0	0	2	0
Gallbladder: Pigment, mucosa	0	0	0	0	0	0	2	0
Jejunum: Distention, mucosal gland	0	0	0	0	0	0	2	0
Ileum: Lymphoid depletion, Peyer's patch	0	0	0	0	0	0	2	1
Pancreas: Inflammation, peripancreatic fat	0	0	0	0	0	0	2	0
Lymph node, mesenteric: Lymphoid depletion	0	0	0	0	0	0	3	1
Lymph node, other: Lymphoid depletion	0	0	0	0	0	0	2	0
Thymus: Lymphoid depletion	0	1	0	1	1	1	3	2
Cyst, embryonic duct remnant	2	0	2	3	2	1	2	1
Testis: Degeneration, seminiferous tubule	0	NA	0	NA	0	NA	2	NA
Prostate: Secretion decreased	0	NA	0	NA	0	NA	3	NA
Marrow sternum: Degeneration/ necrosis	0	0	0	0	0	0	3	1
Catheter tip:								
Hyperplasia, endotherium	2	2	3	2	3	3	3	2
Inflammation, chronic	1	2	2	0	0	0	1	2
Hemorrhage, acute	2	1	2	1	0	0	1	0
Thrombus	1	1	2	1	0	1	1	0
Inflammation, vascular	0	0	0	0	0	0	0	1

NA = Not applicable.

The severity of renal, lung and liver pathology findings in dogs treated with continuous administration of conivaptan at 0, 2, 10 and 20 mg/kg/day (1= minimal, 2=slight, 3=moderate, 4=moderate severe, MN=mean, TL=total number of animals affected)

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN/TISSUE EXAMINED		SEX:	MALE				FEMALE			
		GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
		NUMBER:	3	3	3	3	3	3	3	3
KIDNEY	NUMBER EXAMINED:		3	3	3	3	3	3	3	3
	NOT REMARKABLE:		0	0	0	0	0	0	0	0
--DEGENERATION, RENAL TUBULE		1>	0	0	0	1	0	0	0	0
		2>	0	0	0	1	0	0	0	0
		TL>	0	0	0	2	0	0	0	0
		MN>	0.0	0.0	0.0	1.5	0.0	0.0	0.0	0.0
--CONGESTION		2>	0	0	0	1	0	0	0	0
		3>	0	0	0	1	0	0	0	0
		TL>	0	0	0	2	0	0	0	0
		MN>	0.0	0.0	0.0	2.5	0.0	0.0	0.0	0.0
--FIBROSIS		1>	0	0	0	2	0	0	0	0
		TL>	0	0	0	2	0	0	0	0
		MN>	0.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0
--CONCRETION, PAPILLA		1>	2	3	2	1	2	3	3	3
		2>	1	0	1	2	1	0	0	0
		TL>	3	3	3	3	3	3	3	3
		MN>	1.3	1.0	1.3	1.7	1.3	1.0	1.0	1.0
--REGENERATION, RENAL TUBULE		1>	0	1	1	0	0	0	0	1
		TL>	0	1	1	0	0	0	0	1
		MN>	0.0	1.0	1.0	0.0	0.0	0.0	0.0	1.0
--LIPIDOSIS, GLOMERULUS		1>	0	0	1	1	0	0	0	0
		TL>	0	0	1	1	0	0	0	0
		MN>	0.0	0.0	1.0	1.0	0.0	0.0	0.0	0.0
--PAS WITHIN NORMAL LIMITS		P>	3	3	3	3	3	3	3	3
		TL>	3	3	3	3	3	3	3	3
LUNG	NUMBER EXAMINED:		3	3	3	3	3	3	3	3
	NOT REMARKABLE:		1	2	0	0	1	3	1	0
--PNEUMONITIS		1>	1	1	2	0	2	0	1	2
		2>	0	0	0	1	0	0	0	0
		3>	0	0	0	2	0	0	1	1
		TL>	1	1	2	3	2	0	2	3
		MN>	1.0	1.0	1.0	2.7	1.0	0.0	2.0	1.7
--INFLAMMATION, VASCULAR		1>	0	0	0	0	0	0	0	1
		2>	0	0	0	1	0	0	0	1
		TL>	0	0	0	1	0	0	0	2
		MN>	0.0	0.0	0.0	2.0	0.0	0.0	0.0	1.5
--HYPERPLASIA, ENDOTHELIUM, ARTERY		1>	1	0	0	0	0	0	0	1
		TL>	1	0	0	0	0	0	0	1
		MN>	1.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0
--EMBOLUS, ARTERY		1>	0	0	1	0	0	0	0	2
		2>	0	0	0	0	0	0	0	1
		4>	0	0	0	0	0	0	1	0
		TL>	0	0	1	0	0	0	1	3
		MN>	0.0	0.0	1.0	0.0	0.0	0.0	4.0	1.3
LIVER	NUMBER EXAMINED:		3	3	3	3	3	3	3	3
	NOT REMARKABLE:		3	3	3	0	2	3	3	1
--PIGMENT		1>	0	0	0	1	0	0	0	0
		2>	0	0	0	1	0	0	0	0
		TL>	0	0	0	2	0	0	0	0
		MN>	0.0	0.0	0.0	1.5	0.0	0.0	0.0	0.0
--DILATATION, SINUSOIDAL		1>	0	0	0	1	0	0	0	1
		2>	0	0	0	2	0	0	0	1
		TL>	0	0	0	3	0	0	0	2
		MN>	0.0	0.0	0.0	1.7	0.0	0.0	0.0	1.5
--HYPERTROPHY, KUPFFER CELL		1>	0	0	0	3	1	0	0	1
		TL>	0	0	0	3	1	0	0	1
		MN>	0.0	0.0	0.0	1.0	1.0	0.0	0.0	1.0
--CYTOPLASMIC ALTERATION, HEPATOCYTE		1>	0	0	0	0	0	0	0	1
		2>	0	0	0	3	0	0	0	0
		TL>	0	0	0	3	0	0	0	1
		MN>	0.0	0.0	0.0	2.0	0.0	0.0	0.0	1.0
--HEMATOPOIESIS, EXTRAMEDULLARY		1>	0	0	0	3	0	0	0	0
		TL>	0	0	0	3	0	0	0	0
		MN>	0.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0
--DEGENERATION, CENTRILOBULAR		1>	0	0	0	2	0	0	0	0
		TL>	0	0	0	2	0	0	0	0
		MN>	0.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0
--MINERALIZATION, CAPSULE		1>	0	0	0	0	1	0	0	0
		TL>	0	0	0	0	1	0	0	0
		MN>	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0

Toxicokinetics:

- Plasma concentration increased with repeated administration conivaptan in dogs suggesting significant CYP3A4 inhibition. Drug accumulation was more prominent at males (43% at LD to 195% at HD. In females drug accumulated by 8% at LD and 90% at HD. The increased toxicity noted in HD male dogs correlated with high drug exposure.
- Drug exposure in males were greater than females measured on Day 1 or Wk 4.

Table 2.6.6-69: 4-Week continuous intravenous infusion toxicity study in dogs – toxicokinetics [R087-TX-074]

Daily Dose (mg/kg) Number of Animals		2 M: 3	F: 3	10 M: 3	F: 3	20 M: 3	F: 3
C_{ss} (ng/mL):	Day 2	352	308	2923	3117	7413	6457
	Day 28	505	334	5727	5007	21900	12273
AUC_{0-24} (ng·hr/mL)*:	Day 2	8448	7392	70152	74808	177912	154968
	Day 28	12120	8016	137448	120168	525600	294552

* $AUC_{0-24} = C_{ss} \times 24$.

Human Exposure Multiples:

Study	NOAEL, mg/kg		AUC, ng.h/ml	Ratio of animal to human AUC/day
4-WK dog, continuous infusion, IV	10	Day 2	M: 70152, F:74808	M: 20, F21
		Day 28	M: 137448, F:120168	M: 38, F: 33.6
Human dose, 20 bolus + 40 mg IV for 4 days			3580 ng.h/ml/day	

KEY STUDY FINDINGS:

- Dogs were treated with continuous IV infusion of conivaptan PG/EtOH at 2, 10 and 20 mg/kg/d for 4 WKs
- Significant deterioration in health in HD dogs (especially 2 HD males) i.e. thin and dehydrated
- Significant dose-dependent increase in water intake and urine output
- No notable changes in cardiovascular parameters
- Yellowish appearance of eyes in 2/3 HD males (jaundice)
- Significant decrease in RBC, PCV and hemoglobin in HD males
- Increase in ALP at MD (20%) and HD males (10 fold)
- Significant increase in liver and lung wt. and decrease in prostate wt in HD males
- Enlarged liver was associated with sinusoidal dilatation, kupffer cell hypertrophy and centrilobular degeneration in HD dogs.
- Minimal to slight renal tubular degeneration (1/3) and fibrosis (2/3) HD male and minimal renal tubular regeneration in 1 MD and HD male and 1 HD female
- Lymphoid depletion of thymus, lymph node, peyer's patch and spleen in HD dogs
- Inflammation and fibrosis was noted in catheter entry and exit point in most animals
- Minimal to slight degeneration/necrosis of sternal bone marrow degeneration in 3 HD males and 1 HD female
- Minimal to slight degeneration of seminiferous tubules in 2 HD males

- The incidence of histopath findings (HD males>HD females>MD males) were associated with conivaptan exposure.
- The NOAEL was 2 mg/kg/d in males (3.4 x) and 10 mg/kg/d in females (34 x clinical dose)

Study Title: 13-Week oral toxicity study in rats

Study no: R087-TX-005

F344 rats were treated with YM087 suspended in 0.5% methylcellulose solution at 3, 10, 30 ad 100 mg/kg/d (6/sex/group). TK was performed at WK 14. There were no deaths. YM087 had no effect on food consumption , hematology, auditory response or ophthalmoscopy. BW was lower at all doses, however, returned to normal during the recovery period. Water consumption increase at all doses of YM087.

13-week repeat-dose oral toxicity study in rats – body weight and water consumption [R087-TX-005]

Daily Dose (mg/kg)	0		3		10		30		100	
No. of Animals	M: 22	F: 22	M: 10	F: 10	M: 10	F: 10	M: 22	F: 22	M: 22	F: 22
Body Weight (g):										
Week 1	125.8	99.8	124.3	101.1	120.8	100.5	127.1	102.0	126.3	101.2
Week 4	211.7	135.5	200.3	137.7	195.6*	136.5	207.0	139.4	200.8	136.9
Week 9	264.5	160.7	246.8*	160.8	242.1*	162.1	249.4	167.3	243.8*	162.2
Week 14	285.2	174.7	274.8	171.2	262.7*	175.4	271.0	178.8	265.2*	172.0
Water Consumption (g/animal/day):										
Week 4	21.0	22.2	86.6*	54.6*	159.3*	104.6*	176.3*	115.5*	165.4*	110.9*
Week 8	19.6	19.9	82.4*	63.2*	161.3*	122.7*	188.1*	133.5*	179.6*	125.5*
Week 12	18.9	16.7	95.4*	66.5*	147.8*	126.4*	176.4*	129.3*	172.5*	122.6*

Dunnett's Test: * - P<0.05

13-week repeat-dose oral toxicity study in rats – organ weight [R087-TX-005]

Daily Dose (mg/kg)		0		3		10		30		100	
No. of Animals		M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Organ Weight:											
Liver:	Absolute (g)	7.0547	4.3946	6.9829	4.4317	6.4705	4.3490	7.1060	4.8159*	8.0870*	5.7244*
	Relative (%)	2.6011	2.7398	2.7147*	2.8120	2.6476	2.7214	2.8356*	2.9414*	3.3440*	3.6963*
Adrenal:	Absolute (g)	0.0423	0.0480	0.0419	0.0480	0.0509*	0.0596*	0.0586*	0.0624*	0.0684*	0.0714*
	Relative (%)	0.0157	0.0300	0.0163	0.0305	0.0208*	0.0373*	0.0237*	0.0382*	0.0283*	0.0461*
Uterus:	Absolute (g)	NA	0.7306	NA	0.5973	NA	0.4160*	NA	0.4046*	NA	0.3519*
	Relative (%)	NA	0.4596	NA	0.3813	NA	0.2593*	NA	0.2472*	NA	0.2248*
Pituitary:	Absolute (g)	0.0097	0.0133	0.0098	0.0127	0.0095	0.0117*	0.0097	0.0112*	0.0098	0.0110*
	Relative (%)	0.0036	0.0083	0.0038	0.0081	0.0039	0.0073*	0.0039	0.0069*	0.0041*	0.0071*

NA = Not applicable. Dunnett's Test: * - P<0.05, ** - p<0.01.

13-week repeat-dose oral toxicity study in rats – blood chemistry and urinalysis [R087-TX-005]

Daily Dose (mg/kg)	0		3		10		30		100	
No. of Animals	M: 22	F: 22	M: 10	F: 10	M: 10	F: 10	M: 22	F: 22	M: 22	F: 22
Blood Chemistry:										
Total Protein (g/dL)	6.7	6.4	6.4*	6.1*	6.5	5.8*	6.8	6.3	7.2*	6.8*
Albumin (g/dL)	4.5	4.5	4.4	4.3*	4.5	4.2*	4.7*	4.5	5.0*	4.9*
Urinalysis:										
Volume (mL):										
Week 4[a]	10.2	10.9	5.8	10.6	26.8*	6.4	32.8*	37.0*	50.3*	45.2*
Week 9[a]	5.0	8.6	10.4	12.3	49.0*	35.1*	57.6*	35.5*	85.3*	36.2*
Week 12[c]	4.0	1.8	15.3*	6.4*	30.7*	14.4*	58.6*	23.4*	94.3*	36.5*
8 hr - Volume (mL):										
Week 12[b]	1.4	0.4	64.1*	37.6*	86.9*	65.6*	89.8*	63.5*	84.7*	43.0*
Osmolality (mOsm/kg):										
Week 4[a]	509	361	452	235*	132*	402	149*	121*	104*	122*
Week 9[a]	1510	1665	373*	276*	133*	122*	118*	138*	84*	122*
Week 12[c]	1767	2288	329*	430*	209*	213*	116*	194*	90*	147*
Creatinine (mg/dL):										
Week 4[a]	39.6	19.0	38.7	13.8	9.4	24.2	11.7	6.0	7.2	6.1
Week 9[a]	122.4	87.5	34.9	18.6	10.0	7.1	9.1	8.9	6.4	8.3
Week 12[c]	130.4	115.0	29.3	26.8	15.7	13.4	8.9	11.5	6.6	8.6
Sodium (mmol/L):										
Week 4[a]	9	8	0	0	0	0	0	0	0	2
Week 9[a]	64	85	4	0	0	0	0	0	0	0
Week 12[c]	71	124	2	9	2	2	0	4	0	0
Potassium (mmol/L):										
Week 4[a]	87	50	51	26	18	49	19	16	15	12
Week 9[a]	240	270	36	28	17	14	15	16	9	12
Week 12[c]	290	324	45	49	31	24	18	21	12	17
Chloride (mmol/L):										
Week 4[a]	26	16	16	2	2	14	2	2	0	3
Week 9[a]	95	119	2	0	0	0	0	0	0	0
Week 12[c]	108	168	13	26	6	4	0	3	0	2

Dunnett's Test: * - P<0.05 ** - p<0.01. a - 16-hour overnight collection.
b - 16-hour collection following 8-hour collection. c - 8-hour collection after dosing.

13-week repeat-dose oral toxicity study in rats – toxicokinetics [R087-TX-005]

Daily Dose (mg/kg)		3		10		30		100	
Gender		M	F	M	F	M	F	M	F
C_{max} (ng/mL):	Day 1*	77.2	47.3	388	499	1853	2060	3577	4553
	Week 14	85.4	84.0	684	928	1593	2620	3667	5523
AUC_{0-24} (ng·hr/mL):	Day 1*	268	372	2343	4988	12710	23320	43889	53579
	Week 14	545	549	4158	6131	18379	17762	49377	68110

* - From Study No. R087-TX-112, 1-Day oral gavage toxicokinetic study with YM087 in F-344 rats.

Key findings:

- The NOAEL was 3 mg/kg in females and < 3 mg/kg in males (0.04x MRHD).
- The 100 mg/kg/d reduced body weight and hematology parameters with no associated histopathology. The AUC exposure at 100 mg dose in males was 3.6 fold and in females 4.9 x MRHD, based on AUC.

Title: 13-Week oral toxicity study in rats

Study no: R087-TX-111

The sponsor repeated the 13-WK male rat study using lower doses of YM087 to determine the NOAEL in male rats. In previous study the NOAEL in male rats was less than 3 mg/kg/d. Similar to previous study, YM087 was suspended in 0.5% methylcellulose solution and administered to F344 rats at 0.3 and 1 mg/kg/d. TK was evaluated at WK 14. There were no deaths or drug related clinical signs, body weight, food intake or histopathology. However, water consumption and urine volume increased and urinary osmolality and electrolytes (Na, K and Cl) decreased.

Additional 13-week repeat-dose oral toxicity study in rats – body weight, water consumption and toxicokinetics [R087-TX-111]

Daily Dose (mg/kg) Number of Animals		0 M: 10	0.3 M: 10	1 M: 10
Body Weight (g):	Week 1	112.2	112.4	115.6
	Week 4	203.5	205.1	208.7
	Week 9	266.4	269.8	269.1
	Week 14	299.2	307.0	303.4
Body Weight gain (g):	Week 1	31.0	32.4	33.2
	Week 4	15.6	14.8	16.1
	Week 9	10.4	12.1	9.7
	Week 13	5.5	3.8	8.0
Water Consumption (g):	Week 4	26.2	29.2*	35.6*
	Week 8	17.7	21.0	30.8*
	Week 10	21.0	23.3	36.6*
	Week 12	20.2	23.7	43.9*
Toxicokinetics				
C_{max} (ng/mL):	Day 1	NA	1.17	2.79
	Week 14	NA	2.36	11.3
AUC_{0-24} (ng·hr/mL):	Day 1	NA	NC	9.56
	Week 14	NA	NC	59.6

NA = Not applicable. NC = Not calculated. Dunnett's Test: * - P<0.05,

Key Findings:

- No change in BW, hematology or histopathology in males at 0.1 or 1 mg/kg/d
- The NOAEL was 1 mg/kg/d in males, approximately 0.01 x MRHD, based on AUC.

Title: 26 Week Oral Gavage YM087 in Rat

Study no: R087-TX-045 (RR 745-03024 in the original IND)
Volume #6.8, and page #: 2
Conducting laboratory and location: [redacted]
Date of study initiation: 8/9/95
GLP compliance: yes
QA report: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: YN0871Z, [redacted]
Formulation/vehicle: 0.5%methylcellulose
Methods (unique aspects): Animals were fed powdered diet.
Dosing:

Species/strain: CDF(F-344)[redacted]BR VAF/Plus rats
#/sex/group or time point (main study): 15
Satellite groups used for toxicokinetics: 12 sex/group
Age: 42-48 days
Weight: 101.9-133.1 g Males and 82.7-106 g Females
Doses in administered units: 0, 1, 3, 10, 100 mg/kg/day
Route, form, volume, and infusion rate: oral gavage, 0.5% methylcellulose, 5 ml/kg

Observations and times:

Clinical signs: 2X daily
Body weights: weekly
Food consumption: weekly
Water consumption: 2 consecutive days during Weeks 13 and 24
Ophthalmoscopy: pre-dose and during Weeks 14, 25
Hematology: Week 26
Clinical chemistry: week 26
Urinalysis: Week 13, 24 from non fasted animals for 8h period
Gross pathology: at necropsy
Organs weighed: at necropsy, see list in addendum
Histopathology: at necropsy, see list in addendum
Toxicokinetics: Week 27 at 2, 4, 8, 24 h
Other: vaginal smear (Estrus evaluation) daily Weeks 11-13 and Week 24 to necropsy
Auditory evaluation: pre dosing and on first day of Week 24 consisting of observation of ear and head response to 10 Khz whistle blown behind animals head

Results:

Mortality:	0 mg/kg/day		1 mg/kg/day		3 mg/kg/day		10 mg/kg/day		100 mg/kg/day	
	M	F	M	F	M	F	M	F	M	F
Tox +TK rats							3/27	5/27	5/27	4/27

Most rats were sacrificed moribund except those found dead (1M @ MD & HD) days 11-27. Cause of death is provided for 1 male given 10 mg/kg/day, sacrificed moribund with a perforated esophagus and 1 male given 100 mg/kg/day with a fracture. The cause of death in the other rats was considered pneumonia occasionally associated with foreign matter (possibly

feed) in the lungs. Animals in this study were fed powdered diet. Azotemia secondary to dehydration was consistent with the insufficient water consumption to compensate for drug related diuresis. The inability to drink may result in difficulty in swallowing the diet could lead to inhalation of feed resulting in pneumonia or the pneumonia could resulting in a weakened state and inability to drink and feed normally. Other findings are consistent with the histopathology of the survivors: lymphocytic depletion of thymus, hypocellularity of bone marrow, adrenocortical hypertrophy/-plasia, atrophy of prostate. Normally some splenic extramedullary hematopoiesis is observed in rats but was not present in any moribund rats.

Clinical signs: Irregular estrous cycles were noted in females given 10, 100 mg/kg/day indicated by long diestrus or metestrus periods and a decreased estrus period. This was more pronounced during Week 24 to necropsy than during Weeks 11-13.

Clinical Signs	0 mg/kg/day		1 mg/kg/day		3 mg/kg/day		10 mg/kg/day		100 mg/kg/day	
	M	F	M	F	M	F	M	F	M	F
Thin						3/15	3/15	7/15	10/15	3/15
Hunched							3/15	3/15	7/15	2/15
Audible respirations						2/15	4/15	7/15	7/15	5/15
Rough Hair						3/15	3/15	6/15	5/15	4/15
Nasal discharge							2/15	2/15	2/15	1/15
Uncoordinated							1/15	2/15	1/15	1/15
Hypoactive/ cold to touch							2/15	4/15	3/15	2/15
Mass	2/15				2/15		3/15	2/15	3/15	1/15
Positive auditory response	15/15	15/15	15/15	15/15	15/15	15/15	13/15	13/15	13/15	15/15

Body weight:

Body Weight, g	0 mg/kg/day		1 mg/kg/day		3 mg/kg/day		10 mg/kg/day		100 mg/kg/day	
	M	F	M	F	M	F	M	F	M	F
Week 27	354.3± 21.2	196.1 ±11.3	337± 22.2	196.9 ±9.1	327.8 ±16.8 *	180.9 ±16.9 *	299 ±31.5 *	181.2 ±18.5 *	239.5 ±41.3*	178.8 ±13.7*
% Control					-7	-7	-16	-8	-32	-9

The sponsor believes there is a possible correlation between pneumonia and the body weight effects. Lung histopathology is found in all groups including controls without differences in incidence/severity. Body weight effects are significant in males given ≥ 3 mg/kg/day.

Organ Weights:

- Significant decrease in kidney, liver, salivary gland, thyroid, spleen, adrenal, brain, pituitary and reproductive organs in most MHD and all HD rats correlated with severe dehydration noted in rats as consequence of AVP antagonist treatment.
- Changes in organ to body weight ratios is shown in table next page

Organ to body weight percentages are shown in table below:

Summary of Organ-to-Body Weight Percentages Week 27 Sacrifice

TABLE INCLUDES:
SEX=ALL;GROUP=1,2,3,4,5;WEEKS=ALL
DEATH=T;SUBSET=ALL

SEX:	MALE					FEMALE				
GROUP:	1	2	3	4	5	1	2	3	4	5
NUMBER:	15	15	15	12	11	15	15	15	11	13
KD - KIDNEY										
# IN GRP :	15	15	15	12	11	15	15	15	11	13
M E A N :	0.6509	0.6554	0.6754*	0.7081*	0.8424*	0.7250	0.7462	0.8025*	0.7880*	0.8401*
STAND DEV:	0.0295	0.0278	0.0246	0.0227	0.0724	0.0326	0.0251	0.0534	0.0454	0.0623
LI - LIVER										
# IN GRP :	15	15	15	12	11	15	15	15	11	13
M E A N :	2.5736	2.5747	2.6148	2.5744	3.7730*	2.6221	2.7636*	2.7908*	2.8140*	3.9746*
STAND DEV:	0.1080	0.1117	0.1203	0.1185	0.3827	0.1024	0.1680	0.0811	0.1764	0.2680
SG - SUBMAX SALIV GL										
# IN GRP :	15	15	15	12	11	15	15	15	11	13
M E A N :	0.1865	0.1847	0.1826	0.2064*	0.2694*	0.2213	0.2191	0.2407	0.2651*	0.2810*
STAND DEV:	0.0114	0.0080	0.0120	0.0095	0.0463	0.0115	0.0142	0.0332	0.0512	0.0417
TY - THYROID/PARA										
# IN GRP :	15	15	15	12	11	15	15	15	11	13
M E A N :	0.0052	0.0057	0.0056	0.0061	0.0091*	0.0084	0.0075	0.0083	0.0081	0.0093
STAND DEV:	0.0016	0.0012	0.0014	0.0017	0.0021	0.0021	0.0019	0.0021	0.0021	0.0023
TH - THYMUS										
# IN GRP :	15	15	15	12	11	15	15	15	11	13
M E A N :	0.0372	0.0362	0.0357	0.0300*	0.0225*	0.0710	0.0668	0.0624	0.0506*	0.0479*
STAND DEV:	0.0041	0.0079	0.0046	0.0077	0.0101	0.0078	0.0094	0.0114	0.0173	0.0091
HT - HEART										
# IN GRP :	15	15	15	12	11	15	15	15	11	13
M E A N :	0.3115	0.3116	0.3075	0.3145	0.3627*	0.3645	0.3784	0.3861	0.3859	0.3989*
STAND DEV:	0.0144	0.0185	0.0176	0.0178	0.0212	0.0159	0.0187	0.0286	0.0326	0.0228
LU - LUNG										
# IN GRP :	15	15	15	12	11	15	15	15	11	13
M E A N :	0.3814	0.3834	0.3991	0.4351*	0.5677*	0.5200	0.5187	0.5821*	0.5897*	0.6246*
STAND DEV:	0.0283	0.0121	0.0251	0.0326	0.1057	0.0496	0.0290	0.0699	0.1002	0.0757
SP - SPLEEN										
# IN GRP :	15	15	15	12	11	15	15	15	11	13
M E A N :	0.2282	0.2200	0.2279	0.2317	0.1814*	0.3137	0.3222	0.3217	0.2950	0.2874*
STAND DEV:	0.0110	0.0127	0.0159	0.0159	0.0390	0.0239	0.0267	0.0345	0.0470	0.0246
AD - ADRENAL										
# IN GRP :	15	15	15	12	11	15	15	15	11	13
M E A N :	0.0132	0.0134	0.0147*	0.0198*	0.0401*	0.0281	0.0284	0.0333*	0.0413*	0.0534*
STAND DEV:	0.0018	0.0013	0.0015	0.0033	0.0104	0.0017	0.0019	0.0041	0.0079	0.0039
BR - BRAIN										
# IN GRP :	15	15	15	12	11	15	15	15	11	13
M E A N :	0.5832	0.6025	0.6149*	0.6891*	0.8477*	0.9603	0.9630	1.0593*	1.0253	1.0437*
STAND DEV:	0.0359	0.0314	0.0374	0.0611	0.1239	0.0594	0.0389	0.0838	0.1005	0.0844
PI - PITUITARY										
# IN GRP :	15	15	15	12	11	15	15	15	11	13
M E A N :	0.0027	0.0028	0.0028	0.0030	0.0041*	0.0063	0.0063	0.0063	0.0063	0.0053
STAND DEV:	0.0003	0.0004	0.0006	0.0004	0.0007	0.0013	0.0011	0.0007	0.0009	0.0012
PR - PROSTATE										
# IN GRP :	15	15	15	12	11	0	0	0	0	0
M E A N :	0.2153	0.1920	0.1890	0.1956	0.1374*					
STAND DEV:	0.0441	0.0360	0.0511	0.0375	0.0505					
TE - TESTES										
# IN GRP :	15	15	15	12	11	0	0	0	0	0
M E A N :	0.9278	0.9687	1.0221*	1.0812*	1.0594*					
STAND DEV:	0.0559	0.0864	0.0475	0.0779	0.0886					
SV - SEMINAL VESICLES										
# IN GRP :	15	15	15	12	11	0	0	0	0	0
M E A N :	0.3999	0.4014	0.3712	0.4101	0.1660*					
STAND DEV:	0.0820	0.0836	0.0595	0.0646	0.0646					
UT - UTERUS/CERVIX										
# IN GRP :	0	0	0	0	0	15	15	15	11	13
M E A N :						0.4575	0.5153	0.4631	0.2526*	0.1719*
STAND DEV:						0.1323	0.2190	0.2479	0.0791	0.0325
OV - OVARIES										
# IN GRP :	0	0	0	0	0	15	15	15	11	13
M E A N :						0.0552	0.0508	0.0550	0.0537	0.0426*
STAND DEV:						0.0106	0.0049	0.0077	0.0088	0.0078

Food Intake:

Food consumption:	0 mg/kg/day		1 mg/kg/day		3 mg/kg/day		10 mg/kg/day		100 mg/kg/day	
	M	F	M	F	M	F	M	F	M	F
Week 26	19.5± 1.2	13.5± 0.8	18.9± 1.7	13.6± 0.8	18.9± 1.3	13.6± 1.5	17.9± 1.7	12.8± 1.7	14.4± 3*	12.5± 1.4
% Control									-26	

Water Intake:

Mean water consumption	0 mg/kg/day		1 mg/kg/day		3 mg/kg/day		10 mg/kg/day		100 mg/kg/day	
	M	F	M	F	M	F	M	F	M	F
Day 85-86 Ml/rat/day	21.1± 1.6	19.5± 1.6	46.5± 4.3*	32.3± 4.5*	93.9± 12.8*	57.8± 10.8*	161.1± 19.9*	97.9± 22.3	165.6± 24.5*	115.5± 17*
Day 162-163 ml/rat/day	19.7± 1.5	20.7± 1.7	45.9± 9.3*	37.2± 3.8*	114.6± 20*	73± 8.2*	170± 52.5*	116.4± 16.2*	201.4± 42.8*	132.4± 20.3*

Ophthalmoscopy: unremarkable

Hematology:

Hematology:	0 mg/kg/day		1 mg/kg/day		3 mg/kg/day		10 mg/kg/day		100 mg/kg/day	
Week 26	M	F	M	F	M	F	M	F	M	F
MCV (fl)	48±.7	52±.4	49±.8	52±.6	49±.8*	53±.6	50±.7*	53±.8*	50±1.1 *	53±.8
MCHC (%)	36.8±.5	36.9±.5 2	36.5±.5	36.9±.4	36.8±.4	37.1±.6	36.5±.7	36.8±.6	36.1±.4	36.2±.7 *
PLT x10^3/µl	648±40	629±35	624±27	631±25	623±29	635±36	632±57	610±26	764±54 *	704±60 *
PT (sec)	15.9±.3 3	15.5±.5	15.8±.4 6	15.5±.4	16±.9	15.5±.7	16.8±.7 2*	16.7±.9 *	17.3±.7 *	16.8±.6 *
WBC x10^3/µl	4.2 ±.8	6.7±.6	4.6±.7	6.7±.8	5.2±.5*	7±.9	6.4±1.2 *	7.6±.7	5.7±1*	6.8±1.6
Lymph (%)	75	70	75	73	76*	73	72*	67	71*	63
Mono (%)	2	3	2	3	2	3	3*	3	5*	4

Clinical Chemistry:

Clinical chemistry	0 mg/kg/day		1 mg/kg/day		3 mg/kg/day		10 mg/kg/day		100 mg/kg/day	
	M	F	M	F	M	F	M	F	M	F
Urea nitrogen (mg/dl)	14±1	16±1	16±1*	18±2*	18±2*	21±3*	16±3*	19±3*	17±5*	13±3
Total protein (g/dl)	7.5±.3	7.3±.3	7.4±0.4	7.5±.4	7.2±0.3	6.9±.3*	7.4±0.4	6.8±.3*	8±0.4*	7.8±.5*
Chol (mg/dl)	70±4	116±7	72±9	122±10	68±8	92±13*	65±8	69±8*	105±30 *	107±16
Trig (mg/dl)	81±32	38±7	74±25	37±4	89±30	32±6	53±19*	33±6	40±11*	42±12
Na (mmol/l)	148±2	147±2	149±3	145±2	148±4	145±2	149±3	147±3	154±5*	151±5
Cl (mmol/l)	105±2	16±2	104±2	104±2*	104±2	103±2*	104±2	103±2*	108±4*	107±4
ALB (g/dl)	4.9±.2	4.9±.2	4.9±.3	5±.3	4.7±.3	4.6±.2*	4.8±.2	4.5±.1*	5.1±.3	5.2±.3*
Inorganic Phos (mg/dl)	7.6±.9	6.1±.8	7.9±.4	6.5±.4	7.9±.7	7±1	8.2±.6	7.6±1*	8±.6	8±1.7*

* Significantly different from control

Urinalysis:

26-week repeat-dose oral toxicity study in rats – urinalysis [R087-TX-045]

Daily Dose (mg/kg)	0		1		3		10		100	
Number of Animals	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15
Number Examined										
Week 13	15	15	15	15	15	15	15	15	14	15
Week 24	15	15	15	15	15	15	13	13	13	15
8 hr - Volume (mL)										
Week 13	2.4	2.0	25.7*	17.8*	60.8*	41.7*	93.4*	48.4*	83.1*	52.0*
Week 24	1.3	1.6	22.8*	23.5*	76.8*	50.3*	101.4*	54.5*	90.6*	59.7*
16 hr - Volume (mL)										
Week 13	8.0	3.8	2.4*	1.8*	8.6	7.4*	43.3*	34.1*	81.1*	34.7*
Week 24	5.4	3.5	1.7*	2.2	13.9*	11.7*	64.0*	38.6*	88.9*	50.6*
24 hr - Volume (mL)										
Week 13	10.3	5.7	28.0*	19.5*	69.4*	49.1*	136.7*	82.5*	164.2*	86.7*
Week 24	6.7	5.1	24.5*	25.9*	90.7*	62.0*	160.5*	93.0*	179.5*	110.2*
Osmolality (mOsm/kg)										
Week 13	1068	1390	1549*	1348	558*	416*	156*	176*	101*	196*
Week 24	1516	1412	1573	1141	378*	293*	100*	166*	88*	127*
pH										
Week 13	7.5	6.7	6.8*	6.4	7.7	7.0	7.5	6.8	7.5	7.3*
Week 24	7.2	6.5	6.7*	6.5	7.4	6.7	7.3	6.5	7.2	6.9*
8 hr - Sodium (mmol/L)										
Week 13	120	120	26*	35*	12*	15*	8*	10*	8*	10*
Week 24	175	107	39*	24*	10*	12*	8*	10*	8*	8*
8 hr - Potassium (mmol/L)										
Week13	236	245	44*	45*	24*	24*	17*	23*	18*	24*
Week24	405	228	66*	38*	21*	24*	17*	23*	19*	22*
8 hr - Chloride (mmol/L)										
Week13	a	100	30	39	13	17	7	14	7	12
Week24	156	118	43	27	11	14	7	12	7	8
8 hr - Sodium Excretion (mmol)										
Week 13	0.27	0.20	0.64*	0.56*	0.66*	0.59*	0.70*	0.47*	0.62*	0.49*
Week 24	0.20	0.16	0.72*	0.54*	0.76*	0.59*	0.68*	0.52*	0.70*	0.42*
8 hr - Potassium Excretion (mmol)										
Week13	0.53	0.40	1.10*	0.77*	1.36*	0.97*	1.57*	0.99*	1.44*	1.16*
Week24	0.47	0.34	1.24*	0.85*	1.57*	1.15*	1.55*	1.22*	1.68*	1.14*
8 hr - Chloride Excretion (mmol)										
Week13	a	0.33	0.73	0.64	0.74	0.66	0.67	0.60	0.51	0.58
Week24	0.43	0.29	0.80	0.60	0.83	0.68	0.69	0.63	0.62	0.43
16hr - Sodium (mmol/L)										
Week 13	49	35	a	a	8*	7	4*	4	4*	4
Week 24	62	40	a	7*	5*	5*	4*	4*	3*	4*
16 hr - Potassium (mmol/L)										
Week13	149	95	a	a	50*	34	19*	18	11*	19
Week24	196	136	a	107	33*	27*	10*	23*	7*	11*
16 hr - Chloride (mmol/L)										
Week13	42	32	a	a	5*	b	b	b	b	b
Week24	60	a	a	a	14	a	a	a	a	a
16 hr - Sodium Excretion (mmol)										
Week 13	0.37	0.24	a	a	0.07*	0.05	0.15*	0.13	0.30	0.14
Week 24	0.34	0.18	a	0.02*	0.07*	0.05*	0.25*	0.12*	0.34	0.18
16 hr - Potassium Excretion (mmol)										
Week13	1.18	0.66	a	a	0.50*	0.27	0.70*	0.52	0.83*	0.44
Week24	1.09	0.62	a	0.34*	0.47*	0.27*	0.60*	0.45*	0.66*	0.48*
16 hr - Chloride Excretion (mmol)										
Week13	0.43	0.24	a	a	0.05*	b	b	b	b	b
Week24	0.40	a	a	a	0.14	a	a	a	a	a

a = The number of animals with reportable values is 1 or less, therefore no data was reported for the mean urine concentration or excretion.
b = More than half of the animals do not have a measurable concentration value, therefore no data was reported for the mean urine concentration and excretion.
Dunnett's Test: * - P<0.05

Significant changes in urinalysis are noted in table below:

Urinalysis:	0 mg/kg/day		1 mg/kg/day		3 mg/kg/day		10 mg/kg/day		100 mg/kg/day	
Week 24	M	F	M	F	M	F	M	F	M	F
24 h volume (ml)	6.7± 4	5± 2	24.5± 11.4*	25.9± 5*	90.7± 21.8*	62± 11*	160.5± 53.9*	93± 23*	179.5± 36.2*	110± 41*
MOSM/kg	1516± 854	1412± 570	1573± 673	1141± 612	378± 304*	293± 121*	100± 17*	166± 203*	88± 19*	127± 65*
PH	7.2±.3	6.5±.2	6.7±.3*	6.5±.3	7.4±.3	6.7±.3	7.3±.3	6.5±.4	7.2±.3	6.9±.4*

Organ Weights:

26-week repeat-dose oral toxicity study in rats – organ weight [R087-TX-045]

Daily Dose (mg/kg)		**0**		**1**		**3**		**10**		**100**	
Number of animals		**M: 15**	**F: 15**	**M: 15**	**F: 15**	**M: 15**	**F: 15**	**M: 15**	**F: 15**	**M: 15**	**F: 15**
Number Examined		15	15	15	15	15	15	12	11	11	13
Terminal Body Weight:		332.0	183.1	315.1	182.9	302.8*	166.0*	273.2*	168.6*	217.4*	168.1*
Liver:	Absolute (g)	8.5389	4.8012	8.1267	5.0494	7.9259	4.6310	7.0318*	4.7219	8.1369	6.6700*
	Relative (%)	2.5736	2.6221	2.5747	2.7636*	2.6148	2.7908*	2.5744	2.8140*	3.7730*	3.9746*
Kidney:	Absolute (g)	2.1608	1.3265	2.0649	1.3628	2.0460	1.3261	1.9309*	1.3219	1.8126*	1.4057*
	Relative (%)	0.6509	0.7250	0.6554	0.7462	0.6754*	0.8025*	0.7081*	0.7880*	0.8424*	0.8401*
Adrenal:	Absolute (g)	0.0435	0.0514	0.0420	0.0519	0.0444	0.0548	0.0534*	0.0685*	0.0839*	0.0895*
	Relative (%)	0.0132	0.0281	0.0134	0.0284	0.0147*	0.0333*	0.0198*	0.0413*	0.0401*	0.0534*
Pituitary:	Absolute (g)	0.0088	0.0115	0.0089	0.0116	0.0085	0.0105	0.0083	0.0107	0.0088	0.0089*
	Relative (%)	0.0027	0.0063	0.0028	0.0063	0.0028	0.0063	0.0030	0.0063	0.0041*	0.0053
Uterus:	Absolute (g)	NA	0.8385	NA	0.9404	NA	0.7937	NA	0.4350*	NA	0.2917*
	Relative (%)	NA	0.4575	NA	0.5153	NA	0.4631	NA	0.2526*	NA	0.1719*
Ovary:	Absolute (g)	NA	0.1012	NA	0.0928	NA	0.0914	NA	0.0915	NA	0.0718*
	Relative (%)	NA	0.0552	NA	0.0508	NA	0.0550	NA	0.0537	NA	0.0426*

NA = Not applicable. Dunnett's test: * - P<0.05

Gross Pathology:

Gross pathology:	0 mg/kg/day		1 mg/kg/day		3 mg/kg/day		10 mg/kg/day		100 mg/kg/day	
	M	F	M	F	M	F	M	F	M	F
Thin						2/15		3/11	8/11	4/13
GI dark fluid									3/11	
Lg. esophagus		1/15			3/15	7/15	10/12	9/11	11/11	12/13
Kidney diffuse dark									2/11	
Small Thymus								1/11	4/11	
Stomach glandular erosion/ulceration						1/15	1/12		5/11	1/13
Mass skin					1/15				1/15	
Mass peritoneum		3/15		2/15				1/11	1/11	1/13
Mass tongue										½ TK rat
Small seminal vesicles									5/11	

Histopathology Findings:

Histopathology	0 mg/kg/day		1 mg/kg/day		3 mg/kg/day		10 mg/kg/day		100 mg/kg/day	
	M	F	M	F	M	F	M	F	M	F
Lung: Minimal severity in all rats all groups: Granulomatous inflammation, alveolar macrophage infiltrate, hemorrhage, vascular mineralization, lymphohistiocytic infiltrate, foreign material, congestion, ,intravascular leukocytes										
ALL RATS EXAMINED HAD AT MINIMAL SEVERITY FOR THESE FINDINGS **DOSE RELATED INCREASES IN SEVERITY** ARE NOTED BELOW										
Bone Marrow Femur/sternum Hypocellular + erythroid hypoplasia	15/15	15/15	Not examined						11/11	13/13
Esophagus luminal dilation		2/15 sl			2/15sl 2/15mod	2/15 sl 8/15mod 1/15sev	3/12 sl 2/12mod 6/12mkd	1/11 sl 4/15mod 5/15mkd	5/11mod 4/11mkd 2/11 scv	2/13 sl 2/13mod 9/13 scv
Kidney tubular epith regen.									8/11 sl	3/13 sl 1/13 mod
Thymus lymphocyte depletion			1/14 mod						3/9 sl 2/9 mod	
Adrenal hyper-trophy/plasia Cortical								5/11mod	4/11 sl 6/11mod	3/13 sl 10/13 sev
Pituitary hyperplasia										1/13 sl
Glandular stomach erosion									2/11 sl	
Submax. LN plasmacytic hyperplasia										1/12 sl
Prostate chronic active inflammation									2/11 sl	
Prostate atrophy									6/11mod 1/11mkd	

Toxicokinetic Parameters:

26-week repeat-dose oral toxicity study in rats – toxicokinetics [R087-TX-045]

Daily Dose (mg/kg)		1		3		10		100	
Gender		M	F	M	F	M	F	M	F
C_{max} (ng/mL):	Week 27	19.0	22.2	98.3	156	505	763	4387	4127
AUC_{0-24} (ng·hr/mL):	Week 27	86.0	117	643	1006	4612	7271	31015	35952

Key findings in the 26-WK oral gavage Study in rats:

- Diuresis characterized by increased urine volume and decreased urine electrolytes were observed at all doses. A 22-27x higher 24h volume in rat given 100 mg/kg/day. Electrolytes were increased 8h immediately post dose. At 3 and 10 mg/kg/day, lower urine sodium and potassium excretion in the in the 8-24h period post dose. At the same interval HD rats had lower potassium excretion.
- **Estrus disruption was noted by vaginal smears at doses ≥ 10 mg/kg/day.** Several females remained in diestrus during week 24 and never went into estrus during this 3 week period. This is supported by elevated progesterone effect demonstrated in conivaptan treated Long Evans rats.

- The sponsor NOAEL=1 mg/kg/day
- Relative organ weight changes correspond to the observed histopathology: dilated esophagus ≥ 3 mg/kg/day; granulomatous / pyogranulomatous inflammation of lungs (both lobes more pronounced Left) ≥ 3 mg/kg/day; thymic lymphocytic depletion in males at 100 mg/kg/day, adrenocortical hypertrophy/-plasia ≥10 mg/kg/day, decreased splenic extramedullar hematopoiesis ≥10 mg/kg/day, atrophy of prostate at 100 mg/kg/day and tubular epithelial regeneration of kidney at 100 mg/kg/day
- The study appears to be confounded based on the absence of increased water consumption in response to continued diuresis. The multiple histopath findings present in all groups regardless of treatment supports a compromised health status of the rats. However, moribund/early deaths consisted of drug treated groups. This would explain why the findings were present in all groups without morbidity in the controls. The sponsor suggests that the pulmonary effects are attributed to aspiration of powdered food used in this study accompanied by reduced water consumption (see study repeat Yamanouchi #396302) however this is inconsistent with the dose responsive morbidity.

Study Title: Additional 26-Week Oral Gavage toxicity study with YM087 (CI-1025) in male rats. Investigation on the reproducibility of deaths and decreased body weight

Note: The sponsor repeated the 26-WK study to examined findings in the previous 26-WK study (ie. Pneumonia and related changes).

Study no: R087-TX-046 (RR 745-03025 in the original IND)
Volume # 8, and page #: 2
Conducting laboratory and location: Yamanouchi Pharmaceutical Co, Ltd. Tokyo, Japan
Date of study initiation: April 2, 96
GLP compliance: yes
QA report: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: YN0871Z; [redacted]
Formulation/vehicle: 0.5%methylcellulose

Methods (unique aspects): Animals were fed a pelleted diet
Dosing:

Species/strain: 105 Male Fischer Rats (F344/ [redacted]
#/sex/group or time point (main study): 20 males /group
Age: 7 Weeks old
Weight:148-182 g males
Doses in administered units: 0, 10 and 100 mg/kg/day
Route, form, volume, and infusion rate: oral gavage, 0.5% methylcellulose, 10 ml/kg

Observations and times:

Clinical signs: 2 x daily
Body weights: weekly
Food consumption: weekly
Water consumption: 2 consecutive days during Weeks 13 and 24
Ophthalmoscopy: pre-dose and during Weeks 1, 2, 3, 4, 8, 12, 16, 19 and 24
Hematology: Week 26
Clinical chemistry: week 26 from fasted animals.
Urinalysis: Week 13, 24 from non fasted animals for 8h period
Gross pathology: at necropsy,

Organs weighed: at necropsy, see list in addendum
Histopathology: at necropsy, see list in addendum

Statistical Analysis: Continuous data were first analyzed by Bartlett's test for homogeneity. When the variance in each group was homogeneous, the group mean values were analyzed for significant differences between the control and dosed groups by Dunnett's multiple comparison. If Bartlett's test failed to show homogeneity of variance, the group mean values were analyzed for significant difference between the control and dosed groups by Dunnett's rank multiple comparison. Frequency data were not analyzed for significance of differences.

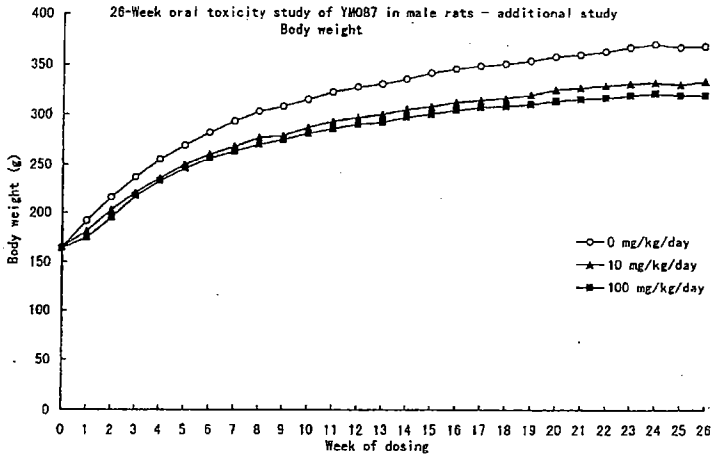
Results:
Clinical Signs: No death occurred in any group.

- One control (week 20), 5 HD (between week 4 and 18) manifested with breath sound.
- Only HD groups showed salivation between week 4 and 24 (only two animals on the same day).
- One animal in each of YM087 treated group had soiled coat or discharge around the eye.
- One animal at 10 mg/kg (MHD) had hemorrhage in the oral cavity on day 55.

Body weight:

Body Weight	0 mg/kg/day	10 mg/kg/day	100 mg/kg/day
Week 14	355.3±5	305±3**	297±5**
Week 26	367±6	332±4**	318±6**
WK26 % of Control		-9.5	-13.4

**P less than 0.01



Food Intake:
Except for temporary decrease in food intake in the first 3 weeks, there were no difference in food intake among groups.

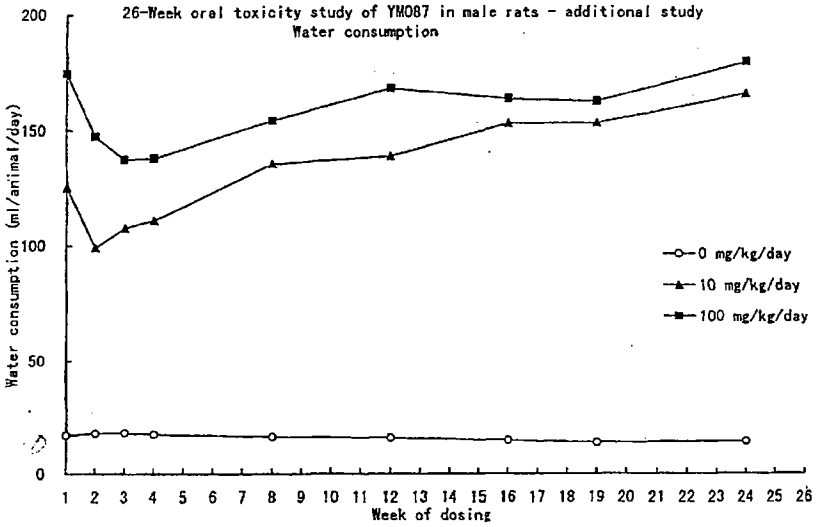
Food Intake	0 mg/kg/day	10 mg/kg/day	100 mg/kg/day
Week 2	17.9±0.3	16.7±0.2**	15.1±0.3**
Week 14	16.1±0.2	16.3±0.2	16.0±0.3
Week 26	16.5±0.3	16.7±0.3	16.0±0.4

**P less than 0.01

Water Intake:

Water Intake	0 mg/kg/day	10 mg/kg/day	100 mg/kg/day
Week 2	17.9±0.4	99.1±2.5**	147.3±3.7**
Week 16	14.5±0.3	152.7±4.8**	163.4±4.8**
Week 26	114.0±0.4	165.5±5.1**	179.0±5.1**
WK 26, % of Control		1082 % (>10x)	1178% (>12 x)

**P less than 0.01



Ophthalmoscopy: unremarkable

Hematology:

Platelet counts (10000/cmm) increased with HD (100 mg/kg) from 65±1 in control to 72±2.

Additional 26-week repeat-dose oral toxicity study in rats – hematology [R087-TX-046]

Daily Dose (mg/kg) Number of Animals	0 M: 20	10 M: 20	100 M: 20
Hematology: Week 26			
Platelet (10^3/μL)	640	630	720**
PT (sec)	15.1	14.5	15.9

Dunnett's test: ** - P<0.01

Clinical Chemistry:

Clinical chemistry	0 mg/kg/day	10 mg/kg/day	100 mg/kg/day
Urea nitrogen (mg/dl)	19±0	23±1**	18±1
Total protein (g/dl)	6.1±0.1	6.0±0.0	6.8±0.1**
Albumin (g/dl)	3.7±0.0	3.7±0.0	4.2±0.0**
Na (mmol/l)	145±0.0	143±0.0**	145±1
Cl (mmol/l)	104±0	102±0*	104±0

* P less than 0.05, ** P less than 0.01

Organ Weights:

26-Week oral toxicity study of YM087 in male rats - additional study -

Absolute organ weights

Dose	Final bodyweight		Adrenals		Liver	Seminal vesicle
(mg/kg)	n	(g)	n	(mg)	(g)	(g)
0	20	345.7 ± 5.9	20	46 ± 1	7.95 ± 0.16	1.06 ± 0.03
10	20	307.5 ± 4.3**	20	58 ± 2**	7.30 ± 0.14*	1.00 ± 0.03
100	20	294.5 ± 5.7**	20	70 ± 1**	9.49 ± 0.23**	0.82 ± 0.03**

Organ weights relative to body weight

Dose		Adrenals	Liver	Seminal vesicle
(mg/kg)	n	(mg%)	(g%)	(g%)
0	20	13 ± 0	2.30 ± 0.01	0.31 ± 0.01
10	20	19 ± 0**	2.37 ± 0.02	0.33 ± 0.01
100	20	24 ± 1**	3.22 ± 0.04**	0.28 ± 0.01*

Absolute organ weights

Dose	Heart		Submaxillary glands		Prostate	Pituitary
(mg/kg)	n	(g)	n	(g)	(g)	(mg)
0	20	0.98 ± 0.02	20	0.53 ± 0.01	0.45 ± 0.02	10 ± 0
10	20	0.89 ± 0.01**	20	0.48 ± 0.01**	0.46 ± 0.02	10 ± 0
100	20	0.86 ± 0.01**	20	0.47 ± 0.02**	0.37 ± 0.02**	9 ± 0

Organ weights relative to body weight

Dose	Heart		Submaxillary glands		Prostate	Pituitary
(mg/kg)	n	(g%)	n	(g%)	(g%)	(mg%)
0	20	0.28 ± 0.00	20	0.15 ± 0.00	0.13 ± 0.01	2.9 ± 0.1
10	20	0.29 ± 0.00	20	0.16 ± 0.00	0.15 ± 0.01	3.2 ± 0.1**
100	20	0.29 ± 0.00	20	0.16 ± 0.01	0.12 ± 0.00	3.2 ± 0.1*

Absolute organ weights

Dose	Brain		Lungs		Testes	Kidneys
(mg/kg)	n	(g)	n	(g)	(g)	(g)
0	20	2.06 ± 0.02	20	1.21 ± 0.02	3.20 ± 0.03	2.01 ± 0.03
10	20	2.04 ± 0.01	20	1.16 ± 0.02	3.06 ± 0.11	1.89 ± 0.03*
100	20	1.99 ± 0.01**	20	1.09 ± 0.02**	2.95 ± 0.05**	1.87 ± 0.04*

Organ weights relative to body weight

Dose	Brain		Lungs		Testes	Kidneys
(mg/kg)	n	(g%)	n	(g%)	(g%)	(g%)
0	20	0.60 ± 0.01	20	0.35 ± 0.01	0.93 ± 0.01	0.58 ± 0.01
10	20	0.67 ± 0.01**	20	0.38 ± 0.00**	1.00 ± 0.04**	0.61 ± 0.01*
100	20	0.68 ± 0.01**	20	0.37 ± 0.01*	1.01 ± 0.02**	0.63 ± 0.01*

Absolute organ weights

Dose	Spleen		Thymus		Thyroids	
(mg/kg)	n	(g)	n	(g)	n	(mg)
0	20	0.64 ± 0.02	19#1	0.12 ± 0.00	19#1	22 ± 0
10	20	0.57 ± 0.01**	20	0.11 ± 0.00	20	20 ± 1
100	20	0.64 ± 0.02	19#1	0.11 ± 0.00	20	20 ± 1

Organ weigths relative to body weight

Dose	Spleen		Thymus		Thyroids	
(mg/kg)	n	(g%)	n	(g%)	n	(mg%)
0	20	0.19 ± 0.00	19#1	0.034 ± 0.001	19#1	6.4 ± 0.2
10	20	0.18 ± 0.00	20	0.035 ± 0.001	20	6.6 ± 0.2
100	20	0.22 ± 0.00**	19#1	0.036 ± 0.001	20	7.0 ± 0.3

n: Number of animals weighed
Values are mean±S.E.
Significantly different from control, ** P<0.01
#1: Lost during histology procedure, Animal numbers 964206 and 964244.

Gross Pathology:

26-Week oral toxicity study of YM087 in male rats - additional study -

Summary of gross pathology

	Dose (mg/kg/day)	0	10	100
	Number of Animals Examined	20	20	20
Stomach	Number of Animals Examined	20	20	20
	Not Remarkable	19	20	18
Fundus / Dark		0	0	1 #1
Fundus / Red dot(s)		1 #2	0	1
Testes	Number of Animals Examined	20	20	20
	Not Remarkable	20	19	19
NOS / Small		0	1	1 #3
Eyes	Number of Animals Examined	20	20	20
	Not Remarkable	19	20	18
NOS / Congestion/Hemorrhage		1	0	2 #4

NOS: Not otherwise specified. #1: Red-brown area 5x2mm. #2: Dark-brown contents, ileum has also similar dark contents. #3: Slightly decreased in size of right testis only. Also slightly edematous. #4: Eyeball was embedded in the blood coagulative (right side only). Left eye was normal.

Histopathology: Animals in the 10 mg/kg were not examined

Additional 26-week repeat-dose oral toxicity study in rats – histopathology [R087-TX-046]

Daily Dose (mg/kg) **Number of Animals**		**0** **M: 20**	**10** **M: 20**	**100** **M: 20**
Organ Weight				
Liver:	Absolute (g)	7.95	7.30*	9.49**
	Relative (%)	2.30	2.37	3.22**
Seminal Vesicle:	Absolute (g)	1.06	1.00	0.82**
	Relative (%)	0.31	0.33	0.28*
Histopathology: Week 26 Sacrificed No. Examined		20	0	20
Adrenal:				
Cortex/ Hyperplasia/ diffuse[a]		0	NA	15
Zona fasciculata/ Decreased fatty vacuoles		0	NA	12
Kidney:				
Proximal tubule/ Basophilic change				
Slight or a few		5	NA	4
Moderate		0	NA	3
Proximal tubule/ Hyaline droplets		0	NA	1
Collecting tubule/ Protein cast				
Very slight		8	NA	2
Slight or a few		0	NA	3
Collecting tubule/Hyaline droplets		0	NA	2

NA = Not applicable. a - Diffuse cortical hyperplasia with slight hypertrophy.

Additional 26-week repeat-dose oral toxicity study in rats – toxicokinetics [R087-TX-046]

Daily Dose (mg/kg) **Number of Animals**		**10** **M**	**100** **M**
C_{max} (ng/mL):	Week 25	800	3390
AUC_{0-24} (ng·hr/mL):	Week 25	6012	45270

From Study No. R087-TX-119, Analysis of toxicokinetic samples from an additional 26-week oral toxicity study of YM087 in male rats (Yamanouchi project No.: 396302).

Key Findings in the 26-WK repeat oral gavage in male rats:

- Both 10 and 100 mg/kg/d doses of YM087 suppressed body weight gain
- Significant increase in water consumption at 10 and 100 mg/kg/d
- Platelet counts, total protein and albumin increase in the 100 mg/kg/d group
- No significant change in diameter of the esophagus
- Increased adrenal weight at 10 mg/kg
- Increased in liver and decrease in seminal vesicles at 100 mg/kg/d
- Diffuse hyperplasia of adrenal cortex in 15/20 of 100 mg/kg/d primarily in the zona reticularis and fasciculata
- Decreased fatty vacuoles in zona fasciculata in HD rats (12/20)
- Seminal vesicle atrophy, the cortical atrophy of thymus in one animal in 100 mg/kg/d.

Summary of the 26-WK oral toxicology study:

This 26 week study was carried out by the sponsor to validate the 26 week study carried out by outside labs. Male F344 rats (20/group) were given 0, 10, 100 mg/kg/day by oral gavage for 26 weeks to investigate the reproducibility of results obtained from the previous 26 week oral gavage study above. The result supports the previous 13 week rat study but not the findings of the original 26 week study.

Reproducible changes:

1) Platelet counts, albumin and plasma protein were slightly increased to a comparable extent to the previous 26 week study. The 13 week study shows plasma protein and albumin increased (107%, 111% respectively). The change in protein is attributed to hemoconcentration resulting from diuresis by the sponsor.
2) Adrenocortical hypertrophy and hyperplasia with increased adrenal weight occurred at 100 mg/kg/day. The sponsor attributes this to elevated AVP and ACTH as reported in literature for Sprague-Dawley female rats. Renal basophilic tubules and protein casts in the collecting tubules were observed at 100 mg/kg/day and were considered possible early lesions of chronic nephropathy in aging rats according to the sponsor. However, since these findings were enhanced in drug treated groups compared to control the sponsor acknowledges that drug treatment might accelerate nephropathy in aging rats.
3) Since histopathological abnormalities in the testes were not observed in the previous 26 week study the atrophy and decreased seminal vesicle weight observed in this study was considered secondary to suppressed body weight gain rather than a direct toxic effect on the testes according to the sponsor. Cortical atrophy of the thymus (1/20) was considered secondary to suppressed body weight gain.

Findings such as mortality, declining health, body weight, dilation of esophagus, pyogranulomatous pneumonia and atrophy of lymphatic tissue in spleen or atrophy of the prostate were not observed at doses up to 100 mg/kg/day. These findings were considered a secondary result of deteriorated general condition and body weight exacerbated by drug treatment as a result of inhalation of powdered food by dysphagia accompanying reduced water consumption according to the sponsor. Atrophy of the seminal vesicles and lymphatic tissue in the thymus were found in one animal each of the 100 mg/kg/day group. The TK data indicate similar drug exposure to the previous 26 week study and water consumption was comparable or superior to the previous 26 week study by [redacted]

Study Title: 13-week oral capsule toxicity study with YM087 in Beagle dogs with assessment of recovery

Note: This study was reviewed by Tim Links in Cardiorenal Division. Summary of the tables are posted for reference only.

Study No: R087-TX-006 (20030710)
Conducting laboratory and location: [redacted]
Date of study initiation: March 22, 94 (completion date Dec 29, 96)
GLP compliance: Yes
QA- Report: Yes (x) No ()
METHODS:

Conivaptan hydrochloride in gelatin capsules (conivaptan hydrochloride/lactose ratio -1/1), was administered orally to 8-9 month old beagles (3 or 5 animals/sex/group) for 14 weeks. Control animals received gelatin capsules containing lactose (n=5 /sex). All animals except for 1 animal/sex in the control and 30 mg/kg were sacrificed at the end of WK13. The recovery animals were not treated during the 6-WK recovery phase to evaluate reversibility of possible toxicological observations. ECG evaluations were performed before start of the treatment and before dosing during WK 6 and 12. Blood pressure was monitored pre-dose and 4 hrs post dose on Day 2 and WK 13 of the study.

Group	Dose Level (mg/kg)[a]	Number of Animals		Animal Identification	
		Male	Female	Male	Female
1 (Lactose)	60	5[b]	5[b]	H06725, H06728, H06729, H06734, H06742[b]	H06746, H06752, H06757, H06758, H06767[b]
2 (YM087)	1	3	3	H06739, H06740, H06744	H06751, H06753, H06756
3 (YM087)	3	3	3	H06731, H06733, H06736	H06750, H06755, H06760
4 (YM087)	10	3	3	H06738, H06741, H06743	H06747, H06765, H06768
5 (YM087)	30	5[b]	5[b]	H06723, H06724, H06726, H06727, H06737[b]	H06749, H06762, H06763, H06764[b], H06766

a For Groups 2 through 5, YM087 was triturated with lactose (1:1 w/w). The control group received lactose only in gelatin capsules at the same level as Group 5.
b One animal/sex (designated as recovery animals) were treated for 14 weeks (99 days), then remained on study without treatment for 6 weeks. During recovery, animals were observed for reversibility or persistence of toxic effects.

Results:

- There were no deaths at any dose. However, one female dog at 30 mg/kg/d was hypoactive and had lower BW. She had decreased platelet counts, WBC and hematocrit. Bone biopsy at the end of the study showed necrosis, reduced hematopoietic tissues and reticuloendothelial hyperplasia.
- BW was reduced in the 30 mg/kg/d dosed animals.
- Significant dose-related increase in urine excretion with correlated increase in water intake
- No notable change in blood pressure, heart rate or heart rhythm except for 3 dogs at 30 mg/kg/d had ST-T depression during WK6 ECG recording. One dog at 3 mg/kg/d also had mild ST-T depression during WK12.
- Hematology, chemistry and histopathology parameters are shown in tables on the next pages.

Table 2.6.6-41: 13-week repeat-dose oral toxicity study in dogs – clinical sign, body weight, and food and water consumption [R087-TX-006]

Daily Dose (mg/kg)	0		1		3		10		30	
No. of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Clinical Sign:										
Hypoactive	0	0	0	0	0	0	0	0	1	1
Body Weight (kg)										
Week 1	11.3	10.3	11.8	10.2	11.1	10.2	11.1	10.3	11.3	10.1
Week 7	11.8	10.5	11.7	10.0*	11.6	10.1*	11.5	10.4	11.0	9.8*
Week 12	12.1	10.7	12.6	10.2*	11.9	10.5	11.7	10.4	11.1	9.8*
Food Consumption (g/day)										
Week 1	290	281	268	249	261	167	232	196	253	199
Week 7	335	321	349	313	335	277	347	294	306	245
Week 12	316	296	370	321	357	276	359	272	348	281
Water Consumption (g/day)										
Pretreatment	852	640	781	781	815	523	829	600	843	600
Week 2	640	530	1067	983	1550	1550*	2333*	1467*	2240*	2030*
Week 4	920	680	1183	1267	1367	1400*	2333*	1417*	2240*	2090*
Week 6	910	710	1400	1133	1450	1517	2200*	1050	1670	1530
Week 8	1260	750	1800	1217	1433	1683	1950	1050	1870	1650

t-test or Dunnett's Test: * - P<0.05

Table 2.6.6-42: 13-week repeat-dose oral toxicity study in dogs – hematology [R087-TX-006]

Daily Dose (mg/kg)	0		1		3		10		30	
No. of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
RBC (10^6/μL)										
Pretreatment	6.54	6.40	6.40	6.47	5.97	6.47	6.47	6.53	6.56	6.68
Week 4	6.38	6.44	6.50	6.73	6.07	6.33	6.20	6.40	6.98	6.70
Week 8	6.40	6.64	6.93	7.00	6.20	5.90	6.53	6.43	6.74	6.26
Week 12	6.58	6.64	7.10	7.27	6.60	5.80	6.67	6.33	6.60	6.60
Hemoglobin (g/dL)										
Pretreatment	14.9	15.2	15.2	15.1	13.8	15.8	15.7	15.7	14.7	15.6
Week 4	14.5	15.2	15.5	15.8	14.1	15.4	14.9	15.3	15.7	15.6
Week 8	14.8	15.7	16.6	16.6	14.5	14.3	15.8	15.4	15.3	14.6
Week 12	15.1	15.6	16.9	16.7	15.2	14.0	15.9	15.0	15.0	15.4
PCV (%)										
Pretreatment	43.7	43.8	43.7	43.9	40.6	45.6	45.3	44.8	43.2	45.0
Week 4	42.1	43.8	44.2	45.5	40.7	44.2	42.7	43.6	45.1	44.7
Week 8	42.6	44.7	47.3	47.1	41.7	41.0	45.3	43.9	43.8 (39.0)[a]	41.8 (27.6)[b]
Week 12	44.1	44.7	48.5	48.6	44.1	40.3	45.9	43.1	43.1	44.0 (30.0)[b]
Platelet (10^3/μL)										
Pretreatment	340	316	227	367	273	273	253	293	304	290
Week 4	308	294	213	310	277	250	270	237	298	258
Week 6[#]										36[b]
Week 8	302	280	203	277	200	240	263	263	260 (160)[a]	202 (60)[b]
Week 12	282	280	217	300	253	237	247	253	220 (40)[c]	226 (100)[b]
WBC (10^3/μL)										
Pretreatment	8.8	12.1	9.9	12.6	8.3	8.4*	11.2	10.6	8.5	10.1
Week 4	9.2	10.4	11.0	10.8	9.8	8.5	11.7	10.2	11.7	9.6
Week 6[#]										2.9[b]
Week 8	10.3	8.9	10.0	10.9	7.5	8.4	10.6	11.5	9.9	9.7
Week 12	8.5	8.9	11.8	8.7	7.8	8.2	10.5	9.6	8.9 (2.1)[c]	9.0

Dunnett's Test: * - P<0.05. # - Additional examination for health check for one animal only.
a - Individual data from Animal No. H06727. b - Individual data from Animal No. H06764.
c - Individual data from Animal No. H06723.

Table 2.6.6-43: 13-week repeat-dose oral toxicity study in dogs – hematology in animals showed bone marrow changes [R087-TX-006]

Daily Dose (mg/kg)	30		
Animal Number	M: H06723	M: H06727	F: H06764
RBC (10^6/μL)			
Pretreatment	6.0	6.8	6.5
Week 4	6.8	6.4	6.4
Week 8	6.9	6.0	4.2 / 5.3[a]
Week 12	6.1/6.3[b]	5.8	4.6
Recovery Week 2/4			5.7/6.0
PCV (%)			
Pretreatment	39.7	45.6	43.7
Week 4	44.4	42.4	42.9
Week 8	45.7	39.0	27.6 / 35.4[a]
Week 12	39.4/41.8[b]	38.6	30.0
Recovery Week 2/4			38.6/40.1
Hemoglobin (g/dL)			
Pretreatment	13.3	15.6	15.3
Week 4	15.4	14.9	14.8
Week 8	16.1	13.7	9.8 / 12.3[a]
Week 12	14.2/14.3[b]	13.3	10.6
Recovery Week 2/4			12.8/13.7
Platelet (10^4/μL)			
Pretreatment	290	370	320
Week 4	290	340	270
Week 8	270	160	60 / 36[a]
Week 12	40/280[b]	270	100
Recovery Week 2/4			300/310
WBC (10^3/μL)			
Pretreatment	10.0	7.8	11.8
Week 4	10.8	12.7	10.1
Week 8	13.2	7.6	12.8 / 2.9[a]
Week 12	2.1/5.9[b]	12.0	6.6
Recovery Week 2/4			8.9/8.1
C_{max} (ng/mL) at Week 13	10900	12900	13000
$AUC_{0\text{-}24}$ (μg·hr/mL) at Week 13	197	260	256

a - Additional examination at Week 6. b - Additional examination at Week 13.

Table 2.6.6-44: 13-week repeat-dose oral toxicity study in dogs – blood chemistry and urinalysis [R087-TX-006]

Daily Dose (mg/kg)	0		1		3		10		30	
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Blood Chemistry										
ALP (IU/L)										
Pretreatment	64	64	76	77	62	79	84	72	73	69
Week 4	64	65	80	90	62	77	86	67	83	77
Week 8	54	62	70	82	57	75	74	68	109*	97
Week 12	48	70	52	82	55	73	75*	88	81*	91
Cholesterol (mg/dL)										
Pretreatment	170	173	175	161	166	158	182	148	179	163
Week 4	148	172	160	172	160	170	165	142	187	166
Week 8	141	177	146	158	145	212	156	160	197*	168
Week 12	131	200	145	152	146	184	152	169	176	153
Urinalysis										
Volume (mL)										
Pretreatment	98.0	85.4	129.7	82.0	110.3	89.7	108.7	60.0	86.4	189.8
Week 4	160.8	105.2	191.0	176.7	255.3	769.3*	415.7*	313.7	623.6*	440.0
Week 8	346.2	126.0	455.0	280.0	361.7	728.3	565.0	155.0	694.0	286.0
Week 11	73.6	81.2	473.7	184.3	210.0	298.3	415.0	70.7	384.8	315.8
Week 12	41.6	52.6	195.7	98.7	191.7	304.3	432.0	39.3	231.6	274.4
Osmolality (mOsm/L)										
Pretreatment	1568	1653	1577	1834	1900	1905*	1220	1866	1534	1172*
Week 4	1346	1510	587*	841	595*	190*	369*	650	306*	342*
Week 8	1127	1537	702	625	695	467	310	997	491	660
Week 12	1547	1814	837*	1185	1028	904	375*	1531	793*	830

Dunnett's Test: * - P<0.05

Table 2.6.6-45: 13-week repeat-dose oral toxicity study in dogs – blood chemistry in animal numbers H06727, H06737 and H06764 [R087-TX-006]

Daily Dose (mg/kg)	30		
Animal Number	M: H06727	M: H06737	F: H06764
AST (IU/L)			
Pretreatment	25	18	23
Week 4	32	31	31
Week 8	61	27	81[a]/43
Week 12	31	24	57
ALT (IU/L)			
Pretreatment	31	24	26
Week 4	23	32	28
Week 8	49	33	32[a] /28
Week 12	24	34	40
ALP (IU/L)			
Pretreatment	87	83	39
Week 4	82	122	39
Week 8	237	116	78[a] /133
Week 12	88	106	102
Recovery Week 4/5		81/79	46/38
Total Bilirubin (mg/dL)			
Pretreatment	0.1	0.1	0.1
Week 4	0.1	0.0	0.1
Week 8	0.5	0.1	0.1[a] /0.5
Week 12	0.1	0.1	0.3
Cholesterol (mg/dL)			
Pretreatment	157	133	174
Week 4	163	157	165
Week 8	268	146	231[a] /221
Week 12	141	139	173
C_{max} (ng/mL) at Week 13	12900	394	13000
AUC_{0-24} (µg·hr/mL) at Week 13	260	3.95	256

a - Additional examination at Week 6.

Table 2.6.6-46: 13-week repeat-dose oral toxicity study in dogs – histopathology [R087-TX-006]

Daily Dose (mg/kg)	0		1		3		10		30	
Number of Animals	M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Number examined	4	4	3	3	3	3	3	3	4	4
Bone marrow:										
Necrosis, marrow	0	0	0	0	0	0	0	0	1[a]	0
Hemorrhage	0	0	0	0	0	0	0	0	1[a]	0
Hyperplasia, myeloid	0	0	0	0	0	0	0	0	1[a]	0
Hyperplasia, reticuloendothelial	0	0	0	0	0	0	0	0	1[a]	0
Sternum/marrow:										
Hypocellular, marrow	0	0	0	0	0	0	0	0	1[a]	0
Rib/marrow:										
Hypocellular, marrow	0	0	0	0	0	0	0	0	1[a]	0
Hyperplasia, myeloid	0	0	0	0	0	0	0	0	1[a]	0
Femur/marrow:										
Necrosis, marrow	0	0	0	0	0	0	0	0	1[a]	0
Hemorrhage	0	0	0	0	0	0	0	0	1[a]	0
Hyperplasia, myeloid	0	0	0	0	0	0	0	0	1[a]	0
Fibrosis, marrow	0	0	0	0	0	0	0	0	1[b]	0
Liver:										
Hematopoiesis, extramedullary	2	1	3	0	2	2	1	3	2	1
Hyperplasia, bile duct	0	0	0	0	0	0	0	0	1[a]	0
Leukocytosis, sinusoidal	0	0	0	0	0	0	0	0	1[a]	0
Spleen:										
Hematopoiesis, extramedullary	2	3	2	1	1	1	1	1	2	1
Maxillary lymph node:										
Hematopoiesis, extramedullary	2	1	1	1	0	0	1	1	2	1
Bone Marrow Biopsy (13W):										
Number examined	NE	1	NE	NE	NE	NE	NE	NE	NE	1
Hypocellularity, erythroid and myeloid	NE	0	NE	NE	NE	NE	NE	NE	NE	1
Hyperplasia, reticuloendothelial	NE	0	NE	NE	NE	NE	NE	NE	NE	1
Necrosis	NE	0	NE	NE	NE	NE	NE	NE	NE	1

NE – Not examined. a - Observed in Animal No. H06727. b - Observed in Animal No. H06764.

Table 2.6.6-47: 13-week repeat-dose oral toxicity study in dogs – toxicokinetics [R087-TX-006]

Doses (mg/kg)	1		3		10		30	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
C_{max} (ng/mL):								
Day 1	172	198	1100	702	2346	2132	6448	3434
Week 13	231	266	741	1050	2870	2587	6285	7754
AUC_{0-24} (µg·hr/mL):								
Day 1	1.56	1.34	13.7	8.07	39.7	32.9	110.0	58.4
Week 13	2.31	2.09	7.56	11.5	41.0	36.9	114.0	133.0

Key Findings:

- No drug related mortality
- Significant change in BW at HD and dose-related increase in water intake and urine excretion
- No change in organ weight
- No notable change in blood pressure, heart rate or heart rhythm
- 3 HD dogs (1 female and 2 males) with bone marrow findings had the greatest exposure to conivaptan
- One HD female with anemia had focal necrosis, reduced hematopoietic tissue and reticuloendothelial hyperplasia
- One HD males had multiple focal necrosis and reticuloendothelial/myeloid hyperplasia in bone marrow. Another HD male had focal bone marrow fibrosis
- Elevated liver enzymes and total bilirubin at 8 WK in 1 HD male showed bile duct hyperplasia and sinusoidal leukocytosis
- TK parameters increased in dose-proportional manner.
- There were no notable sex differences in TK parameters
- Conivaptan levels on Day 1 was not different than WK13
- The 10 mg/kg/d dose was considered NOAEL in the 13-WK dog study. According to the sponsor, the exposure at NOAEL in dogs was approximately 2.7 to 3 X clinical dose based on AUC.

Study Title: 52-week oral capsule toxicity study with YM087 in dogs

Study No: RR 745-02781 ([redacted] 6478-150)
Amendment # 018, Vol #3/8 and page # 1-954
Conducting laboratory and location: [redacted]
Wisconsin 53704-2595

Date of study initiation: 11/09/1995
GLP compliance: Yes
QA- Report: Yes (x) No ()
METHODS: Dogs were randomized into five groups (4 dogs/sex/group). The YM087 was prepared in 50% w/w in lactose given daily in gelatin capsule based on most recently recorded body weights.

Dosing: 0, 1, 3, 10 and 20 mg/kg/day
species/strain: beagles
age:
weight:
satellite groups used for toxicokinetics or recovery: none
Drug, lot#, radiolabel, and % purity: YN0872Z and AEo873Z [redacted] nonlabled
Formulation/vehicle: 1:1, YM087 : lactose in gelatin capsule size no. 12, ¼ oz.
OBSERVATIONS AND TIMES:

Clinical signs:	Twice a day
Body weights:	Weekly
Food consumption:	Daily
Ophthalmoscopy:	Before and on Week 26 and 50
EKG:	Before and on Week 26 and 50. Blood pressure was recorded at the same time intervals.
Hematology:	A complete hematology test: packed cell volume (PCV), hemoglobin (Hb), red blood cell (RBC), white blood cells (WBC), hematocrit (Ht) or mean cell volume (MCV), platelet count (PC), hemoglobin (Hb), mean cell hemoglobin concentration (MCHC), were done on blood samples collected prior to and on Week 26 and 50.
Clinical chemistry:	Standard battery of clinical chemistry were done in over night fasted animals prior to and on Week 13, 26, 39 and 50. The tests included glucose, blood urea nitrogen (BUN), creatinine, bilirubin, cholesterol, triglycerides (TG), phospholipids, alkaline phosphatase (ALP), glutamic oxaloacetic transaminase (GOT or aspartate aminotransferase, AST), glutamic pyruvic transaminase (GPT or alanine aminotransferase, ALT). Heparinized plasma was used for CPK. Plasma Ca, Na, P, K, Cl and fractionates of plasma proteins.
Urinalysis:	Eight hour urine was collected from non-fasted animals prior to and on Week 1, 14, 26, 39 and 50. Sixteen hour urine sample were also collected post-dose from fasted animals. The following parameters were determined: pH, specific gravity (SG), protein, Na, K, Cl, glucose, ketone bodies, occult blood, urinary sediment, bilirubin, urobilinogen, appearance, volume, sodium, potassium, Na/K ratio, RBC, WBC, epithelial cells, bacteria and casts per power field were examined.
Gross pathology:	At the end of the study. See the addendum

Organ weights: At the end of the study. See the addendum
Histopathology: At the end of the study. See the addendum (page 44)

Toxicokinetics: Blood samples (approximately 3 ml) were collected from a jugular vein on Day 1 at approximately 2, 4, 8, and 2/l hours postdose and during Weeks 26 and 52 pre-dose and at approximately 2, 4, 8, and 24 hours postdose. Sodium heparin was used as the anticoagulant. Plasma was harvested and stored in a freezer set to maintain -70°C +-10° until analyzed. Plasma samples were analyzed by [redacted] using a HPLC method with a detection limit of [redacted] that was validated by [redacted] (I-BVI 6478-137). Toxicokinetic analyses included determinations for maximum plasma concentration (Cmax), and total area under the curve (AUC_{0-24}).

Statistical Analyses
The homogeneity of data was tested with Levene's test. Non-normally distributed data were analyzed using rank, or Log 10 transformed for further analysis. Analysis of variance was done on the homogeneous or transformed data. If the ANOVA was significant, Dunnett's t-test was used for pairwise comparisons between treated and control groups. One-way ANOVA was used to analyze initial body weights; body weight gains; food consumption; water consumption; heart rates; rectal body temperatures; respiration rates; blood pressure measurements; electrocardiographic parameters (PR, QRS, and QT intervals); clinical chemistry and hematology values; urine osmolality, volume, and pH; urine chemistry values; organ weights; and organ-to-body weight percentages. One-way ANCOVA was used to analyze body weights, with initial body weights as the covariate using untransformed data. If the ANCOVA was significant, least squares means t-test (SAS, 1989) was used for pairwise comparisons between treated and control groups. P value equal to and less than 0.05 was considered significant.

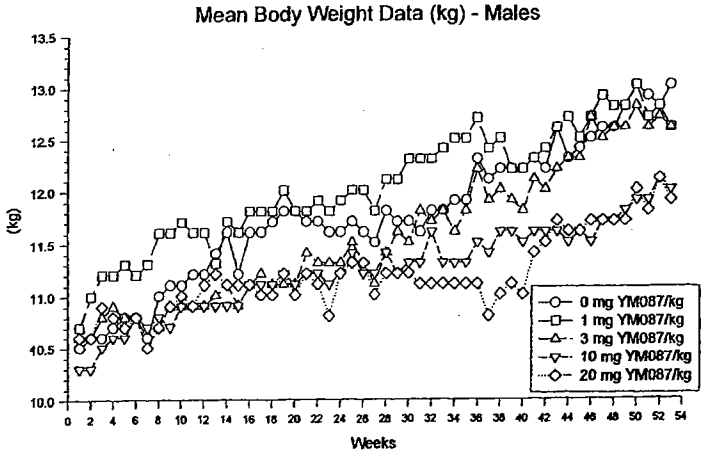
RESULTS:
Clinical signs:

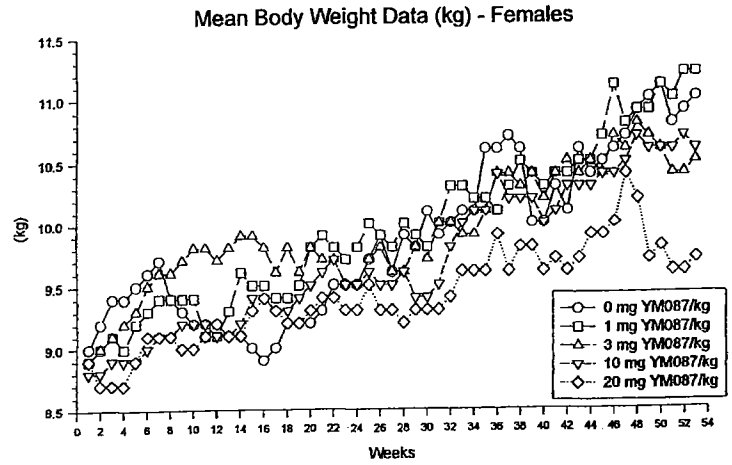
- All animals survived to the end of the study.
- Pale mucous membrane of the oral mucosa and hypoactivity was seen in two (2/4) HD males (day 44 and 283), perhaps due to anemia.
- Red discolored feces (positive for blood) in one male in MHD and in one control female. All females (except for one control) had evidence of estrous heat/estrous bleeding on 2 or 3 occasions before study termination.

Body weights: The differences in the body weight were not statistically significant. With the covariate adjusted mean, body weights for the males in the MD, MHD and HD group were lower than controls. Similar observations (with covariate adjustment) were noted in MDH and HD females.

	Percent change in Body weight relative to control at WK 52		
	MD, 3 mg/kg/day	MHD, 10 mg/kg/day	HD, 20 mg/kg/day
Males	-3	-7.6	-8.4
Females	-4.5	-4.5	-11.8

	Percent change in Body weight gain relative to control at WK 52		
	MD, 3 mg/kg/day	MHD, 10 mg/kg/day	HD, 20 mg/kg/day
Males	-20	-32	-48
Females	-20	-10	-60





Food consumption: Except for incidental change, food intake of YM087 treated dogs were similar to controls. One male in HD group has several days of low food intake that corresponded to lower body weight.

Water Consumption: YM087 treatment increased water consumption in a dose-dependent manner in both males and females.

	Percent change in water intake relative to control at WK 52			
Dogs	1 mg/kg/day, LD	3 mg/kg/day, MD	10 mg/kg/day, MHD	20 mg/kg/day, HD
Males	-6	66	29	116
Females	99	97	73	100

Physical, Cardiovascular, ECG analysis:

- Mean heart rate, respiration rate and rectal temperature at WK 26 and 50 in treated animals were similar to controls.
- The Q-T interval during WK 50 was prolonged in all doses of YM087 in females relative to controls. Whether this was related to the compound is not clear since the control female dogs had shorter than normal Q-T interval because of slightly higher heart rate.
- The increase in blood pressure in the 10 mg/kg males at WK 26 but not at 50 WK was considered unrelated to test drug. Although the HD males had slightly higher BP than controls, it was not significant.

Ophthalmology: No ophthalmic lesions were found except for one female at 10 mg/kg had retinal bleeding in one eye. Retinal dysplasia was also seen in both eyes of a HD male.

Hematology:

- At 39 WK, the 20 mg/kg/day dosed males had lower RBC, platelet, hemoglobin and WBC.
- The overall hematological changes in other treated group were not significant.
- Most notable hematological findings in HD males are presented in table below.

Table 2.6.6-49: 52-week repeat-dose oral toxicity study in dogs – hematology [R087-TX-048]

Daily Dose (mg/kg)	0		1		3		10		20	
Number of Animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Hematology										
RBC (10^6/µL)										
Pretreatment	7.05	6.72	6.65	6.55	6.72	6.48	6.85	7.00	6.35	6.62
Week 13	7.00	6.75	6.65	6.95	6.90	6.50	6.90	7.10	6.25	6.65
Week 26	6.70	6.92	6.65	6.95	7.15	6.85	6.82	7.02	6.28	6.42
Week 39	7.00	6.88	6.98	6.98	7.08	6.58	7.08	7.20	5.52*	6.88
Week 50	7.30	6.98	6.88	7.35	7.20	6.95	7.20	7.38	6.45	6.58
Hemoglobin (g/dl)										
Pretreatment	16.2	16.2	15.9	15.8	16.0	16.2	16.2	16.2	15.4	16.1
Week 13	16.2	16.3	16.1	17.1	16.6	16.3	16.6	16.7	15.1	16.1
Week 26	15.6	16.9	16.5	17.1	17.2	17.3	16.3	16.6	15.2	15.8
Week 39	16.4	17.0	17.2	17.3	17.2	16.6	17.2	17.3	13.2	17.0
Week 50	17.0	17.1	17.1	18.2	17.5	17.6	17.6	17.7	15.6	16.2
PCV (%)										
Pretreatment	45.8	45.7	45.2	45.1	45.5	45.0	46.0	45.6	43.1	45.6
Week 13	45.4	45.1	45.1	47.4	46.1	44.8	46.2	46.7	42.2	45.3
Week 26	43.9	47.1	45.8	47.5	48.0	47.8	45.8	46.2	42.0	44.0
Week 39	45.7	46.6	47.9	47.5	47.4	45.8	47.7	47.5	36.8	47.2
Week 50	47.5	47.8	47.7	50.5	48.2	48.4	49.0	48.9	43.1	45.1

Clinical chemistry:

- At 39 WK, the HD males had significantly higher globulin, lower albumin levels, which corresponded with similar decline in hematological parameters at WK 39.
- GOT levels in two HD males doubled at various time point, starting WK 26.
- Most notable difference in HD males are noted in table below.

Table 2.6.6-49: 52-week repeat-dose oral toxicity study in dogs – [R087-TX-048]

Daily Dose (mg/kg)	0		1		3		10		20	
Number of Animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Albumin (g/dL)										
Pretreatment	4.2	4.2	4.2	4.2	4.2	4.1	4.3	4.0	4.1	4.4
Week 13	4.1	4.0	4.0	4.2	4.0	4.0	4.0	4.0	3.8	3.9
Week 26	4.2	4.2	4.1	4.2	4.2	4.2	4.0	3.9	4.0	4.0
Week 39	3.9	4.1	3.9	4.1	3.9	3.8	3.9	3.7*	3.5	3.9
Week 50	4.0	4.0	3.8	4.0	3.9	4.0	3.8	3.8	3.5	3.8
Globulin (g/dL)										
Pretreatment	2.1	1.9	1.9	1.9	1.9	2.0	1.9	1.9	2.0	2.0
Week 13	2.6	2.4	2.2	2.3	2.6	2.5	2.4	2.4	2.8	2.5
Week 26	2.6	2.3	2.2	2.2	2.3	2.3	2.4	2.3	2.8	2.2
Week 39	2.8	2.6	2.3	2.3	2.6	2.6	2.7	2.5	3.5*	2.6
Week 50	2.8	2.6	2.4	2.4	2.7	2.5	2.8	2.7	3.5*	2.7
A/G Ratio										
Pretreatment	2.0	2.2	2.2	2.2	2.2	2.1	2.3	2.2	2.0	2.2
Week 13	1.6	1.7	1.8	1.8	1.6	1.6	1.7	1.7	1.4	1.6
Week 26	1.6	1.8	1.9	2.0	1.8	1.8	1.7	1.8	1.4	1.8
Week 39	1.4	1.6	1.7	1.8	1.5	1.5	1.5	1.5	1.0*	1.5
Week 50	1.4	1.6	1.6	1.7	1.4	1.6	1.4	1.4	1.0*	1.4

Dunnett's test: * - P<0.05

Urinalysis:

- All treated animals had a dose-depend and significantly higher urine volumes, lower urine osmolality, and lower urine creatinine levels at 1 week. These findings diminished with time (WK1 vs. WK14, 26, 39 and 50).
- The total urine electrolyte excretion in treated group and control were similar.
- All treated animals had higher incidence of positive urine occult than controls during WK 1. This finding was not consistent at later sampling time intervals.

Table 2.6.6-52: 52-week repeat-dose oral toxicity study in dogs – urinalysis [R087-TX-048]

Daily Dose (mg/kg)	0		1		3		10		20	
No. of Animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
8 hr - Volume (mL)										
Pretreatment	85	60	74	35	55	52	45	43	42	49
Week 1	48	84	994*	1288*	1149*	1150*	871*	793*	1013*	1347*
Week 14	69	48	66	549*	437*	376*	204	283	474*	275
Week 26	58	50	54	299	335	293	138	170	200	172
Week 39	37	47	42	284*	167	209	142	172	187	141
Week 50	84	66	113	312	418	206	178	246	336	220
16 hr - Volume (mL)										
Pretreatment	125	152	84	91	73	92	77	91	140	110
Week 1	67	90	690	729	1265*	1756*	1318*	1331*	1556*	1559*
Week 14	145	120	98	202	426	330	297	356	780*	309
Week 26	64	167	70	185	405*	209	268	354	572*	206
Week 39	95	107	102	260	526*	359	237	274	465*	437
Week 50	82	98	135	321	612*	222	227	348	556*	338
24 hr - Volume (mL)										
Pretreatment	210	211	158	126	128	144	121	134	182	158
Week 1	115	174	1684*	2017*	2413*	2906*	2190*	2123*	2569*	2906*
Week 14	214	167	164	751*	862*	706*	501	638	1254*	584
Week 26	122	217	124	484	740*	503	407	524	772	378
Week 39	132	154	144	544	693*	567	379	446	652*	578
Week 50	166	164	248	633	1030*	428	405	594	892*	558
Osmolality (mOsm/kg)										
Pretreatment	1677	1519	1750	1654	1954	1902	1833	2066	1578	1806
Week 1	2036	1820	218*	219*	180*	138*	232*	147*	116*	170*
Week 14	2341	1578	1109*	721*	690*	821*	919*	608*	529*	664*
Week 26	2590	1666	1570*	831*	832*	745*	1018*	618*	715*	868*
Week 39	2364	1533	1358*	525	565*	744	1022*	734	606*	566
Week 50	2188	2016	1342	696*	574*	949*	1018*	847*	820*	780*

Dunnett's test: * - P<0.05

Gross pathology:

- No esophageal dilatation was noted in any of dogs in contrast to esophageal findings in chronic rat studies.
- Macroscopic findings (i.e. alopecia) were considered normal in laboratory dogs.

Organ Weights:

- There were no significant differences in absolute organ weights among groups.
- The relative liver to body weight was higher in HD females by 22%.

Histopathology:

- One HD male (H09257) had multifocal bone marrow necrosis in the sternum and femur. The distal epiphysis had increased marrow cellularity suggesting hematopoietic hyperplasia. No other animal showed any bone marrow changes. This animal also had degenerative necrosis of heart.
- Vascular inflammation in the epididymides of 2 males treated with 20 mg/kg/d characterized by fibrinoid degeneration and necrosis of all layers of the arterial vessel walls.
- Atrophy of testes were noted in one LD, MHD and HD male.
- Endocardiosis of heart valve was noted in one HD female.

Histopath Findings in dogs treated with YM087 for 52-week

Tissue	Sex	Dose, mg/kg/day				
		0	1	3	10	20
Adrenal Cortex	M	2	0	0	1	0
Vaculation, Zona glomerulosa	F	0	1	0	0	1
	M	0	0	0	0	1
Vaculation, Zona reticularis	F	0	1	1	0	0
Bone Marrow,	M	0	0	0	0	1
Hyperplasia, hematopoietic Femur	F	0	0	0	0	0
	M	0	0	0	0	1
Necrosis, Femur	F	0	0	0	0	0
	M	0	0	0	0	1
NECROSIS, STERNUM	F	0	0	0	0	0
Heart	M	0	1	0	0	1
Degenerative/ necrosis	F	0	0	0	0	0
	M	0	0	0	0	0
Endocardiosis, heart valve	F	0	0	0	0	1
Liver	M	1	2	2	0	3
Hematopoiesis, extramedullary	F	1	1	2	2	2
Pancreas	M	0	1	0	0	0
Increased individual cell necrosis	F	0	0	1	0	0
Lung/Bronchi	M	0	3	1	3	4
Infiltrate, macrophage	F	1	2	1	1	3
	M	0	0	0	0	3
Inflammation, Acute	F	0	0	1	0	1
Urinary Bladder	M	0	0	0	0	0
Mineralization, vascular	F	0	0	0	1	1
Testes,	M	0	1	0	1	1
Degeneration/atrophy						
Epididymides,	M	0	0	0	0	2
Necrosis of vessel inflammatory cells						

Table 2.6.6-53: 52-week repeat-dose oral toxicity study in dogs – histopathology [R087-TX-048]

Daily Dose (mg/kg)	0		1		3		10		20	
Number of Animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Femur/Bone Marrow [a]:										
Hyperplasia, hematopoietic	0	0	0	0	0	0	0	0	1	0
Necrosis, marrow	0	0	0	0	0	0	0	0	1	0
Sternum/Marrow [a]:										
Necrosis, marrow	0	0	0	0	0	0	0	0	1	0

a - Number of animals affected.

Toxicokinetics:

- Drug exposure increased with increasing dose up to 10 mg/kg/d. The exposure at 20 mg/kg/d increased in males but not in females.
- With repeated drug administration, conivaptan exposure increased from Day 1 to WK 26 at 3, 10 and 20 mg/kg/d, suggesting that conivaptan inhibits its metabolizing enzyme, CYP3A4, leading to drug accumulation. Conivaptan is metabolized by and is a powerful inhibitor of CYP3A4.
- PK parameters during WK 26 were similar to WK52.
- At 52 WKS, the Cmax and AUC of males and females were nearly similar; however, males appeared to have higher histopath findings.
- The male with bone marrow necrosis had significant drug exposure (AUC 16419 ng.h/ml, Cmax 9150 ng/ml)

Table 2.6.6-54: 52-week repeat-dose oral toxicity study in dogs – toxicokinetics [R087-TX-048]

Daily Dose (mg/kg)	1		3		10		20	
Number of Animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
C_{max} (ng/mL):								
Day 1	318	380	610	1146	2128	2715	3324	2567
Week 26	356	333	917	769	3728	5865	6895	4950
Week 52	292	339	659	979	4590	6193	5744	5285
AUC_{0-24} (ng·hr/mL) :								
Day 1	2959	3077	5720	12146	28815	41362	53842	38834
Week 26	3661	3056	9172	8347	54174	95080	114862	88385
Week 52	2878	3276	7051	13485	75092	111683	97202	87844

KEY STUDY FINDINGS:

- Dogs were treated with 1, 3, 10 and 20 mg/kg/d of conivaptan in capsule for 52 wks.
- The 20 mg/kg/day caused a periodic decrease in food consumption, body weight in two males. These two animals also had pale mucus membrane, increased plasma globulin and elevated GOT.
- Urine volume significantly increased with increasing dose level but with repeated administration, urine volume returned to normal levels. The aquaretic effect of conivaptan subsided with chronic administration in spite of drug accumulation overtime.
- Total urine osmolality was similar to control in all animals.
- Bone marrow necrosis was seen in one out of four HD males but none of the females. The bone marrow necrosis was associated with the highest drug exposure.
- Degenerative heart tissue necrosis was noted in one low dose male (1 mg/kg). The significance of this finding at low dose is not clear.
- Heart valve endocardiosis was noted in one female treated with 20 mg/kg YM087.
- The highest AUC (16419 ng.hr/ml) HD male had bone marrow necrosis.
- The two other males with slightly lower AUC had epididymal vasculitis. One male in LD, MHD and HD had degenerative atrophy of testes.
- The NOAEL dose was 10 mg/kg/d. The drug exposure at the NOAEL was 21-31 x greater than IV clinical dose based on AUC.

Drug exposure relative to clinical dose

Toxicology Study	Dose, mg/kg/d	AUC_{0-24} ng.h/ml	Animal to human dose exposure ratio
52-WK oral dog toxicology study	1	M: 2878, F: 3276	M: 0.8 F: 0.9
	3	M: 7051 F: 13485	M: 2 F: 3.8
	10, NAOEL	M: 75092 F: 111683	M: 21 F: 31
	20	M: 97202 F: 87844	M: 27 F: 24.5
Clinical Dose: 20 mg bolus + 40 mg IV infusion for 4 days, average daily AUC		3580	

SUMMARY

The most significant findings were limited to males given 20 mg/kg/day. Clinical observations of pale mucous membranes and hypoactivity were seen in two of four males given 20 mg/kg/day. Periodic slightly lower body weights, body weight gains, and food consumption were observed in these same two males given 20 mg/kg/day. Pale mucous membrane and hypoactivity finding appear primarily due to lower red cell mass (anemia). Histopathologic findings in the bone marrow (necrosis and hematopoietic cell hyperplasia) were evident in one of three males with clinical pathology findings (decreased red blood cell count, hemoglobin concentration, and hematocrit).

Other clinical pathology findings observed in association with the findings described above (pale mucous membranes, anemia, body weight loss, low food consumption) were increased plasma globulin and decreased plasma albumin and elevated GOT in two of the animals. In this study, the toxicological significance of these plasma protein and liver enzyme changes is unknown. The two males that had anemia also had histopathologic evidence of epididymal vasculitis. The cause of this vasculitis is unknown, but because these two animals had other adverse test material-related findings and because a similar vasculitis was not observed in controls or at lower test material treatment levels, a test material relationship to this finding cannot be ruled out.

At Week 52, the Cmax value of one male with bone marrow necrosis was 9,820 ng/ml. The Cmax values of the two males with vasculitis were 5,560 and 8,510 ng/ml suggesting that high plasma concentration of the drug was responsible for the toxicological effects in the two males.

The TK data suggests accumulation of YM087 in plasma with repeated treatments. Since YM087 is substrate to CYP 3A4 and strongly inhibits this P-450 isozyme, drug accumulation and drug interaction may become critical. Whether, YM087 alters blood flow or total vascular resistance is not known. Although there were no significant changes in blood pressure and heart rate, a significant decrease in blood flow to vital organs may occur due to significant dehydration and aquaresis. In addition, YM087 may alter plasma reproductive hormones by direct effect or via ACTH, ADH and plasma volume contraction produced by significant aquaresis.

Histopathology inventory (optional)

Study	R087-TX-007	R087-TX-008	R087-TX-045	R087-TX-046	R087-TX-048
Species	4WK Rat, IV	4WK Dog IV	6-Mo rat	26-WK rat	52-Wk dog
Adrenals	X*	X*	X*	X*	X*
Aorta	X	X	X	X	X
Bone Marrow smear	X	X	X	X	X
Bone (femur)	X	X	X	X	X
Brain	X*	X*	X*	X*	X*
Cecum	X	X	X	X	X
Cervix	X*	X*	X*	X*	X*
Colon	X	X	X	X	X
Duodenum	X	X	X	X	X
Epididymis	X	X	X	X	X
Esophagus	X	X	X	X	X
Eye	X	X	X	X	X
Fallopian tube					
Gall bladder	X		X	X	X
Gross lesions	X	X	X	X	X
Harderian gland	X	X	X	X	X
Heart	X*	X*	X*	X*	X*
Ileum	X	X	X	X	X
Injection site					
Jejunum	X	X	X	X	X
Kidneys	X*	X*	X*	X*	X*
Lacrimal gland	X	X	X	X	X
Larynx					
Liver	X*	X*	X*	X*	X*
Lungs	X*	X*	X*	X*	X*
Lymph nodes, cervical					
Lymph nodes mandibular	X	X	X	X	X
Lymph nodes, mesenteric	X	X	X	X	X
Mammary Gland	X	X	X	X	X
Nasal cavity					
Optic nerves	X	X	X	X	X
Ovaries	X*	X*	X*	X*	X*
Pancreas	X	X	X	X	X
Parathyroid	X*	X*	X*	X*	X*
Peripheral nerve	X	X	X	X	X
Pharynx					
Pituitary	X*	X*	X*	X*	X*
Prostate	X*	X*	X*	X*	X*
Rectum	X	X	X	X	X
Salivary gland	X*	X*	X*	X*	X*
Sciatic nerve	X	X	X	X	X
Seminal vesicles	X*	X*	X*	X*	X*
Skeletal muscle	X	X	X	X	X
Skin	X	X	X	X	X
Spinal cord	X	X	X	X	X
Spleen	X*	X*	X*	X*	X*
Sternum	X	X	X	X	X
Stomach	X	X	X	X	X
Testes	X*	X*	X*	X*	X*
Thymus	X*	X*	X*	X*	X*
Thyroid	X*	X*	X*	X*	X*
Tongue	X	X	X	X	X
Trachea	X	X	X	X	X
Urinary bladder	X	X	X	X	X
Uterus	X*	X*	X*	X*	X*
Vagina	X	X	X	X	X
Zymbal gland					

X, histopathology performed, * organ weight obtained

6.6.6.4 Genetic toxicology

The sponsor had submitted an Ames assay, chromosomal aberration using human peripheral blood lymphocytes and *in vivo* rat micronucleus assay. The Ames assay in Salmonella Typhimurium (TA98, TA100, TA1530 and TA1537) and E.coli (WP2uvrA) with and without metabolic activation (S9mix), conivaptan did not significantly increase the number of revertant colonies following conivaptan treatment. In the *in vitro* human lymphocyte assay, conivaptan induced chromosomal aberrations were similar to negative controls with and without metabolite activation. Sporadic and borderline slight increase in polyploidy was not dose dependent thus not considered significant. *In vivo* rat chromosomal aberration study, conivaptan did not significantly increase polychromatic erythrocytes or micronucleated polychromatic erythrocytes/1000 cells. In summary, under the assay conditions, conivaptan was not genotoxic.

2.6.6.5 Carcinogenicity

Carcinogenicity Summary:
The carcinogenicity potential of conivaptan has been evaluated following lifetime exposure in rodent bioassays. Conivaptan was given to mice by oral gavage to males at 3, 10, 30 mg/kg/d and 1, 3, 10 to females. In rats oral gavage doses of 0.3, 1, 3, 10 (males) and 1, 3, 10, 30 mg/kg/d (females) were given for 104 weeks. Significant tumorigenicity was not observed.

Study title: 104-Week carcinogenicity Gavage Study of YM087 in mice

Key study findings:
Sixty male and female mice/dose in the main study and 25/dose in the toxicokinetic study were given conivaptan hydrochloride in 0.5% methylcellulose by oral gavage for 104 weeks and 52 weeks, respectively. Male mice were treated with 3, 10 and 30 mg/kg/d (0.1, 1 and 6 x human dose based on $AUC_{0\text{-}24}$) and females with 1, 3 and 10 mg/kg/d (0.03, 0.2 and 2.5 x human dose based on $AUC_{0\text{-}24}$). Controls received 0.5% methylcellulose solution. Approximately 27 male mice at 30 mg/kg/d died within the first two weeks and were replaced. The survival rate in the 104-WK study in male mice were 80, 86, 85 and 78% at 0, 3, 10 and 30 mg/kg/d, respectively and 79, 75, 65 and 75% in females at 0, 1, 3 and 10 mg/kg/day, respectively. Consistent with the pharmacological effects of conivaptan, a significant dose-dependent increase in urinary output were noted. In addition urinary obstruction, distended abdomen and swollen abdomens were noted in treated groups. Although final body weights were similar, a significant decease in BW gain in the males at 10 and 30 mg/kg/d at WK 78 relative to controls (92.6 and 88.8% of control, respectively) were observed. The water intake in males at 3, 10 and 30 mg/kg/d was 140, 272, 438% of control, respectively and in females at 1, 3 and 10 mg/kg/day was 118, 174 and 389% of control, respectively. Marked increase in water consumption in HD males was associated with urinary bladder distention, renal pelvis dilatation and bladder epithelial hyperplasia. Absence of bladder distention in HD females may in part be related to anatomical differences in the urinary tract of males and females. No significant dose-related increase in mortality was noted in 2-year mouse study. At the end of the study, there were 12, 12, 9 and 13 dead male mice (0, 3 , 10 and 30 mg/kg/d) and 15, 17, 22 and 15 death female mice (0, 1, 3 and 10 mg/kg/d) with respective doses. At final necropsy, a slightly higher incidence of renal cysts (Male: 1, 3, 2, 4 and Female: 0, 0, 1, 1) and bladder distention (M:1, 1, 6, 23 and F:0, 0, 0, 2) were noted in conivaptan treated mice at corresponding doses (M:0, 3, 10, 30 mg/kg/day and F:0, 1, 3 and 10 mg/kg/day). There was no significant conivaptan-related increase in incidence of tumors in the 2-year mouse study. ECAC reviewed the study results on 8/3/04 and considered the study adequate based on deaths at 30 mg/kg/d.

Adequacy of the carcinogenicity study and appropriateness of the test model:
The study was initiated by the sponsor without concurrence with the eCAC. Dose selection by the sponsor was based on the 13-WK dose ranging study in mice (females: 1, 3, 10 mg/kg/d; males: 3, 10, 30 mg/kg/d). In this study, the 30 mg/kg/d reduced BW gains in males by 16% with no notable histopathology at any dose. In addition 1 male at 30 mg/kg/d group was found dead and considered to be drug-related. Therefore for males, 30 mg/kg/d dose was selected as MTD. For the females, the high incidence of mortality (4/5 females) in the 2-WK study at 30 mg/kg/d suggested that 30 mg/kg/d had exceeded the MTD thus 10 mg/kg/d was considered HD for females. In the carci study, the large mortality in males at 30 mg/kg/d in the first two weeks, suggest that 30 mg/kg/d had also exceeded the MTD in males.

Evaluation of tumor findings:
Trend analysis found no significant increase in incidence of neoplastic tumors. Conivaptan did not increase incidence of tumors at any dose. The incidence of renal cysts was higher in conivaptan treated mice; however, it was only significant at 10 mg/kg/d in female mice.

Study no.: R087-TX-054 (20003912, [redacted] #6478-193)
Volume #, and page #: 1-5, 1-2023
Conducting laboratory and location: [redacted]
Date of study initiation: May 20, 1997 (End date June 11, 99; Final report Aug 29, 2003)
GLP compliance: yes
QA report: yes (x) no ( )
Drug, lot #, and % purity:

Lot No.	Date Received	Weeks Used	Purity
BC0874Z	April 28, 1997	Prestudy - Week 49	[redacted]
BC0874Z	April 30, 1998	Weeks 50 - 63	
08701	July 2, 1998	Weeks 64 - 106	[redacted]

CAC concurrence: No
Methods

Doses: males: 3, 10 and 30 mg/kg/day & females: 1, 3, 10 mg/kg/day

Group	Dosage Level mg/kg/day	Concentration mg/mL	Number of Animals[a] Male	Number of Animals[a] Female	Animal Numbers Male	Animal Numbers Female
Main Study						
1 (Control)	0	0.0	60	60	A66359-A66418	A66419-A66478
2 (Low)	1	0.1	-	60	-	A66479-A66538
3 (Mid)	3	0.3	60	60	A66539-A66598	A66599-A66658
4 (Mid-High)	10	1.0	60	60	A66659-A66718	A66719-A66778
5 (High)	30	3.0	60	-	A66779-A66838	-
Satellite Study						
2 (Low)	1	0.1	-	25	-	A66839-A66863
3 (Mid)	3	0.3	25	25	A66864-A66888	A66889-A66913
4 (Mid-High)	10	1.0	25	25	A66914-A66938	A66939-A66963
5 (High)	30	3.0	25	-	A66964-A66988	-

[a] Satellite Study animals include 20, 4 mice/timepoint, as well as 5 spare mice/sex/group as possible replacements.

Basis of dose selection (MTD, MFD, AUC etc.): MTD (decrease in BW gain by16%)
Species/strain: B6C31F1, [redacted]BR VAF/Plus® mice
Number/sex/group (main study): 60/sex/dose + 25/sex/dose for TK
Route, formulation, volume: oral gavage solution at 900 hr, vehicle was 0.5% methylcellulose aqueous solution, 10 ml/kg/day
Frequency of dosing: once a day
Satellite groups used for toxicokinetics or special groups: yes (at interim 53–WK)
Age: 22 to 24 days old, [redacted] (dosed at 36 to 42 days of age)
Animal housing: Stainless steel cages, housed in pairs and fed [redacted] Rodent diet#5002
Restriction paradigm for dietary restriction studies: Mice were fed ad lib
Drug stability/homogeneity: stable for 2 years
Dual controls employed: single control group (10 ml/kg of 0.5 methylcellulose)
Interim sacrifices: No
Deviations from original study protocol: eCAC concurrence was not obtained. The noted changes were not significant, change in room label; incidences of water intake data loss, skipped physical exam, 1 mouse had no access to water for 20 hrs, 1 satellite male mouse (3mkd) was accidentally killed/washed with the dirty cage. Most deviation didn't appear to be critical to integrity of the carci study.

Observation times

Mortality: daily
Clinical signs: daily
Body weights: once a week
Food consumption: weekly
Histopathology: Peer review: yes (x), no ( )
Toxicokinetics: Yes, (Blood samples: 1, 2, 4, 8 and 24 hr at WK 53, satellite group)

Results

Mortality:

- There were no significant differences in the survival rates or dose-related trends excluding the accidental deaths. The survival rates for males at WK 104 were 80, 86, 85 and 78% at 0, 3, 10 and 30 mg/kg/d, respectively. For females the survival rates were 79, 75, 65 and 75% at 0, 1, 3 and 10 mg/kg/day, respectively. The most common cause of death was hepatocellular neoplasm in males and hematopoietic neoplasm in females.
- Dead animals during the first 2 weeks were replaced (1 LD female, 1 MD female, 27 HD males in the main study and 11 HD males in the satellite group)
- Accidental deaths were not included in the survival rate calculations

Table 2.6.6-74: Carcinogenicity study in mice – survival data [R087-TX-054]

Daily Dose (mg/kg)		0		1	3		10		30
Gender		M	F	F	M	F	M	F	M
Animals:	Assigned	60	60	60	60	60	60	60	60
	Week 26	60	60	60	58	58	59	60	59
	Week 52	59	59	60	58	58	58	60	59
	Week 78	57	57	58	54	54	57	56	58
Terminal Sacrifice:		48	45	43	48	38	51	45	47
Survival at Week 104 (%):		80	79	75	86	65†	85	75	78

Cox-Tarone Binary Regression Methods or Gehan-Breslow Nonparametric Methods: †- P<0.01

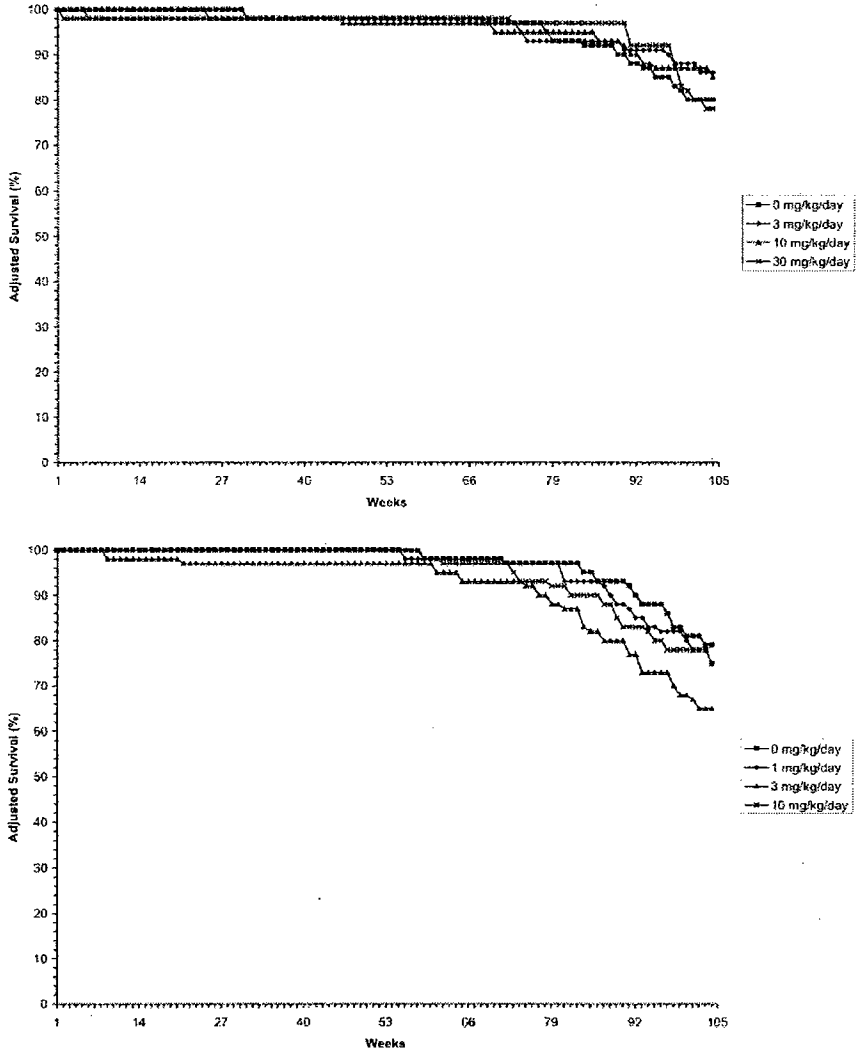
Deaths listed below were not included in mortality rate calculations. High dose males that died during the first 2-weeks possibly due to acute dehydration were replaced. In addition, 5 mice died due to accidents (i.e. cage clean up) during the course of the 2-year study. The accidental deaths were not included in the survival rate calculations but examined histologically*.

Number of dead mice in the 2-year carci study		Carci doses in mice, mg/kg/day				
		0 (M, F)	1 (F)	3 (M, F)	10 (M, F)	30 (M)
Main study, (replaced)	M					27
Deaths during First 2 WKs,	F		1	1		
Satellite group, (replaced)	M					11
Deaths during First 2WKs,	F					
Main study, (not replaced) *	M			3		
Accidental deaths, not drug related	F	1		1		
6Satellite group, (not replaced)	M			1		
Accidental deaths, not drug related	F			3		

*One male (3mkd) was accidentally killed during the cage wash and another was found dead after dosing with head stock in automatic water system. A control female was found outside of the cage and removed from the study.

Survival rate in mice

Males



Clinical signs:

- Due to high mortality in the males at 30 mg/kg/d, males that appeared hypoactive were not dosed during the first week. Animals that died in the first two weeks were replaced.
- Consistent with the pharmacological effects of conivaptan, a significant dose-dependent increase in urinary output, urinary obstruction, distended abdomen, swollen abdomen (ventral, right and left) swollen perineal are were noted.
- A dose-related increase in incidence of urine stains in males was possibly related to powerful diuretic effect of conivaptan.
- Treated mice consumed up to 4 fold more water and excreted large quantities of urine than controls and often had swollen abdomen due to full urinary bladder (especially MD and HD males).

Body weights:

- Significant decease in BW gain in the males at 10 and 30 mg/kg/d at WK 78 relative to controls. The body weight in the 1, 10 and 30 mg/kg/d males were 97.1, 92.6 and 88.8% of control, respectively. The final BW and BW gains were not different from controls.

Table 2.6.6-75: Carcinogenicity study in mice – body weight [R087-TX-054]

Daily Dose (mg/kg)	0		1	3		10		30
Gender	M	F	F	M	F	M	F	M
Body Weight (g): Week 26	32.2	29.4	28.9	32.6	29.2	31.4	29.7	31.3
Week 52	39.4	36.3	35.4	38.3	34.8	37.4*	35.0	35.9*
Week 78	41.9	38.9	38.2	40.7	38.2	38.8*	37.1	37.1*
Week 104	38.7	36.6	35.6	38.8	36.4	38.2	36.3	38.3
Bodyweight Gain (Weeks 1-104):								
(g)	16.4	17.2	16.4	16.6	18.0	16.0	17.4	16.3
(% of Control)	-	-	95	101	105	98	101	99

Dunnett's Test: * - P<0.05

Food consumption:

- There were incidental increases in food intake at 10 and 30 mg/kg/d males and 10 mg/kg/d dosed females at WK104.

Table 2.6.6-76: Carcinogenicity study in mice – food consumption [R087-TX-054]

Daily Dose (mg/kg)	0		1	3		10		30
Gender	M	F	F	M	F	M	F	M
Food Consumption (g/day):								
Week 25	6.5	6.2	6.3	6.7	6.4	6.6	6.3	6.5
Week 53	6.6	6.7	6.6	6.6	6.7	6.8	6.8	6.9
Week 77	6.1	6.5	6.3	6.0	6.4	6.4	6.3	6.5*
Week 104	6.3	6.7	6.5	6.1	7.2	6.7*	7.3*	7.5*

Dunnett's Test: * - P<0.05

Water Consumption:

- A dose-related increase in water intake was due to aquaretic effect of conivaptan.
- The water intake were 140, 272, 438% of control at 3, 10 and 30 mg/kg/d in males and 118, 174 and 389% of control at 1, 3 and 10 mg/kg/day in females, respectively.

Table 2.6.6-77: Carcinogenicity study in mice – water consumption [R087-TX-054]

Daily Dose (mg/kg)	0		1	3		10		30
Gender	M	F	F	M	F	M	F	M
Water Consumption (mL/day):								
Week 26	6.0	6.3	7.3*	7.6*	11.1*	14.8*	22.4*	21.1*
Week 52	5.3	5.8	7.2*	7.5*	10.9*	15.0*	22.4*	24.8*
Week 78	5.8	6.5	7.0	7.6*	9.9*	15.1*	24.6*	27.0*
Week 104	6.4	6.5	7.2	9.0*	12.7*	19.9*	30.3*	32.5*

Dunnett's Test: * - P<0.05

Gross pathology:

Notable macroscopic findings in mice "unscheduled deaths"

- Unscheduled deaths in males:12, 12, 9 and 13 (0, 3 , 10 and 30 mg/kg/d, respectively)
- Unscheduled deaths in females: 15, 17, 22 and 15 (0, 1, 3 and 10 mg/kg/d, respectively)
- There were no clear treatment-related increase in deaths or macroscopic findings except for possibly slight overall increase in incidence of liver mass (M:2, 4, 2, 6 and F:1, 3, 4, 1), bladder distention (M:1, 1, 3, 6 and F:1, 0, 3, 1) at respective male (0, 3, 10 and 30 mg/kg/d) and female doses (0, 1, 3 and 10 mg/kg/d).

Incidence of Macroscopic Observations - Unscheduled Deaths

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN MICE

TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=1-106 DEATH=UNSCHED;SUBSET=ALL		-- NUMBER-OF-ANIMALS-AFFECTED --									
	SEX:	----------MALE----------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND KEYWORD(S) OR PHRASE	NUMBER:	12	0	12	9	13	15	17	22	15	0
*** TOP OF LIST ***											
BRAIN W/STEM (BR)	NUMBER EXAMINED:	12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:	11	0	11	7	13	13	16	15	12	0
SOFT		1	0	1	2	0	0	1	5	2	0
ENLARGED		0	0	0	0	0	1	0	0	0	0
DARK AREA		0	0	0	0	0	1	0	0	0	0
VENTRAL SURFACE, INDENTED		0	0	0	0	0	0	0	1	1	0
H-VENTRAL SURFACE INDENTED		0	0	0	0	0	1	0	1	0	0
PITUITARY (PI)	NUMBER EXAMINED:	12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:	12	0	12	9	13	10	17	20	13	0
DARK		0	0	0	0	0	4	0	0	1	0
ENLARGED		0	0	0	0	0	3	0	1	2	0
H-ENLARGED		0	0	0	0	0	0	0	1	0	0
H-RAISED AREA		0	0	0	0	0	1	0	0	0	0
LUNG (LU)	NUMBER EXAMINED:	12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:	10	0	10	6	11	14	15	16	13	0
DARK		1	0	2	2	1	1	1	1	1	0
MOTTLED		0	0	0	0	0	0	1	2	0	0
MASS		0	0	0	1	1	1	0	4	0	0
LUNG (LU)	NUMBER EXAMINED:	12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:	10	0	10	6	11	14	15	16	13	0
PALE AREA		0	0	0	0	0	0	0	1	0	0
PALE		0	0	0	0	0	0	0	0	1	0
FAILURE TO COLLAPSE		1	0	0	0	0	0	0	0	0	0
HEART (HT)	NUMBER EXAMINED:	12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:	12	0	11	9	13	15	17	22	15	0
ENLARGED		0	0	1	0	0	0	0	0	0	0
SPLEEN (SP)	NUMBER EXAMINED:	12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:	9	0	6	4	13	7	6	13	5	0
ENLARGED		3	0	5	4	0	8	11	8	10	0
SMALL		0	0	1	1	0	0	0	1	0	0
PALE AREA		0	0	0	1	0	0	0	0	0	0
MOTTLED		2	0	1	0	0	2	2	2	1	0
CYST		0	0	0	0	0	0	0	1	0	0
DARK AREA		0	0	0	0	0	0	1	0	0	0
PALE		0	0	0	1	0	0	0	0	1	0
MASS		0	0	0	0	0	1	0	0	0	0
IRREGULARLY SHAPED		0	0	0	0	0	0	1	0	1	0
LIVER (LI)	NUMBER EXAMINED:	12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:	7	0	6	6	5	7	6	13	7	0
PALE		1	0	1	0	0	2	4	1	2	0
ENLARGED		0	0	3	1	2	4	3	2	4	0
MOTTLED		1	0	2	0	1	2	0	2	2	0
MASS		2	0	4	2	6	1	3	4	1	0
LIVER (LI)	NUMBER EXAMINED:	12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:	7	0	6	6	5	7	6	13	7	0
PALE AREA		0	0	1	0	0	1	0	0	0	0
LOBE, THICKENED		0	0	1	0	0	0	0	0	1	0
GRANULAR/PITTED/ROUGH		0	0	0	0	0	1	1	0	0	0
DARK AREA		0	0	0	0	0	0	1	0	0	0
IRREGULARLY SHAPED		0	0	0	0	1	0	0	0	2	0
RAISED AREA		0	0	0	0	0	0	0	1	0	0
H-RAISED AREA		1	0	0	0	0	0	0	0	0	0
H-DARK AREA		0	0	0	0	0	0	1	0	0	0
H-CYST		0	0	0	0	0	0	0	1	0	0
GALLBLADDER (GB)	NUMBER EXAMINED:	12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:	12	0	12	9	13	14	17	22	15	0
NOT RECOGNIZED AT NECROPSY		0	0	0	0	0	1	0	0	0	0

Incidence of macroscopic findings in mice "unscheduled deaths"

INCIDENCE OF MACROSCOPIC OBSERVATIONS - UNSCHEDULED DEATHS

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN MICE

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=UNSCHED;SUBSET=ALL

ORGAN AND KEYWORD(S) OR PHRASE		-- NUMBER-OF-ANIMALS-AFFECTED --									
SEX:		----------MALE---------					---------FEMALE--------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		12	0	12	9	13	15	17	22	15	0
KIDNEY (KD)	NUMBER EXAMINED:	12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:	10	0	11	8	8	9	13	17	10	0
PALE		1	0	1	0	0	4	3	2	2	0
GRANULAR/PITTED/ROUGH		0	0	0	0	0	2	0	0	0	0
IRREGULARLY SHAPED		0	0	0	0	1	0	0	0	0	0
H-PELVIS DILATED		0	0	0	0	1	1	0	0	1	0
ENLARGED		1	0	0	0	0	1	0	0	1	0
PELVIS, DILATED		0	0	0	0	2	0	1	1	1	0
DARK AREA		0	0	0	0	0	0	0	1	0	0
PALE AREA		1	0	0	0	0	0	0	1	0	0
MOTTLED		0	0	0	0	1	1	0	1	0	0
CYST		0	0	1	1	0	0	0	0	0	0
APLASIA		0	0	0	0	0	0	0	0	1	0
PANCREAS (PA)	NUMBER EXAMINED:	12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:	12	0	12	9	13	15	17	20	15	0
MASS		0	0	0	0	0	0	0	1	0	0
CYST		0	0	0	0	0	0	0	1	0	0
LN, MESENTERIC (MS)	NUMBER EXAMINED:	12	0	12	9	12	15	17	22	15	0
	NOT REMARKABLE:	10	0	11	7	12	14	13	17	12	0
DARK		1	0	1	1	1	1	1	2	1	0
ENLARGED		2	0	1	2	0	0	4	5	3	0
MOTTLED		0	0	0	0	0	0	1	0	0	0
SEMINAL VESICLE (SV)	NUMBER EXAMINED:	12	0	12	9	13	0	0	0	0	0
	NOT REMARKABLE:	9	0	10	8	12	0	0	0	0	0
PALE		0	0	1	1	0	0	0	0	0	0
ENLARGED		2	0	1	0	0	0	0	0	0	0
H-SMALL		1	0	0	0	0	0	0	0	0	0
SMALL		0	0	0	0	1	0	0	0	0	0
URINARY BLADDER (UB)	NUMBER EXAMINED:	12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:	10	0	10	6	6	14	17	19	14	0
DARK AREA		0	0	1	0	1	0	0	1	0	0
DISTENDED		1	0	1	3	6	1	0	3	1	0
LUMEN, FLUID		2	0	1	2	6	1	0	3	1	0
SEROSA, DARK		0	0	0	0	1	0	0	0	0	0
PERFORATED		0	0	0	0	1	0	0	0	0	0
OVARY (OV)	NUMBER EXAMINED:	0	0	0	0	0	15	17	22	15	0
	NOT REMARKABLE:	0	0	0	0	0	12	10	17	12	0
MASS		0	0	0	0	0	1	2	2	0	0
CYST		0	0	0	0	0	2	6	3	3	0
DARK		0	0	0	0	0	0	1	0	0	0
UTERUS (UT)	NUMBER EXAMINED:	0	0	0	0	0	15	17	22	15	0
	NOT REMARKABLE:	0	0	0	0	0	5	9	13	5	0
CYST		0	0	0	0	0	5	6	8	5	0
UTERUS (UT)	NUMBER EXAMINED:	0	0	0	0	0	15	17	22	15	0
	NOT REMARKABLE:	0	0	0	0	0	5	9	13	5	0
WALL, THICKENED		0	0	0	0	0	2	1	1	3	0
MASS		0	0	0	0	0	1	1	1	0	0
LUMEN, FLUID		0	0	0	0	0	0	0	0	3	0
DISTENDED		0	0	0	0	0	2	0	0	3	0
BROAD LIGAMENT, DARK		0	0	0	0	0	0	1	0	0	0
BROAD LIGAMENT, THICKENED		0	0	0	0	0	0	2	0	0	0
H-CYST		0	0	0	0	0	1	0	0	0	0
UTERUS, CERVIX (CV)	NUMBER EXAMINED:	0	0	0	0	0	15	17	22	15	0
	NOT REMARKABLE:	0	0	0	0	0	15	17	21	14	0
MASS		0	0	0	0	0	0	0	0	1	0
WALL, THICKENED		0	0	0	0	0	0	0	1	0	0
VAGINA (VA)	NUMBER EXAMINED:	0	0	0	0	0	15	17	22	15	0
	NOT REMARKABLE:	0	0	0	0	0	15	17	22	15	0
LN, MANDIBULAR (MN)	NUMBER EXAMINED:	12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:	11	0	11	9	13	14	15	22	13	0
ENLARGED		1	0	1	0	0	1	2	0	2	0
DARK		1	0	1	0	0	0	0	0	0	0
MAND SALIVARY GL (SG)	NUMBER EXAMINED:	12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:	12	0	12	9	13	15	17	21	15	0
ENLARGED		0	0	0	0	0	0	0	1	0	0
THYMUS (TH)	NUMBER EXAMINED:	12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:	11	0	11	9	13	14	17	22	14	0
ENLARGED		1	0	1	0	0	1	0	0	1	0
MOTTLED		1	0	0	0	0	0	0	0	0	0
AORTA, THORACIC (AO)	NUMBER EXAMINED:	12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:	12	0	12	9	13	15	17	22	15	0
EYE (EY)	NUMBER EXAMINED:	12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:	12	0	12	9	12	15	17	22	14	0
EXTERNAL, OPAQUE		0	0	0	0	0	0	0	0	1	0
SMALL		0	0	0	0	1	0	0	0	0	0

Incidence of macroscopic findings in mice "unscheduled deaths"

INCIDENCE OF MACROSCOPIC OBSERVATIONS - UNSCHEDULED DEATHS

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN MICE

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=UNSCHED;SUBSET=ALL

-- N U M B E R - O F - A N I M A L S - A F F E C T E D -

ORGAN AND KEYWORD(S) OR PHRASE		SEX:	MALE					FEMALE				
		GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
		NUMBER:	12	0	12	9	13	15	17	22	15	0
HARDERIAN GLAND (HG)	NUMBER EXAMINED:		12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:		12	0	12	9	13	15	17	22	14	0
ENLARGED			0	0	0	0	0	0	0	0	1	0
CAVITY, CRANIAL (CC)	NUMBER EXAMINED:		12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:		12	0	12	9	12	15	17	22	15	0
DARK MATERIAL			0	0	0	0	1	0	0	0	0	0
PENIS (PE)	NUMBER EXAMINED:		12	0	12	9	13	0	0	0	0	0
	NOT REMARKABLE:		9	0	11	8	12	0	0	0	0	0
PARAPHIMOSIS			1	0	1	1	1	0	0	0	0	0
SWOLLEN			1	0	0	0	0	0	0	0	0	0
SORE			1	0	0	0	0	0	0	0	0	0
LN, OTHER (LN)	NUMBER EXAMINED:		12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:		10	0	10	7	13	9	10	20	11	0
MULTIPLE, ENLARGED			1	0	1	0	0	1	3	1	1	0
DARK			0	0	1	0	0	0	0	0	0	0
ENLARGED			1	0	0	2	0	2	3	0	1	0
MAJORITY, ENLARGED			0	0	1	0	0	3	1	1	2	0
SKIN, OTHER (SS)	NUMBER EXAMINED:		12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:		7	0	6	6	10	3	1	7	4	0
ALOPECIA			4	0	6	3	3	11	15	13	11	0
MASS-VFR			0	0	0	0	0	1	0	1	0	0
FOOT/PAW, SWOLLEN			0	0	0	0	0	0	0	1	1	0
FOOT/PAW, SORE(S)			0	0	0	0	0	0	0	0	1	0
MASS-DFM			0	0	0	0	0	0	0	1	0	0
SORE			1	0	0	1	0	1	2	2	0	0
EAR, SORE			1	0	0	0	0	0	1	0	0	0
TAIL, SORE			0	0	0	0	0	0	1	0	0	0
CAVITY, THORACIC (TA)	NUMBER EXAMINED:		12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:		12	0	11	7	12	15	17	22	15	0
FLUID			0	0	1	2	0	0	0	0	0	0
PALE MATERIAL			0	0	0	1	0	0	0	0	0	0
DARK MATERIAL			0	0	0	0	1	0	0	0	0	0
CAVITY, ABDOM (PC)	NUMBER EXAMINED:		12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:		11	0	10	8	11	13	11	20	12	0
PALE MATERIAL			0	0	0	1	0	0	0	0	0	0
FLUID			1	0	2	0	2	2	3	2	3	0
ADHESION			0	0	0	0	0	1	0	0	0	0
MASS			0	0	0	0	0	0	3	0	0	0
SUBCUTANEOUS TIS (SQ)	NUMBER EXAMINED:		12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:		11	0	7	7	13	14	13	21	15	0
DARK MATERIAL			0	0	1	0	0	0	0	0	0	0
GELATINOUS			0	0	2	0	0	1	2	0	0	0
SUBCUTANEOUS TIS (SQ)	NUMBER EXAMINED:		12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:		11	0	7	7	13	14	13	21	15	0
MASS-DFR			0	0	1	1	0	0	1	0	0	0
MASS-DFL			1	0	0	0	0	0	0	0	0	0
MASS-VHM			0	0	0	1	0	0	0	0	0	0
MASS-DHR			0	0	0	0	0	0	1	0	0	0
MASS-DFM			0	0	1	0	0	0	0	1	0	0
MASS-VFR			0	0	1	0	0	0	0	0	0	0
MASS-VFM			0	0	1	0	0	0	0	0	0	0
MASS-VHL			0	0	1	0	0	0	0	0	0	0
PREPUTIAL GLAND (PG)	NUMBER EXAMINED:		12	0	12	9	13	0	0	0	0	0
	NOT REMARKABLE:		9	0	11	9	11	0	0	0	0	0
ENLARGED			2	0	1	0	1	0	0	0	0	0
UNEQUALLY SIZED			1	0	0	0	1	0	0	0	0	0
HEAD, CORONAL (HC)	NUMBER EXAMINED:		12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:		12	0	12	9	12	15	17	21	15	0
ORBIT, FLUID			0	0	0	0	0	0	0	1	0	0
MASS			0	0	0	0	1	0	0	0	0	0
CLITORAL GLAND (CL)	NUMBER EXAMINED:		0	0	0	0	0	15	17	22	15	0
	NOT REMARKABLE:		0	0	0	0	0	15	17	22	14	0
MASS			0	0	0	0	0	0	0	0	1	0
MAMMARY, MALE (MM)	NUMBER EXAMINED:		12	0	12	9	13	0	0	0	0	0
	NOT REMARKABLE:		12	0	11	9	13	0	0	0	0	0
MASS-VHR			0	0	1	0	0	0	0	0	0	0
PINNA (PN)	NUMBER EXAMINED:		12	0	12	9	13	15	17	22	15	0
	NOT REMARKABLE:		12	0	12	9	13	15	17	22	15	0
MAMMARY, FEMALE (MF)	NUMBER EXAMINED:		0	0	0	0	0	15	17	22	15	0
	NOT REMARKABLE:		0	0	0	0	0	15	17	22	15	0

*** END OF LIST ***

Incidence of macroscopic findings in mice "Terminal Sacrifice"

- Slightly higher incidence of cysts in the kidneys treated mice (M: 1, 3, 2, 4 and F: 0, 0, 1, 1), bladder distention (M:1, 1, 6, 23 and F:0, 0, 0, 2) mice at corresponding doses (M:0, 3, 10, 30 mg/kg/day and F:0, 1, 3 and 10 mg/kg/day)

Incidence of Macroscopic Observations - Terminal Sacrifice

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN MICE

		-- N U M B E R - O F - A N I M A L S - A F F E C T E D									
TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=1-106 DEATH=T;SUBSET=ALL	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND KEYWORD(S) OR PHRASE	NUMBER:	48	0	48	51	47	45	43	38	45	0
*** TOP OF LIST ***											
BRAIN W/STEM (BR)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	48	0	48	51	47	44	39	37	45	0
VENTRAL SURFACE, INDENTED		0	0	0	0	0	1	4	1	0	0
PITUITARY (PI)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	48	0	48	51	47	38	33	36	41	0
DARK		0	0	0	0	0	1	3	0	0	0
ENLARGED		0	0	0	0	0	5	4	2	3	0
IRREGULARLY SHAPED		0	0	0	0	0	0	1	1	0	0
RAISED AREA		0	0	0	0	0	0	3	0	0	0
DARK AREA		0	0	0	0	0	1	0	0	1	0
MOTTLED		0	0	0	0	0	1	1	0	0	0
CYST		0	0	0	0	0	1	2	0	0	0
ADRENAL, CORTEX (AC)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	48	0	48	51	47	44	43	36	45	0
UNEQUALLY SIZED		0	0	0	0	0	0	0	2	0	0
ADRENAL, CORTEX (AC)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	48	0	48	51	47	44	43	36	45	0
CYST		0	0	0	0	0	1	0	0	0	0
THYROID (TY)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	48	0	48	51	47	45	43	38	44	0
ENLARGED		0	0	0	0	0	0	0	0	1	0
LUNG (LU)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	43	0	47	49	42	43	41	37	43	0
MASS		3	0	1	0	2	1	1	1	1	0
PALE AREA		1	0	0	1	1	1	1	0	1	0
RAISED AREA		0	0	0	1	0	0	0	0	0	0
LUNG (LU)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	43	0	47	49	42	43	41	37	43	0
H-RAISED AREA		1	0	0	0	0	0	0	0	0	0
H-MASS		0	0	0	0	2	0	0	0	0	0
H-PALE AREA		0	0	0	0	1	0	0	0	0	0
SPLEEN (SP)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	42	0	45	49	42	27	24	24	27	0
ENLARGED		3	0	3	2	4	17	18	13	18	0
MOTTLED		1	0	1	0	1	3	0	0	2	0
CYST		0	0	0	0	0	0	1	0	1	0
MASS		2	0	0	0	0	0	1	0	0	0
IRREGULARLY SHAPED		0	0	0	0	3	1	0	0	0	0
RAISED AREA		1	0	1	0	0	3	0	1	0	0
LIVER (LI)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	29	0	32	39	35	28	36	31	42	0
PALE		2	0	0	1	0	4	1	0	0	0
MOTTLED		1	0	0	0	0	0	0	0	0	0
MASS		14	0	15	7	8	8	5	4	2	0
PALE AREA		0	0	1	1	2	3	0	0	0	0
DARK AREA		1	0	0	2	0	1	0	1	0	0
INTERLOBAR ADHESION		2	0	0	0	0	0	0	0	0	0
RAISED AREA		3	0	0	3	0	1	1	0	0	0
CYST		0	0	0	0	0	0	0	1	0	0

Incidence of macroscopic findings in mice "Terminal Sacrifice"

INCIDENCE OF MACROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN MICE

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=T;SUBSET=ALL

ORGAN AND KEYWORD(S) OR PHRASE		-- NUMBER-OF-ANIMALS-AFFECTED --									
	SEX:	----------MALE---------					---------FEMALE---------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
	NUMBER:	48	0	48	51	47	45	43	38	45	0
*** FROM PREVIOUS PAGE ***											
LIVER (LI)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	29	0	32	39	35	28	36	31	42	0
ADHESION		0	0	0	0	0	0	0	0	1	0
DARK		0	0	0	0	1	0	0	0	0	0
H-MASS		1	0	0	0	0	1	0	0	0	0
H-RAISED AREA		0	0	0	0	1	0	0	1	0	0
H-DARK AREA		0	0	0	0	1	1	0	0	0	0
H-PALE AREA		0	0	0	0	1	0	0	0	0	0
H-DARK		1	0	0	0	0	0	0	0	0	0
KIDNEY (KD)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	47	0	45	48	34	45	43	37	42	0
PALE		0	0	0	0	0	0	0	0	1	0
IRREGULARLY SHAPED		0	0	0	0	0	0	0	0	1	0
H-PELVIS DILATED		0	0	0	0	5	0	0	0	0	0
ENLARGED		0	0	0	0	0	0	0	0	1	0
PELVIS, DILATED		0	0	0	0	3	0	0	0	0	0
PALE AREA		0	0	0	1	1	0	0	0	0	0
CYST		1	0	3	2	4	0	0	1	1	0
UNEQUALLY SIZED		0	0	0	0	0	0	0	0	1	0
DARK		0	0	0	0	1	0	0	0	0	0
STOMACH, NONGL (SU)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	47	0	48	51	47	45	43	38	45	0
RAISED AREA		1	0	0	0	0	0	0	0	0	0
STOMACH, GL (ST)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	48	0	46	46	47	44	43	38	45	0
DARK AREA		0	0	0	4	0	1	0	0	0	0
MASS		0	0	2	1	0	0	0	0	0	0
DUODENUM (DU)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	48	0	48	51	47	45	42	38	43	0
MASS		0	0	0	0	0	0	1	0	2	0
JEJUNUM (JE)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	48	0	47	50	47	43	41	38	44	0
PEYER'S PATCH, ENLARGED		0	0	0	1	0	0	0	0	0	0
MASS		0	0	1	0	0	2	2	0	1	0
ILEUM (IL)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	48	0	48	51	47	45	43	38	45	0
PANCREAS (PA)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	48	0	48	51	47	45	41	37	43	0
MASS		0	0	0	0	0	0	1	0	1	0
CYST		0	0	0	0	0	0	1	1	1	0
COLON (CO)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	48	0	47	51	47	45	43	38	45	0
MASS		0	0	1	0	0	0	0	0	0	0
LN, MESENTERIC (MS)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	38	0	45	45	40	44	37	36	42	0
DARK		5	0	1	3	5	0	2	0	1	0
ENLARGED		5	0	3	4	2	1	5	2	2	0
H-ENLARGED		0	0	0	0	1	0	0	0	0	0
TESTIS (TE)	NUMBER EXAMINED:	48	0	48	51	47	0	0	0	0	0
	NOT REMARKABLE:	47	0	48	49	43	0	0	0	0	0
DARK		0	0	0	2	0	0	0	0	0	0
SMALL		1	0	0	1	2	0	0	0	0	0
H-IRREGULARLY SHAPED		0	0	0	0	2	0	0	0	0	0
EPIDIDYMIS (EP)	NUMBER EXAMINED:	48	0	48	51	47	0	0	0	0	0
	NOT REMARKABLE:	48	0	48	50	45	0	0	0	0	0
SMALL		0	0	0	0	2	0	0	0	0	0
MASS		0	0	0	1	0	0	0	0	0	0
PROSTATE (PR)	NUMBER EXAMINED:	48	0	48	51	47	0	0	0	0	0
	NOT REMARKABLE:	48	0	47	51	47	0	0	0	0	0
SMALL		0	0	1	0	0	0	0	0	0	0
SEMINAL VESICLE (SV)	NUMBER EXAMINED:	48	0	48	51	47	0	0	0	0	0
	NOT REMARKABLE:	44	0	41	48	46	0	0	0	0	0
ENLARGED		2	0	4	1	0	0	0	0	0	0
SMALL		0	0	1	0	1	0	0	0	0	0
UNEQUALLY SIZED		1	0	1	2	1	0	0	0	0	0
IRREGULARLY SHAPED		0	0	1	0	0	0	0	0	0	0
DARK		1	0	0	0	0	0	0	0	0	0
URINARY BLADDER (UB)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	47	0	47	45	24	45	43	38	43	0
DISTENDED		1	0	1	6	23	0	0	0	2	0
LUMEN, FLUID		1	0	0	5	11	0	0	0	2	0

Incidence of macroscopic findings in mice "Terminal Sacrifice"

INCIDENCE OF MACROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN MICE

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=T;SUBSET=ALL

ORGAN AND KEYWORD(S) OR PHRASE	NUMBER:	-- NUMBER-OF-ANIMALS-AFFECTED --									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
		48	0	48	51	47	45	43	38	45	0
OVARY (OV)	NUMBER EXAMINED:	0	0	0	0	0	45	43	38	45	0
	NOT REMARKABLE:	0	0	0	0	0	26	30	22	30	0
MASS		0	0	0	0	0	3	1	0	0	0
CYST		0	0	0	0	0	18	12	15	14	0
DARK AREA		0	0	0	0	0	0	0	0	1	0
H-ENLARGED		0	0	0	0	0	0	0	1	0	0
UTERUS (UT)	NUMBER EXAMINED:	0	0	0	0	0	45	43	38	45	0
	NOT REMARKABLE:	0	0	0	0	0	6	5	5	9	0
CYST		0	0	0	0	0	38	37	29	34	0
UTERUS (UT)	NUMBER EXAMINED:	0	0	0	0	0	45	43	38	45	0
	NOT REMARKABLE:	0	0	0	0	0	6	5	5	9	0
WALL, THICKENED		0	0	0	0	0	1	0	0	0	0
MASS		0	0	0	0	0	0	1	1	0	0
LUMEN, FLUID		0	0	0	0	0	0	0	1	1	0
DISTENDED		0	0	0	0	0	0	1	3	2	0
H-CYST		0	0	0	0	0	0	0	1	0	0
H-WALL THICKENED		0	0	0	0	0	0	0	1	0	0
UTERUS, CERVIX (CV)	NUMBER EXAMINED:	0	0	0	0	0	45	43	38	45	0
	NOT REMARKABLE:	0	0	0	0	0	45	43	38	44	0
WALL, THICKENED		0	0	0	0	0	0	0	0	1	0
VAGINA (VA)	NUMBER EXAMINED:	0	0	0	0	0	45	43	38	45	0
	NOT REMARKABLE:	0	0	0	0	0	45	43	38	45	0
LN, MANDIBULAR (MN)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	48	0	48	50	47	45	43	38	45	0
ENLARGED		0	0	0	1	0	0	0	0	0	0
THYMUS (TH)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	48	0	48	51	46	44	42	38	45	0
ENLARGED		0	0	0	0	0	0	1	0	0	0
DARK		0	0	0	0	1	0	0	0	0	0
H-DARK AREA		0	0	0	0	0	1	0	0	0	0
EYE (EY)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	47	0	45	48	46	41	42	37	43	0
EXTERNAL, OPAQUE		1	0	1	2	1	1	0	1	1	0
EXOPHTHALMUS		1	0	0	0	0	0	0	0	2	0
GLOBE RUPTURED ANTE MORTEM		0	0	1	1	0	2	1	0	0	0
EXTERNAL, PALE MATERIAL		0	0	1	0	0	2	0	0	0	0
INTERNAL, OPAQUE		0	0	0	0	0	1	0	0	0	0
HARDERIAN GLAND (HG)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	47	0	46	47	47	43	41	38	42	0
UNEQUALLY SIZED		1	0	2	4	0	2	2	0	3	0
PALE		0	0	0	0	0	0	0	0	1	0
LN, OTHER (LN)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	48	0	46	49	45	39	38	30	37	0
MULTIPLE, ENLARGED		0	0	0	0	0	0	1	4	2	0
ENLARGED		0	0	1	1	2	4	1	3	3	0
MAJORITY, ENLARGED		0	0	1	0	0	1	2	0	3	0
UNEQUALLY SIZED		0	0	0	1	0	1	1	1	0	0
SKIN, OTHER (SS)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	24	0	19	23	26	4	6	13	12	0
ALOPECIA		23	0	29	27	21	41	37	25	33	0
FOOT/PAW, SWOLLEN		0	0	0	0	0	0	0	0	1	0
SORE		0	0	2	0	1	2	0	0	1	0
TAIL, SWOLLEN		0	0	0	1	0	0	0	0	0	0
DARK AREA		0	0	0	0	0	0	0	0	1	0
H-ALOPECIA		1	0	0	0	0	0	0	0	0	0
CAVITY, ABDOM (PC)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	47	0	48	48	45	43	43	38	45	0
FLUID		0	0	0	1	0	1	0	0	0	0
ADHESION		1	0	0	2	1	0	0	0	0	0
MASS		0	0	0	0	1	0	0	0	0	0
ADIPOSE TISSUE, MASS		0	0	0	0	0	1	0	0	0	0
SUBCUTANEOUS TIS (SQ)	NUMBER EXAMINED:	48	0	48	51	47	45	43	38	45	0
	NOT REMARKABLE:	47	0	47	51	47	43	43	38	44	0
MASS-VHM		1	0	0	0	0	1	0	0	0	0
MASS-DFM		0	0	1	0	0	0	0	0	0	0
MASS-VFR		0	0	0	0	0	1	0	0	1	0
PREPUTIAL GLAND (PG)	NUMBER EXAMINED:	48	0	48	51	47	0	0	0	0	0
	NOT REMARKABLE:	38	0	30	36	36	0	0	0	0	0
ENLARGED		7	0	12	8	5	0	0	0	0	0
UNEQUALLY SIZED		1	0	3	6	2	0	0	0	0	0
MASS		2	0	3	1	2	0	0	0	0	0
RAISED AREA		0	0	0	0	2	0	0	0	0	0
MAMMARY, FEMALE (MF)	NUMBER EXAMINED:	0	0	0	0	0	45	43	38	45	0
	NOT REMARKABLE:	0	0	0	0	0	44	41	38	45	0
THICKENED		0	0	0	0	0	0	2	0	0	0
MASS-VFL		0	0	0	0	0	1	0	0	0	0

Histopathology:

Non-neoplastic:

- Microscopic examination revealed significantly greater incidences of urinary bladder distention, pelvis dilatation in males at 30 mg/kg/day. No notable increase in females up to 10 mg/kg/day. Renal dilatation and bladder distention appear to be directly related to pharmacological effect of conivaptan. The absence of urinary distention in females was likely due to anatomical difference in the urinary tracts.
- Although a significant increase in urinary balder hyperplasia was noted in the HD males, there was no notable change in incidence of urinary bladder tumors in the study.
- The incidence of renal cysts was higher in treated female and male mice, however it was only significant in high dose females (10 mg/kg/d)
- Significant increase in incidence of pigmented renal tubules in females at 10 mg/kg/d.

Table 2.6.6-79: Carcinogenicity study in mice – non-neoplastic lesions [R087-TX-054]

Daily Dose (mg/kg)	0		1	3		10		30
Gender	M	F	F	M	F	M	F	M
Kidney: N	60	60	60	60	60	60	60	60
Cyst	16	0	0	10	1	4**	5*	23
Increased Microconcretion, Tubule	5	0	0	0*	0	0*	0	1
Increased Pigment, Tubule	0	5	0*	0	3	0	31**	0
Pelvis, Dilatation	0	2	1	1	0	4	2	22**
Urinary Bladder: N	60	59	58	60	59	59	60	60
Distention	1	0	0	2	1	7*	2	44**
Hyperplasia	1	0	0	1	0	5	0	35**

N = Number of animals examined.
Cochran-Armitage Test and Fisher-Irwin Exact Test: * - P<0.05, ** - P<0.01.

Neoplastic:

- There was no significant increase in incidence of neoplastic tumors in conivaptan treated mice relative to control.

Table 2.6.6-78: Carcinogenicity study in mice – neoplastic lesions [R087-TX-054]

Daily Dose (mg/kg)	0		1	3		10		30
Gender	M	F	F	M	F	M	F	M
Adrenal, Cortex: N	60	60	59	60	60	60	60	60
Adenoma, Subcapsular Cell	2	1	1	0	1	0	0	2
Adrenal, Medulla: N	59	60	59	60	57	59	59	60
Pheochromocytoma	0	1	0	0	1	1	0	0
Harderian Gland: N	60	60	60	59	60	60	60	60
Adenoma	5	2	3	5	1	10	2	2
Carcinoma	1	0	1	0	0	0	2	0
Hematopoietic Neoplasia: N	60	60	60	60	60	60	60	60
Leukemia, Granulocytic	0	1	1	0	0	0	0	0
Leukemia, Mast Cell	0	1	0	0	0	0	0	0
Malignant Lymphoma, Lymphocytic	4	7	10	3	7	2	13	1
Sarcoma, Histiocytic	3	3	4	3	3	1	5	0
Kidney: N	60	60	60	60	60	60	60	60
Adenoma, Tubular Cell	1	0	1	0	0	0	0	0
Papilloma, Transitional Cell	0	0	0	0	0	1	0	0
Liver: N	60	60	60	60	60	60	60	60
Adenoma, Hepatocellular	10	9	6	7	5	8	3*	10
Carcinoma, Hepatocellular	9	3	2	10	3	3*	0	7
Hemangioma	1	0	0	0	1	1	0	0
Hemangiosarcoma	0	0	1	5	0	1	0	0
Lung: N	60	60	60	60	60	60	60	60
Adenoma, Bronchiolar - Alveolar	7	2	1	6	2	14	3	4
Carcinoma, Bronchiolar - Alveolar	7	3	0	2	2	0**	2	3
Marrow, Femur: n	60	60	60	60	60	60	59	60
Hemangiosarcoma	0	1	0	0	0	0	0	0
Pancreas: N	60	60	60	60	59	60	59	60
Adenoma, Islet Cell	0	1	0	1	0	0	0	0
Pituitary: n	58	58	60	60	55	58	59	56
Adenoma	0	16	10	0	5*	1	8*	0
Spleen: N	60	60	60	60	58	59	60	60
Hemangioma	0	0	1	0	0	0	1	0
Hemangiosarcoma	2	2	0	2	2	2	1	2
Subcutaneous Tissue: N	1	3	3	6	3	3	1	0
Fibrosarcoma	1	1	1	2	3	2	1	0
Thyroid: N	60	59	60	60	59	60	60	60
Follicular Cell Adenoma	0	0	0	1	0	1	0	0
Follicular Cell Carcinoma	0	0	0	1	0	0	0	0
Uterus: N		60	60		59		60	
Endometrial Stromal Polyp		1	1		2		3	
Carcinoma		0	1		2		1	
Hemangioma		1	0		0		0	
Hemangiosarcoma		0	1		1		1	
Leiomyoma		1	0		1		1	

N = Number of animals examined.
Dinse and Lagakos Logistic Prevalence Methods and Cox-Tarone Binary Regression Methods:
* - P<0.05, ** - P<0.01,

Incidence of microscopic findings in mice "Unscheduled deaths"

Incidence of Microscopic Observations - Unscheduled Deaths

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN MICE

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=UNSCHED;FIND=ALL;SUBSET=ALL

-- N U M B E R - O F - A N I M A L S - A F F E C T E D --

ORGAN AND FINDING DESCRIPTION		SEX:	-------MALE-------				------FEMALE------			
		GROUP:	-1-	-3-	-4-	-5-	-1-	-2-	-3-	-4-
		NUMBER:	12	12	9	13	15	17	22	15
*** TOP OF LIST ***										
BRAIN W/STEM (BR)	NUMBER EXAMINED:		12	12	9	13	15	17	22	15
	NOT REMARKABLE:		12	12	9	13	14	17	20	14
--VENTRICLE, DILATATION			0	0	0	0	1	0	0	0
--COMPRESSION, VENTRAL			0	0	0	0	0	0	2	1
--HEMORRHAGE			0	0	0	0	0	0	1	1
CORD, CERVICAL (CS)	NUMBER EXAMINED:		12	12	9	13	15	17	22	15
	NOT REMARKABLE:		12	12	9	13	14	17	22	15
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			0	0	0	0	1	0	0	0
CORD, THORACIC (TC)	NUMBER EXAMINED:		12	12	9	13	15	17	22	15
	NOT REMARKABLE:		11	12	9	13	14	17	22	15
--KERATIN CYST			1	0	0	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			0	0	0	0	1	0	0	0
CORD, LUMBAR (LC)	NUMBER EXAMINED:		12	12	8	13	15	17	22	15
	NOT REMARKABLE:		11	12	8	13	14	17	22	15
--DEGENERATION, SPINAL NERVES			1	0	0	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			0	0	0	0	1	0	0	0
PITUITARY (PI)	NUMBER EXAMINED:		12	12	9	13	14	17	17	14
	NOT REMARKABLE:		11	12	9	13	9	16	15	10
--HYPERPLASIA			1	0	0	0	0	1	0	1
--B-ADENOMA			0	0	0	0	5	0	2	2
--CYST			0	0	0	0	0	0	0	1
ADRENAL, CORTEX (AC)	NUMBER EXAMINED:		12	12	9	13	15	16	22	15
	NOT REMARKABLE:		8	8	8	13	12	13	19	14
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			3	2	1	0	1	2	1	1
--UNILATERALLY EXAMINED			1	2	0	0	0	0	2	1
--B-ADENOMA, SUBCAPSULAR CELL			0	0	0	0	1	0	0	0
--AMYLOIDOSIS			0	0	0	0	1	1	0	0
ADRENAL, MEDULLA (AM)	NUMBER EXAMINED:		12	12	9	13	15	16	22	15
	NOT REMARKABLE:		10	10	9	13	15	16	19	14
--UNILATERALLY EXAMINED			2	2	0	0	0	0	3	1
THYROID (TY)	NUMBER EXAMINED:		12	12	9	13	15	17	21	15
	NOT REMARKABLE:		11	11	8	13	15	17	20	15
--B-FOLLICULAR CELL ADENOMA			0	0	1	0	0	0	0	0
--PERIARTERITIS			1	0	0	0	0	0	0	0
--FOLLICLE, CYST			0	0	0	0	0	0	1	0
--M-FOLLICULAR CELL CARCINOMA			0	1	0	0	0	0	0	0
PARATHYROID (PT)	NUMBER EXAMINED:		10	10	9	12	13	17	18	14
	NOT REMARKABLE:		10	10	9	12	13	17	17	14
--CYST			0	0	0	0	0	0	1	0
ESOPHAGUS (ES)	NUMBER EXAMINED:		12	12	9	13	15	17	22	15
	NOT REMARKABLE:		12	12	9	13	15	17	22	15
LUNG (LU)	NUMBER EXAMINED:		12	12	9	13	15	17	22	15
	NOT REMARKABLE:		10	5	6	11	9	7	11	7
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			2	3	0	0	4	6	2	8
--INFLAMMATION, ACUTE			0	1	1	0	1	0	0	0
--M-CARCINOMA, BRONCHIOLAR-ALVEOLAR			0	0	0	0	2	0	1	0
--INCREASED LYMPHOID INFILTRATE			0	0	0	0	0	0	2	0
--B-ADENOMA, BRONCHIOLAR-ALVEOLAR			0	3	1	1	0	0	1	0
--ALVEOLUS, MACROPHAGES, PIGMENTED			0	0	0	0	0	0	1	0
--N-CARCINOMA, BILE DUCT			0	0	0	0	0	0	1	0
--N-SQUAMOUS CELL CARCINOMA			0	0	0	1	0	0	0	0
--HEMORRHAGE			0	0	0	0	1	1	0	0
--N-OSTEOSARCOMA			0	0	0	0	0	0	2	0
--N-FIBROSARCOMA			0	0	0	0	0	1	0	0
--ALVEOLAR MACROPHAGES			0	0	0	0	0	1	0	0
--N-CARCINOMA, HEPATOCELLULAR			0	0	1	0	0	0	1	0
--N-SARCOMA NOS			0	0	0	0	0	1	0	0
--INFLAMMATION, GRANULOMATOUS			0	1	0	0	0	0	0	0
HEART (HT)	NUMBER EXAMINED:		12	12	9	13	15	17	22	15
	NOT REMARKABLE:		8	8	7	9	12	12	21	13
--MINERALIZATION			0	0	0	1	0	0	1	0
--CARDIOMYOPATHY, DEGENERATIVE			2	1	0	3	2	1	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			1	2	0	0	1	3	0	1
--PERIARTERITIS			1	1	0	0	0	0	0	0
--ATRIAL THROMBUS			0	0	1	0	0	0	0	0
--THROMBUS, VENTRICLE			0	0	1	0	0	0	0	0
--INFLAMMATION, ACUTE			0	0	0	0	0	1	0	1
--SEPTIC THROMBUS			0	0	0	0	0	1	0	0

Incidence of microscopic findings in mice "Unscheduled deaths"

INCIDENCE OF MICROSCOPIC OBSERVATIONS - UNSCHEDULED DEATHS

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN MICE

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=UNSCHED;FIND=ALL;SUBSET=ALL

-- N U M B E R - O F - A N I M A L S - A F F E C T E D --

ORGAN AND FINDING DESCRIPTION		SEX:	MALE				FEMALE			
		GROUP:	-1-	-3-	-4-	-5-	-1-	-2-	-3-	-4-
		NUMBER:	12	12	9	13	15	17	22	15
SPLEEN (SP)	NUMBER EXAMINED:		12	12	9	13	15	17	20	15
	NOT REMARKABLE:		5	3	3	10	3	3	9	5
--EXTRAMEDULLARY HEMATOPOIESIS, INCREASED			4	4	4	1	3	10	5	3
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			2	3	1	0	6	5	4	8
--DEPLETION, LYMPHOID			1	2	1	2	1	0	1	0
--ABSCESS			0	0	1	0	0	0	0	0
--M-HEMANGIOSARCOMA			0	2	0	1	0	0	1	0
--LYMPHOID HYPERPLASIA			0	0	0	0	1	4	1	0
--FIBROSIS, CAPSULE			1	0	0	0	0	0	0	0
--ANGIECTASIS			0	0	0	1	0	0	0	0
--AMYLOIDOSIS			0	0	0	0	1	1	0	0
--INCREASED PIGMENT			0	0	0	0	1	0	0	0
--NECROSIS			0	0	0	0	1	1	0	0
--HEMORRHAGE			0	0	0	0	0	1	0	0
LIVER (LI)	NUMBER EXAMINED:		12	12	9	13	15	17	22	15
	NOT REMARKABLE:		3	4	5	6	7	5	11	6
--DEGENERATION/NECROSIS, CENTRILOBULAR			0	1	1	1	0	2	0	0
--HEPATOCELLULAR ENLARGEMENT			0	1	0	2	0	0	0	0
--M-CARCINOMA, HEPATOCELLULAR			2	2	2	3	1	2	3	0
--B-ADENOMA, HEPATOCELLULAR			1	1	0	3	0	0	1	1
--FOCUS OF VACUOLATED HEPATOCYTES			0	0	0	0	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			3	3	0	0	5	5	4	8
--MINERALIZED FOCI			0	0	0	0	0	0	1	0
--EXTRAMEDULLARY HEMATOPOIESIS, INCREASED			1	1	1	0	1	0	0	0
--PIGMENT			1	1	0	0	0	0	0	0
--LYMPHOHISTIOCYTIC INFILTRATE			2	2	0	1	1	2	2	0
--FOCAL NECROSIS			1	1	1	3	1	0	1	1
--M-HEMANGIOSARCOMA			0	2	0	0	0	1	0	0
--M-CARCINOMA, BILE DUCT			0	0	0	0	0	0	1	0
--ANGIECTASIS			0	0	1	0	1	0	0	0
LIVER (LI)	NUMBER EXAMINED:		12	12	9	13	15	17	22	15
	NOT REMARKABLE:		3	4	5	6	7	5	11	6
--AMYLOIDOSIS			0	0	0	0	0	1	0	0
--FOCAL SUBACUTE INFLAMMATION			1	0	0	0	0	0	0	0
--M-SARCOMA NOS			0	0	0	0	0	1	0	0
GALLBLADDER (GB)	NUMBER EXAMINED:		9	10	6	12	12	13	12	9
	NOT REMARKABLE:		9	9	6	12	11	13	12	9
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			0	1	0	0	1	0	0	0
KIDNEY (KD)	NUMBER EXAMINED:		12	12	9	13	15	17	22	15
	NOT REMARKABLE:		2	5	3	3	7	5	7	4
--PYELONEPHRITIS			3	1	0	2	1	1	0	0
--NEPHROPATHY, CHRONIC PROGRESSIVE			5	6	5	9	5	7	6	5
--PELVIS, DILATATION			0	0	0	3	2	1	0	1
--INFARCT			0	0	0	1	0	0	3	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			3	1	0	0	2	4	3	4
--GLOMERULAR AMYLOIDOSIS			1	0	0	0	0	2	2	1
--INCREASED MICROCONCRETION, TUBULE			1	0	0	1	0	0	0	0
--INCREASED VACUOLIZATION, TUBULES			0	0	1	0	0	0	0	0
--INCREASED LYMPHOID INFILTRATE			0	1	0	0	1	1	2	1
--MINERALIZATION, PAPILLA			1	0	0	0	0	0	0	0
--CYST			1	1	0	1	0	0	0	0
--UNILATERALLY EXAMINED			0	0	0	0	0	0	0	1
--PAPILLA, NECROSIS			0	0	0	1	0	0	0	0
--OSSEOUS METAPLASIA			0	0	0	0	0	1	0	1
--PERIARTERITIS			1	0	0	0	0	0	0	0
--INCREASED PIGMENT, TUBULE			0	0	0	0	0	0	1	4
STOMACH, NONGL (SU)	NUMBER EXAMINED:		12	12	8	13	15	17	21	14
	NOT REMARKABLE:		11	12	8	12	15	16	21	13
--HYPERKERATOSIS			0	0	0	1	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			0	0	0	0	0	1	0	0
--CYST			1	0	0	0	0	0	0	0
STOMACH, GL (ST)	NUMBER EXAMINED:		12	12	8	13	15	17	21	13
	NOT REMARKABLE:		10	11	8	10	15	15	21	13
--INFILTRATE, EOSINOPHIL			0	1	0	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			2	0	0	0	0	1	0	0
--FOCAL HYPERPLASIA			0	0	0	1	0	0	0	0
--MINERALIZATION			0	0	0	2	0	0	0	0
--FOCAL NECROSIS			0	0	0	0	0	1	0	0
DUODENUM (DU)	NUMBER EXAMINED:		10	9	7	12	14	14	17	11
	NOT REMARKABLE:		10	8	7	12	14	14	17	11
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			0	1	0	0	0	0	0	0
JEJUNUM (JE)	NUMBER EXAMINED:		11	8	6	11	15	12	16	10
	NOT REMARKABLE:		10	8	6	11	14	11	16	10
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			1	0	0	0	1	1	0	0
ILEUM (IL)	NUMBER EXAMINED:		11	9	6	11	13	12	18	9
	NOT REMARKABLE:		10	9	6	11	13	12	18	8
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			1	0	0	0	0	0	0	0
--AMYLOIDOSIS			0	0	0	0	0	0	0	1

Incidence of microscopic findings in mice "Unscheduled deaths"

INCIDENCE OF MICROSCOPIC OBSERVATIONS - UNSCHEDULED DEATHS

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN MICE

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=UNSCHED;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		-- NUMBER-OF-ANIMALS-AFFECTED --							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-3-	-4-	-5-	-1-	-2-	-3-	-4-
	NUMBER:	12	12	9	13	15	17	22	15
PANCREAS (PA)	NUMBER EXAMINED:	12	12	9	13	15	17	21	14
	NOT REMARKABLE:	9	11	8	13	12	13	18	12
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		3	1	1	0	3	1	1	1
--INCREASED ZYMOGEN, PERI-INSULAR		0	0	0	0	0	3	0	1
--I-CARCINOMA, BILE DUCT		0	0	0	0	0	0	1	0
--DUCT ECTASIA		0	0	0	0	0	0	1	0
CECUM (CE)	NUMBER EXAMINED:	11	11	7	13	14	16	20	13
	NOT REMARKABLE:	11	11	7	13	14	15	20	12
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	0	0	1
--HEMORRHAGE		0	0	0	0	0	1	0	0
COLON (CO)	NUMBER EXAMINED:	12	12	8	13	15	17	21	14
	NOT REMARKABLE:	12	12	7	13	15	17	21	14
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	0	0	0	0
RECTUM (RE)	NUMBER EXAMINED:	12	12	8	13	15	17	21	15
	NOT REMARKABLE:	12	12	8	13	15	17	21	15
LN, MESENTERIC (MS)	NUMBER EXAMINED:	11	11	9	11	15	16	21	13
	NOT REMARKABLE:	7	6	5	8	10	8	17	8
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		3	3	1	0	5	6	4	5
--ANGIECTASIS		0	2	3	3	0	0	0	0
--LYMPHOID DEPLETION		1	1	0	0	0	1	0	0
--AMYLOIDOSIS		1	0	0	0	0	0	0	0
--HYPERPLASIA, RETICULOENDOTHELIAL		0	0	0	0	0	1	0	0
LN, MANDIBULAR (MN)	NUMBER EXAMINED:	11	12	9	13	15	16	20	14
	NOT REMARKABLE:	8	9	9	13	10	10	16	8
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	3	0	0	4	4	2	5
--DEPLETION, LYMPHOID		0	0	0	0	1	0	0	0
--LYMPHOID HYPERPLASIA		0	0	0	0	0	2	1	1
--INCREASED PIGMENT		1	0	0	0	0	0	1	0
MAND SALIVARY GL (SG)	NUMBER EXAMINED:	12	12	9	13	15	17	22	15
	NOT REMARKABLE:	11	10	9	13	12	15	22	13
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	2	0	0	3	2	0	2
PAROTID SALIVARY (SG0)	NUMBER EXAMINED:	11	11	8	13	15	17	22	15
	NOT REMARKABLE:	11	10	8	13	12	16	22	13
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	0	2	1	0	2
--DEGENERATION		0	0	0	0	1	0	0	0
THYMUS (TH)	NUMBER EXAMINED:	6	9	8	11	12	12	18	14
	NOT REMARKABLE:	4	6	7	11	9	9	16	9
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	3	1	0	3	3	2	5
AORTA, THORACIC (AO)	NUMBER EXAMINED:	12	12	9	13	15	17	22	15
	NOT REMARKABLE:	12	12	9	13	15	17	22	15
EYE (EY)	NUMBER EXAMINED:	12	12	9	13	15	17	22	14
	NOT REMARKABLE:	12	12	9	13	15	16	22	13
--UNILATERALLY EXAMINED		0	0	0	0	0	0	0	1
--PHTHISIS		0	0	0	0	0	1	0	0
HARDERIAN GLAND (HG)	NUMBER EXAMINED:	12	12	9	13	15	17	22	15
	NOT REMARKABLE:	10	8	7	11	14	17	19	13
--UNILATERALLY EXAMINED		0	0	0	0	0	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	2	0	0	1	0	0	1
--M-CARCINOMA		0	0	0	0	0	0	0	1
--HYPERPLASIA		0	0	1	1	0	0	1	0
--DUCT ECTASIA		0	1	0	0	0	0	0	0
--B-ADENOMA		1	0	1	1	0	0	0	0
--DEGENERATION		0	1	0	0	0	0	1	0
MUSCLE, SKELETAL (SM)	NUMBER EXAMINED:	12	12	9	13	15	17	22	15
	NOT REMARKABLE:	9	11	9	13	13	16	21	14
--DEGENERATION		2	0	0	0	2	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	1	0	1
--LYMPHOID INFILTRATE		1	1	0	0	0	0	1	0
NERVE, SCIATIC (SN)	NUMBER EXAMINED:	12	12	9	13	15	17	22	15
	NOT REMARKABLE:	7	8	5	4	4	4	9	5
--DEGENERATION		5	4	4	9	11	13	13	9
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	1	0	1
TONGUE (TO)	NUMBER EXAMINED:	12	12	9	13	15	17	21	15
	NOT REMARKABLE:	11	12	9	13	15	17	19	15
--INFLAMMATION, GRANULOMATOUS		0	0	0	0	0	0	1	0
--PERIARTERITIS		1	0	0	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	0	1	0

Incidence of microscopic findings in mice "Unscheduled deaths"

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104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN MICE

- N U M B E R - O F - A N I M A L S - A F F E C T E D

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=UNSCHED;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		SEX:	-------MALE-------				------FEMALE------			
		GROUP:	-1-	-3-	-4-	-5-	-1-	-2-	-3-	-4-
		NUMBER:	12	12	9	13	15	17	22	15
TESTIS (TE)	NUMBER EXAMINED:		12	12	9	13	0	0	0	0
	NOT REMARKABLE:		8	12	8	10	0	0	0	0
--DEGENERATION			4	0	1	3	0	0	0	0
EPIDIDYMIS (EP)	NUMBER EXAMINED:		12	12	9	13	0	0	0	0
	NOT REMARKABLE:		8	10	7	9	0	0	0	0
--SPERM, ABNORMAL MORPHOLOGY			2	0	1	3	0	0	0	0
--HYPOSPERMIA			1	0	0	1	0	0	0	0
--UNILATERALLY EXAMINED			0	0	1	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			1	2	0	0	0	0	0	0
PROSTATE (PR)	NUMBER EXAMINED:		12	12	9	13	0	0	0	0
	NOT REMARKABLE:		9	10	9	13	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			1	2	0	0	0	0	0	0
--INFLAMMATION, CHRONIC ACTIVE			2	0	0	0	0	0	0	0
SEMINAL VESICLE (SV)	NUMBER EXAMINED:		12	12	9	13	0	0	0	0
	NOT REMARKABLE:		11	10	9	12	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			1	2	0	0	0	0	0	0
--ATROPHY			0	0	0	1	0	0	0	0
URINARY BLADDER (UB)	NUMBER EXAMINED:		12	12	9	13	14	15	21	15
	NOT REMARKABLE:		7	10	8	2	8	9	16	9
--LYMPHOHISTIOCYTIC INFILTRATE			2	0	0	3	4	5	3	5
--DISTENTION			1	1	1	7	0	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			0	0	0	0	2	1	1	1
--NECROSIS			1	0	0	0	0	0	0	0
--HEMORRHAGE			1	0	0	0	0	0	0	0
URINARY BLADDER (UB)	NUMBER EXAMINED:		12	12	9	13	14	15	21	15
	NOT REMARKABLE:		7	10	8	2	8	9	16	9
--INFLAMMATION, ACUTE			3	0	0	0	0	0	1	0
--HYPERPLASIA			1	1	0	4	0	0	0	0
OVARY (OV)	NUMBER EXAMINED:		0	0	0	0	15	17	21	14
	NOT REMARKABLE:		0	0	0	0	8	6	12	7
--B-TERATOMA			0	0	0	0	0	0	1	0
--UNILATERALLY EXAMINED			0	0	0	0	0	2	2	1
--ABSCESS			0	0	0	0	1	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			0	0	0	0	4	5	3	2
--FOLLICLE, CYST			0	0	0	0	1	3	3	3
--HEMATOCYST			0	0	0	0	1	2	1	1
UTERUS (UT)	NUMBER EXAMINED:		0	0	0	0	15	17	21	15
	NOT REMARKABLE:		0	0	0	0	5	8	11	4
--HYPERPLASIA, CYSTIC ENDOMETRIAL			0	0	0	0	9	5	8	8
--DILATATION			0	0	0	0	0	1	1	1
--M-HEMANGIOSARCOMA			0	0	0	0	0	1	1	0
--ANGIECTASIS			0	0	0	0	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			0	0	0	0	1	3	0	2
--B-ENDOMETRIAL STROMAL POLYP			0	0	0	0	0	0	1	0
--THROMBUS			0	0	0	0	1	0	0	0
--FIBROSIS			0	0	0	0	0	0	0	1
--M-CARCINOMA			0	0	0	0	0	0	1	0
UTERUS, CERVIX (CV)	NUMBER EXAMINED:		0	0	0	0	15	17	21	15
	NOT REMARKABLE:		0	0	0	0	15	15	21	13
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			0	0	0	0	0	2	0	2
VAGINA (VA)	NUMBER EXAMINED:		0	0	0	0	15	17	21	15
	NOT REMARKABLE:		0	0	0	0	15	15	20	14
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			0	0	0	0	0	2	1	1
MAMMARY/F-CRAN (MF0)	NUMBER EXAMINED:		0	0	0	0	14	14	18	12
	NOT REMARKABLE:		0	0	0	0	12	13	17	10
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			0	0	0	0	0	1	0	1
--GALACTOCELE			0	0	0	0	2	0	1	1
MAMMARY/F-CAUD (MF1)	NUMBER EXAMINED:		0	0	0	0	8	12	16	11
	NOT REMARKABLE:		0	0	0	0	7	11	14	9
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			0	0	0	0	0	1	1	1
--GALACTOCELE			0	0	0	0	1	0	1	1
SKIN (SK)	NUMBER EXAMINED:		12	12	9	13	15	17	22	15
	NOT REMARKABLE:		11	12	9	13	15	16	21	14
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			0	0	0	0	0	0	0	1
--NECROTIZING DERMATITIS			1	0	0	0	0	0	1	0
--HEMORRHAGE			0	0	0	0	0	1	0	0
MARROW, STERNUM (SE)	NUMBER EXAMINED:		12	12	9	13	15	17	22	14
	NOT REMARKABLE:		6	7	5	13	12	10	17	9
--HYPERCELLULAR			3	3	4	0	2	3	2	5
--HYPOCELLULAR			3	0	0	0	1	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			0	2	0	0	0	4	3	0

Incidence of microscopic findings in mice "Unscheduled deaths"

INCIDENCE OF MICROSCOPIC OBSERVATIONS - UNSCHEDULED DEATHS

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN MICE

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=UNSCHED;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		-- NUMBER-OF-ANIMALS-AFFECTED --							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-3-	-4-	-5-	-1-	-2-	-3-	-4-
	NUMBER:	12	12	9	13	15	17	22	15
BONE, STERNUM (SB)	NUMBER EXAMINED:	12	12	9	13	15	17	22	15
	NOT REMARKABLE:	12	12	9	13	8	9	13	8
--FIBROUS-OSSEOUS CHANGE		0	0	0	0	7	8	9	7
MARROW, FEMUR (FM)	NUMBER EXAMINED:	12	12	9	13	15	17	22	14
	NOT REMARKABLE:	8	6	5	12	12	11	15	9
--HYPERCELLULAR		2	3	4	0	2	3	3	5
--HYPOCELLULAR		2	0	0	1	0	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	2	0	0	1	3	3	0
--FIBROSIS		0	1	0	0	0	0	0	0
--ANGIECTASIS		0	1	0	1	0	0	0	0
BONE, FEMUR (FE)	NUMBER EXAMINED:	12	12	9	13	15	17	22	15
	NOT REMARKABLE:	10	12	9	13	15	15	16	15
--OSTOSIS		0	0	0	0	0	1	0	0
--M-OSTEOSARCOMA		0	0	0	0	0	0	1	0
--FIBROUS-OSSEOUS CHANGE		2	0	0	0	0	1	5	0
VERTEBRAE, L1 (OB0)	NUMBER EXAMINED:	12	12	9	13	15	17	22	15
	NOT REMARKABLE:	12	10	9	12	12	13	16	12
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	2	0	0	1	1	2	0
--FIBROUS-OSSEOUS CHANGE		0	0	0	0	2	2	4	3
--I-FIBROSARCOMA		0	0	0	0	0	1	0	0
--N-HEMANGISARCOMA		0	0	0	1	0	0	0	0
VERTEBRAE, L2 (OB1)	NUMBER EXAMINED:	12	12	9	13	15	17	22	15
	NOT REMARKABLE:	11	9	9	13	8	14	14	12
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	3	0	0	0	1	2	0
VERTEBRAE, L2 (OB1)	NUMBER EXAMINED:	12	12	9	13	15	17	22	15
	NOT REMARKABLE:	11	9	9	13	8	14	14	12
--FIBROUS-OSSEOUS CHANGE		0	0	0	0	7	1	6	3
--I-FIBROSARCOMA		0	0	0	0	0	1	0	0
^DEATH COMMENT (DC)	NUMBER EXAMINED:	12	12	9	13	15	17	22	15
	NOT REMARKABLE:	0	0	0	0	0	0	0	0
--HEPATOCELLULAR NEOPLASM		2	1	2	5	1	1	2	0
--UNDETERMINED		3	2	1	6	1	2	4	3
--NEPHROPATHY		1	1	1	0	1	3	2	0
--HEMATOPOIETIC NEOPLASM		4	3	1	0	5	6	5	8
--SUBCUTANEOUS NEOPLASM		1	1	1	0	1	1	3	0
--INFLAMMATION, ABDOMINAL CAVITY		0	0	2	0	0	0	0	0
--OVARIAN ABSCESS		0	0	0	0	1	0	0	0
--HARDERIAN GLAND NEOPLASM		0	0	0	0	0	0	0	1
--ACCIDENTAL		0	1	0	0	0	0	0	0
--HEMANGIOSARCOMA		0	2	0	0	0	2	1	0
--PULMONARY NEOPLASM		0	0	0	0	1	0	1	0
--RHABDOMYOSARCOMA		0	0	0	0	0	0	0	1
--URINARY BLOCKAGE/INFLAMMATION		1	1	1	1	0	0	0	0
--PITUITARY NEOPLASM		0	0	0	0	3	0	2	1
--CLITORAL/PREPUTIAL GLAND NEOPLASM		0	0	0	0	0	0	0	1
--CUTANEOUS NEOPLASM		0	0	0	1	0	1	0	0
--ENDOMETRIAL POLYP		0	0	0	0	0	0	1	0
--CARCINOMA, BILE DUCT		0	0	0	0	0	0	1	0
--SARCOMA NOS, LIVER		0	0	0	0	0	1	0	0
--REMOVED FROM STUDY		0	0	0	0	1	0	0	0
HEMATO NEOPLASIA (HN)	NUMBER EXAMINED:	12	12	9	13	15	17	22	15
	NOT REMARKABLE:	8	9	8	13	9	8	17	6
--M-SARCOMA, HISTIOCYTIC		3	1	0	0	3	3	3	3
--M-MALIGNANT LYMPHOMA, LYMPHOCYTIC		1	2	1	0	3	5	2	6
--M-LEUKEMIA, GRANULOCYTIC		0	0	0	0	0	1	0	0
SKIN, OTHER (SS)	NUMBER EXAMINED:	5	6	3	4	11	16	14	10
	NOT REMARKABLE:	3	3	3	3	10	11	12	9
--HYPOTRICHOSIS		0	2	0	0	0	1	1	0
--M-SQUAMOUS CELL CARCINOMA		0	0	0	1	0	1	0	0
--ACUTE INFLAMMATION		0	0	0	0	0	1	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	0	0	0	0	1
--NECROTIZING DERMATITIS		2	0	0	0	0	2	1	0
--ACANTHOSIS		0	0	0	0	1	1	0	0
CAVITY, ABDOM (PC)	NUMBER EXAMINED:	1	0	2	1	1	4	1	0
	NOT REMARKABLE:	0	0	0	0	1	1	0	0
--INFLAMMATION, CHRONIC ACTIVE		0	0	1	1	0	0	0	0
--ABSCESS		0	0	1	0	0	0	0	0
--I-CARCINOMA, BILE DUCT		0	0	0	0	0	0	1	0
--PERITONITIS		1	0	0	0	0	0	0	0
--N-FIBROSARCOMA		0	0	0	0	0	1	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	1	0	0
--FAT NECROSIS		0	0	0	0	0	1	0	0
PREPUTIAL GLAND (PG)	NUMBER EXAMINED:	3	1	0	1	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0
--ABSCESS		1	1	0	0	0	0	0	0
--DUCT ECTASIA		2	0	0	1	0	0	0	0

Incidence of microscopic findings in mice "Unscheduled deaths"

INCIDENCE OF MICROSCOPIC OBSERVATIONS - UNSCHEDULED DEATHS

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN MICE

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=UNSCHED;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		- NUMBER OF ANIMALS AFFECTED - SEX:	-MALE-				-FEMALE-			
		GROUP:	-1-	-3-	-4-	-5-	-1-	-2-	-3-	-4-
		NUMBER:	12	12	9	13	15	17	22	15
LN, OTHER (LN)	NUMBER EXAMINED:		4	2	3	0	6	9	2	5
	NOT REMARKABLE:		0	0	2	0	2	2	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA"	FOR TYPE)		3	2	1	0	3	5	2	4
--HYPERPLASIA, LYMPHOID			0	0	0	0	0	1	0	1
--LYMPHANGIECTASIS			1	0	0	0	1	1	0	0
--HEMORRHAGE			1	0	0	0	1	0	0	0
--DEPLETION, LYMPHOID			0	0	0	0	1	0	0	0
SUBCUTANEOUS TIS (SQ)	NUMBER EXAMINED:		1	5	2	0	2	3	3	0
	NOT REMARKABLE:		0	0	0	0	0	0	0	0
--M-FIBROSARCOMA			1	1	1	0	1	1	3	0
--EDEMA			0	1	0	0	1	2	0	0
--HEMORRHAGE			0	1	0	0	0	0	0	0
--GRANULOMATOUS INFLAMMATION			0	0	1	0	0	0	0	0
--ABSCESS			0	1	0	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA"	FOR TYPE)		0	1	0	0	0	0	0	0
CAVITY, THORACIC (TA)	NUMBER EXAMINED:		1	0	1	0	0	1	1	0
	NOT REMARKABLE:		0	0	0	0	0	1	0	0
--CHRONIC-ACTIVE INFLAMMATION			0	0	1	0	0	0	0	0
--I-FIBROSARCOMA			1	0	0	0	0	0	1	0
PENIS (PE)	NUMBER EXAMINED:		3	1	1	1	0	0	0	0
	NOT REMARKABLE:		2	0	0	0	0	0	0	0
--NECROSIS			1	1	0	0	0	0	0	0
--INFLAMMATION, ACUTE			1	0	1	1	0	0	0	0
MUSCLE, OTHER (OM)	NUMBER EXAMINED:		1	0	0	0	0	1	0	1
	NOT REMARKABLE:		0	0	0	0	0	1	0	0
--M-RHABDOMYOSARCOMA			0	0	0	0	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA"	FOR TYPE)		1	0	0	0	0	0	0	0
CLITORAL GLAND (CL)	NUMBER EXAMINED:		0	0	0	0	0	1	0	1
	NOT REMARKABLE:		0	0	0	0	0	1	0	0
--M-CARCINOMA			0	0	0	0	0	0	0	1
BONE, OTHER (OB)	NUMBER EXAMINED:		0	0	0	0	0	0	1	0
	NOT REMARKABLE:		0	0	0	0	0	0	0	0
--M-OSTEOSARCOMA			0	0	0	0	0	0	1	0
URETER (UE)	NUMBER EXAMINED:		0	0	0	1	0	0	0	0
	NOT REMARKABLE:		0	0	0	0	0	0	0	0
--INFLAMMATION, CHRONIC			0	0	0	1	0	0	0	0
--DILATATION			0	0	0	1	0	0	0	0

*** END OF LIST ***

Incidence of microscopic findings in mice "Terminal Sacrifice"

Incidence of Microscopic Observations – Terminal Sacrifice

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN MICE

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		- NUMBER - OF - ANIMALS - AFFECTED -							
SEX:		-------MALE-------				------FEMALE------			
GROUP:		-1-	-3-	-4-	-5-	-1-	-2-	-3-	-4-
NUMBER:		48	48	51	47	45	43	38	45
*** TOP OF LIST ***									
BRAIN W/STEM (BR)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	48	48	51	47	44	40	37	45
--COMPRESSION, VENTRAL		0	0	0	0	0	2	1	0
--PERIVASCULAR MONONUCLEAR CELL INFILTRATION		0	0	0	0	1	2	0	0
CORD, CERVICAL (CS)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	48	48	51	47	45	41	38	45
--PERIVASCULAR MONONUCLEAR CELL INFILTRATION		0	0	0	0	0	2	0	0
CORD, THORACIC (TC)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	48	48	51	47	45	41	38	45
--PERIVASCULAR MONONUCLEAR CELL INFILTRATION		0	0	0	0	0	2	0	0
CORD, LUMBAR (LC)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	48	48	51	47	45	40	38	45
--PERIVASCULAR MONONUCLEAR CELL INFILTRATION		0	0	0	0	0	3	0	0
PITUITARY (PI)	NUMBER EXAMINED:	46	48	49	43	44	43	38	45
	NOT REMARKABLE:	45	47	48	42	24	30	33	31
--HYPERPLASIA		0	1	0	1	6	3	1	5
--B-ADENOMA		0	0	1	0	11	10	3	6
--CYST		1	1	0	0	1	0	1	0
--FOCAL ANGIECTASIS		0	0	0	0	2	0	0	3
--HEMATOCYST		0	0	0	0	0	0	0	1
ADRENAL, CORTEX (AC)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	40	42	47	41	42	39	34	43
--UNILATERALLY EXAMINED		3	1	0	1	0	3	1	1
--B-ADENOMA, SUBCAPSULAR CELL		2	0	0	2	0	1	1	0
--AMYLOIDOSIS		0	0	0	0	1	0	0	0
--HYPERTROPHY		3	4	4	4	1	0	0	1
--HYPERPLASIA, FOCAL, SUBCAPSULAR CELL		0	1	0	0	0	0	0	0
--CYST		0	0	0	0	1	0	0	0
--VACUOLIZATION		0	0	0	0	0	0	2	0
ADRENAL, MEDULLA (AM)	NUMBER EXAMINED:	47	48	50	47	45	43	35	44
	NOT REMARKABLE:	43	43	46	45	41	39	30	39
--UNILATERALLY EXAMINED		4	5	2	2	2	4	3	5
--B-PHEOCHROMOCYTOMA		0	0	1	0	1	0	1	0
--HYPERPLASIA		0	0	1	0	1	0	1	0
THYROID (TY)	NUMBER EXAMINED:	48	48	51	47	44	43	38	45
	NOT REMARKABLE:	48	47	50	45	42	41	35	43
--B-FOLLICULAR CELL ADENOMA		0	1	0	0	0	0	0	0
--FOLLICLE, CYST		0	0	1	1	1	2	2	1
--HYPERPLASIA, FOLLICULAR CELL		0	0	0	1	1	0	2	1
PARATHYROID (PT)	NUMBER EXAMINED:	43	38	35	44	41	32	27	42
	NOT REMARKABLE:	43	38	34	43	41	31	27	42
--CYST		0	0	1	1	0	1	0	0
ESOPHAGUS (ES)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	48	48	51	47	45	43	38	45
LUNG (LU)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	28	39	31	34	39	38	34	38
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	0	0	0	0	1
--INFLAMMATION, ACUTE		1	0	0	0	0	0	0	0
--M-CARCINOMA, BRONCHIOLAR-ALVEOLAR		7	2	0	3	1	0	1	2
--INCREASED LYMPHOID INFILTRATE		0	0	1	0	0	1	1	0
--B-ADENOMA, BRONCHIOLAR-ALVEOLAR		7	3	13	3	2	1	1	3
--ALVEOLUS, MACROPHAGES, PIGMENTED		0	0	1	0	0	0	0	0
--ALVEOLAR MACROPHAGES		0	1	0	0	0	1	0	0
--ALVEOLUS/BRONCHUS EPITHELIAL HYPERPLASIA		4	2	4	4	1	0	1	1
--N-CARCINOMA, HEPATOCELLULAR		0	1	1	1	0	0	0	0
--EMBOLUS		0	0	0	1	0	0	0	0
--FOCAL SUBACUTE INFLAMMATION		0	0	1	1	0	0	0	0
--CARTILAGINOUS METAPLASIA		0	0	0	0	1	0	0	0
--CHRONIC INFLAMMATION, PLEURA		0	0	0	0	1	1	0	1
--N-CARCINOMA, UTERUS		0	0	0	0	0	1	0	0
--MINERALIZATION		0	0	1	0	0	0	0	0
HEART (HT)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	47	47	49	40	43	40	36	43
--MINERALIZATION		0	0	0	3	0	0	0	0
--CARDIOMYOPATHY, DEGENERATIVE		1	1	1	3	1	1	0	0
--PERIARTERITIS		0	0	0	1	1	2	2	2
--INFLAMMATION, ACUTE		0	0	1	0	0	0	0	0
SPLEEN (SP)	NUMBER EXAMINED:	48	48	50	47	45	43	38	45
	NOT REMARKABLE:	38	30	36	38	25	17	19	27
--EXTRAMEDULLARY HEMATOPOIESIS, INCREASED		2	11	5	4	2	4	3	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		3	2	0	1	4	2	4	6
--ABSCESS		0	0	0	0	0	1	0	0
--M-HEMANGIOSARCOMA		2	0	2	1	2	0	1	1
--LYMPHOID HYPERPLASIA		3	4	4	3	12	17	12	10
--ANGIECTASIS		0	1	3	1	0	3	0	0
--B-HEMANGIOMA		0	0	0	0	0	1	0	1
--LYMPHORETICULAR HYPERPLASIA		0	2	0	0	0	0	0	0

Incidence of microscopic findings in mice "Terminal Sacrifice"

INCIDENCE OF MICROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN MICE

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		NUMBER OF ANIMALS AFFECTED							
SEX:		MALE				FEMALE			
GROUP:		-1-	-3-	-4-	-5-	-1-	-2-	-3-	-4-
	NUMBER:	48	48	51	47	45	43	38	45
LIVER (LI)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	20	19	32	19	13	17	8	13
--M-CARCINOMA, HEPATOCELLULAR		7	8	1	4	2	0	0	0
--B-ADENOMA, HEPATOCELLULAR		9	6	8	7	9	6	4	2
--FOCUS OF VACUOLATED HEPATOCYTES		4	4	0	5	2	7	1	3
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	1	3	2	3	4
--EXTRAMEDULLARY HEMATOPOIESIS, INCREASED		0	0	0	0	2	0	0	1
--PIGMENT		0	0	1	1	1	1	0	2
--LYMPHOHISTIOCYTIC INFILTRATE		9	8	8	9	13	17	17	14
--FOCAL NECROSIS		2	4	1	4	0	0	1	1
--M-HEMANGIOSARCOMA		0	3	1	0	0	0	0	0
--ANGIECTASIS		0	1	0	0	0	0	1	0
--B-HEMANGIOMA		1	0	1	0	0	0	1	0
--CELLULAR ALTERATION, EOSINOPHILIC		2	0	0	0	0	0	0	0
--KUPFFER CELL, HYPERPLASIA		1	0	0	0	0	0	0	0
--VACUOLIZATION		1	0	0	0	1	0	0	2
--CELLULAR ALTERATION, BASOPHILIC		1	2	3	7	3	1	0	0
--FOCAL SUBACUTE INFLAMMATION		0	2	0	2	7	3	9	14
--DEGENERATION, LOBAR		0	0	0	0	1	0	0	0
--M-ITO-CELL NEOPLASM		0	0	0	0	1	0	0	0
KIDNEY (KD)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	0	2	3	1	17	24	22	6
--PYELONEPHRITIS		0	0	0	2	0	1	0	0
--NEPHROPATHY, CHRONIC PROGRESSIVE		47	46	48	44	18	10	10	22
--PELVIS, DILATATION		0	1	4	19	0	0	0	1
--INFARCT		0	4	0	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	0	2	0	1	1
--GLOMERULAR AMYLOIDOSIS		0	0	0	0	0	0	0	1
--INCREASED MICROCONCRETION, TUBULE		4	0	0	0	0	0	0	0
--INCREASED VACUOLIZATION, TUBULES		2	0	0	0	0	0	0	0
--INCREASED LYMPHOID INFILTRATE		2	3	4	6	8	12	4	10
--MINERALIZATION, PAPILLA		0	0	0	0	0	1	0	0
--CYST		15	9	4	22	0	0	1	5
--UNILATERALLY EXAMINED		0	0	0	0	1	0	0	0
--B-ADENOMA, TUBULAR CELL		1	0	0	0	0	1	0	0
--TUBULE, SIMPLE HYPERPLASIA		3	0	1	3	0	0	0	0
--OSSEOUS METAPLASIA		0	1	2	2	1	0	0	0
--B-PAPILLOMA, TRANSITIONAL CELL		0	0	1	0	0	0	0	0
--PERIARTERITIS		0	0	0	0	1	1	0	0
--INCREASED PIGMENT, TUBULE		0	0	0	0	5	0	2	27
--FOCAL SUBACUTE INFLAMMATION		0	0	1	0	0	0	0	0
STOMACH, NONGL (SU)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	47	48	48	44	43	42	38	42
--HYPERKERATOSIS		0	0	0	0	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	1	0	0	0
--CYST		0	0	2	1	1	0	0	2
--M-SQUAMOUS CELL CARCINOMA		1	0	0	0	0	0	0	0
--INFILTRATE, MAST CELL		0	0	0	1	0	0	0	0
--FOCAL NECROSIS		0	0	0	1	0	0	0	0
--ACANTHOSIS		0	0	1	0	0	1	0	1
STOMACH, GL (ST)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	47	48	50	46	45	42	37	44
--INFILTRATE, EOSINOPHIL		1	0	0	0	0	0	0	0
--MINERALIZATION		0	0	0	0	0	1	0	0
--FOCAL NECROSIS		0	0	1	1	0	0	1	1
DUODENUM (DU)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	48	45	49	47	45	42	38	43
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	0	1	0	2
--B-ADENOMATOUS POLYP		0	3	1	0	0	0	0	0
JEJUNUM (JE)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	48	46	50	47	43	40	38	44
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	1	0	0	2	0	1
--HYPERPLASIA, LYMPHOID		0	0	0	0	2	0	0	0
--AMYLOIDOSIS		0	1	0	0	0	0	0	0
--INFLAMMATION, CHRONIC		0	0	0	0	0	1	0	0
PANCREAS (PA)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	48	47	49	46	42	42	34	44
--DUCT ECTASIA		0	0	0	0	1	1	2	1
--ISLET CELL, HYPERPLASIA		0	0	0	1	0	0	0	0
--INFILTRATE, LYMPHOID		0	0	0	0	1	0	0	0
--PANCREATOLITHS		0	0	0	0	0	1	0	0
--B-ADENOMA, ISLET CELL		0	1	0	0	1	0	0	0
--DEGENERATION		0	0	2	0	0	0	3	0
CECUM (CE)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	48	48	51	47	45	43	37	45
--HYPERPLASIA, LYMPHOID		0	0	0	0	0	0	1	0
COLON (CO)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	48	47	51	47	45	43	38	45
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	0	0	0	0	0
RECTUM (RE)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	48	48	51	47	45	43	38	45
LN, MESENTERIC (MS)	NUMBER EXAMINED:	46	46	50	47	43	43	38	42
	NOT REMARKABLE:	35	41	39	40	37	36	34	36
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	2	1	0	2	3	2	5

Incidence of microscopic findings in mice "Terminal Sacrifice"

INCIDENCE OF MICROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN MICE

		- N U M B E R - O F - A N I M A L S - A F F E C T E D							
TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=1-106 DEATH=T;FIND=ALL;SUBSET=ALL	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-3-	-4-	-5-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	48	48	51	47	45	43	38	45
*** FROM PREVIOUS PAGE ***									
LN, MESENTERIC (MS)	NUMBER EXAMINED:	46	46	50	47	43	43	38	42
	NOT REMARKABLE:	35	41	39	40	37	36	34	36
--ANGIECTASIS		7	2	7	4	0	2	0	1
--LYMPHOID DEPLETION		1	0	1	0	0	0	0	0
--HYPERPLASIA, RETICULOENDOTHELIAL		3	1	2	2	4	2	1	0
--INCREASED PIGMENT		0	0	0	1	0	1	0	0
--ABSCESS		0	0	0	0	0	0	1	0
LN, MANDIBULAR (MN)	NUMBER EXAMINED:	47	47	49	44	45	43	38	45
	NOT REMARKABLE:	47	45	43	41	41	38	30	39
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	2	1	2	3
--LYMPHOID HYPERPLASIA		0	0	0	0	2	1	1	2
--INCREASED PIGMENT		0	2	6	3	0	3	5	1
MAND SALIVARY GL (SG)	NUMBER EXAMINED:	48	48	51	47	45	41	38	45
	NOT REMARKABLE:	48	48	50	47	41	40	38	39
--INCREASED LYMPHOID INFILTRATE		0	0	0	0	1	0	0	1
--DILATED DUCTS		0	0	0	0	2	1	0	5
--DEGENERATION		0	0	1	0	1	0	0	0
PAROTID SALIVARY (SG0)	NUMBER EXAMINED:	48	48	51	47	45	42	38	45
	NOT REMARKABLE:	47	48	50	47	45	41	38	45
--DEGENERATION		0	0	1	0	0	0	0	0
--HYPERTROPHY		1	0	0	0	0	0	0	0
--DILATED DUCTS		0	0	0	0	0	1	0	0
THYMUS (TH)	NUMBER EXAMINED:	42	44	48	35	42	42	38	45
	NOT REMARKABLE:	42	44	48	35	37	37	36	44
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	3	1	1
--HYPERPLASIA, LYMPHORETICULAR		0	0	0	0	4	2	1	0
--ANGIECTASIS		0	0	0	0	1	0	0	0
EYE (EY)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	46	46	48	45	41	40	37	42
--UNILATERALLY EXAMINED		1	0	0	0	0	1	0	0
--KERATITIS		1	1	2	1	2	0	1	1
--CHRONIC INFLAMMATION, PERIORBITAL		1	0	0	0	0	0	0	1
--PHTHISIS		0	1	1	1	2	0	0	1
--MINERALIZATION, CORNEA		0	0	0	0	0	2	0	0
HARDERIAN GLAND (HG)	NUMBER EXAMINED:	48	47	51	47	45	43	38	45
	NOT REMARKABLE:	24	14	20	23	29	23	25	27
--UNILATERALLY EXAMINED		3	0	0	0	0	1	0	0
--M-CARCINOMA		1	0	0	0	0	1	0	1
--HYPERPLASIA		0	1	1	0	1	0	0	0
--DUCT ECTASIA		0	0	1	0	0	0	0	0
--B-ADENOMA		4	5	9	1	2	3	1	2
--DEGENERATION		20	31	26	23	14	15	12	15
MUSCLE, SKELETAL (SM)	NUMBER EXAMINED:	48	47	50	47	45	42	37	45
	NOT REMARKABLE:	46	44	45	47	45	34	33	45
--DEGENERATION		1	0	0	0	0	0	1	0
--LYMPHOID INFILTRATE		1	3	5	0	0	8	3	0
NERVE, SCIATIC (SN)	NUMBER EXAMINED:	45	47	51	46	44	43	38	42
	NOT REMARKABLE:	9	7	2	3	2	2	7	4
--DEGENERATION		36	40	49	43	42	41	31	38
--LYMPHOCYTIC INFILTRATE		0	0	0	0	0	1	0	0
TONGUE (TO)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	48	48	51	46	45	42	37	45
--PERIARTERITIS		0	0	0	1	0	1	1	0
TESTIS (TE)	NUMBER EXAMINED:	48	48	51	47	0	0	0	0
	NOT REMARKABLE:	37	43	38	40	0	0	0	0
--DEGENERATION		5	4	13	7	0	0	0	0
--MINERALIZATION		5	1	1	0	0	0	0	0
--UNILATERALLY EXAMINED		1	0	0	0	0	0	0	0
--HYPERPLASIA, INTERSTITIAL CELL		0	0	0	2	0	0	0	0
--B-BENIGN INTERSTITIAL CELL TUMOR		0	0	1	0	0	0	0	0
--SPERMATOCELE		0	1	0	0	0	0	0	0
EPIDIDYMIS (EP)	NUMBER EXAMINED:	48	48	51	47	0	0	0	0
	NOT REMARKABLE:	41	43	43	40	0	0	0	0
--SPERM, ABNORMAL MORPHOLOGY		3	0	0	2	0	0	0	0
--HYPOSPERMIA		3	3	6	4	0	0	0	0
--UNILATERALLY EXAMINED		1	0	0	1	0	0	0	0
EPIDIDYMIS (EP)	NUMBER EXAMINED:	48	48	51	47	0	0	0	0
	NOT REMARKABLE:	41	43	43	40	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	1	0	0	0	0	0
--LYMPHOHISTIOCYTIC INFILTRATE		0	1	1	0	0	0	0	0
PROSTATE (PR)	NUMBER EXAMINED:	48	48	51	47	0	0	0	0
	NOT REMARKABLE:	48	47	51	47	0	0	0	0
--INFLAMMATION, CHRONIC ACTIVE		0	1	0	0	0	0	0	0

Incidence of microscopic findings in mice "Terminal Sacrifice"

INCIDENCE OF MICROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN MICE

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		- NUMBER - OF - ANIMALS - AFFECTED							
SEX:		-------MALE-------				------FEMALE------			
GROUP:		-1-	-3-	-4-	-5-	-1-	-2-	-3-	-4-
NUMBER:		48	48	51	47	45	43	38	45
SEMINAL VESICLE (SV)	NUMBER EXAMINED:	48	48	51	47	0	0	0	0
	NOT REMARKABLE:	48	48	51	46	0	0	0	0
--HEMORRHAGE		0	0	0	1	0	0	0	0
URINARY BLADDER (UB)	NUMBER EXAMINED:	48	48	50	47	45	43	38	45
	NOT REMARKABLE:	25	28	27	3	18	10	13	11
--LYMPHOHISTIOCYTIC INFILTRATE		23	20	19	20	27	33	25	34
--DISTENTION		0	1	6	37	0	0	0	2
--INFLAMMATION, ACUTE		0	0	0	2	0	0	0	0
--HYPERPLASIA		0	0	5	31	0	0	0	0
OVARY (OV)	NUMBER EXAMINED:	0	0	0	0	44	41	37	44
	NOT REMARKABLE:	0	0	0	0	16	20	20	22
--UNILATERALLY EXAMINED		0	0	0	0	5	2	1	0
--ABSCESS		0	0	0	0	3	1	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	0	1	1
--FOLLICLE, CYST		0	0	0	0	18	15	13	12
--HEMATOCYST		0	0	0	0	4	5	2	6
--THROMBUS		0	0	0	0	1	0	0	1
--ANGIECTASIS		0	0	0	0	0	1	0	1
--B-PAPILLARY CYSTADENOMA		0	0	0	0	1	0	0	0
--CHOLESTERINIC GRANULOMA		0	0	0	0	1	0	0	0
--BURSA, CYST		0	0	0	0	1	0	0	2
--MINERALIZATION		0	0	0	0	1	0	0	0
--B-GRANULOSA/THECA CELL TUMOR		0	0	0	0	0	0	0	1
--PAPILLARY HYPERPLASIA		0	0	0	0	0	1	2	0
UTERUS (UT)	NUMBER EXAMINED:	0	0	0	0	45	43	38	45
	NOT REMARKABLE:	0	0	0	0	5	1	1	7
--HYPERPLASIA, CYSTIC ENDOMETRIAL		0	0	0	0	36	41	37	32
--DILATATION		0	0	0	0	1	2	1	3
--M-HEMANGIOSARCOMA		0	0	0	0	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	0	0	1
--B-ENDOMETRIAL STROMAL POLYP		0	0	0	0	1	1	1	3
--THROMBUS		0	0	0	0	0	0	0	1
--M-CARCINOMA		0	0	0	0	0	1	1	1
--ABSCESS		0	0	0	0	2	1	1	0
--B-HEMANGIOMA		0	0	0	0	1	0	0	0
--B-LEIOMYOMA		0	0	0	0	1	0	1	1
--DECIDUA		0	0	0	0	0	0	0	1
--HEMORRHAGE		0	0	0	0	0	0	2	0
UTERUS, CERVIX (CV)	NUMBER EXAMINED:	0	0	0	0	45	42	37	45
	NOT REMARKABLE:	0	0	0	0	43	41	37	45
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	1	0	0
--HYPERTROPHY, SMOOTH MUSCLE		0	0	0	0	2	0	0	0
VAGINA (VA)	NUMBER EXAMINED:	0	0	0	0	45	43	38	45
	NOT REMARKABLE:	0	0	0	0	44	43	38	45
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	1	0	0	0
MAMMARY/F-CRAN (MF0)	NUMBER EXAMINED:	0	0	0	0	31	38	38	28
	NOT REMARKABLE:	0	0	0	0	28	34	35	28
--GALACTOCELE		0	0	0	0	1	4	2	0
--M-CARCINOMA		0	0	0	0	2	0	1	0
MAMMARY/F-CAUD (MF1)	NUMBER EXAMINED:	0	0	0	0	26	36	37	21
	NOT REMARKABLE:	0	0	0	0	25	32	36	21
--GALACTOCELE		0	0	0	0	1	4	1	0
SKIN (SK)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	48	48	51	46	45	43	38	44
--FOCUS OF MAST CELLS		0	0	0	1	0	0	0	0
--ACANTHOSIS		0	0	0	0	0	0	0	1
MARROW, STERNUM (SE)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	48	47	50	47	40	40	38	44
--HYPERCELLULAR		0	1	1	0	5	3	0	1
BONE, STERNUM (SB)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	48	48	50	47	4	4	0	0
--CHONDROPATHY		0	0	1	0	2	1	0	0
--FIBROUS-OSSEOUS CHANGE		0	0	0	0	41	38	38	45
MARROW, FEMUR (FM)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	48	47	49	47	37	41	38	41
--HYPERCELLULAR		0	1	2	0	6	2	0	3
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	1	0	0	0
--M-HEMANGIOSARCOMA		0	0	0	0	1	0	0	0
--FOCAL DEPLETION		0	0	0	0	0	0	0	1

Incidence of microscopic findings in mice "Terminal Sacrifice"

INCIDENCE OF MICROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN MICE

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		-- NUMBER OF ANIMALS AFFECTED --							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-3-	-4-	-5-	-1-	-2-	-3-	-4-
	NUMBER:	48	48	51	47	45	43	38	45
BONE, FEMUR (FE)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	46	47	51	47	31	36	26	27
--OSTOSIS		0	0	0	0	5	2	1	0
--FIBROUS-OSSEOUS CHANGE		2	1	0	0	8	4	11	18
--CHRONIC-ACTIVE INFLAMMATION		0	0	0	0	0	1	0	0
--CHONDROPATHY		0	0	0	0	1	0	0	0
VERTEBRAE, L1 (OB0)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	48	47	51	47	17	18	8	8
--FIBROUS-OSSEOUS CHANGE		0	0	0	0	28	25	30	37
--I-FIBROSARCOMA		0	1	0	0	0	0	0	0
VERTEBRAE, L2 (OB1)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	48	47	50	47	15	17	6	7
--FIBROUS-OSSEOUS CHANGE		0	0	1	0	30	26	32	38
--I-FIBROSARCOMA		0	1	0	0	0	0	0	0
^DEATH COMMENT (DC)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	0	0	0	0	0	0	0	0
--SCHEDULED SACRIFICE		48	48	51	47	45	43	38	45
HEMATO NEOPLASIA (HN)	NUMBER EXAMINED:	48	48	51	47	45	43	38	45
	NOT REMARKABLE:	45	45	49	46	39	37	33	36
--M-SARCOMA, HISTIOCYTIC		0	2	1	0	0	1	0	2
--M-MALIGNANT LYMPHOMA, LYMPHOCYTIC		3	1	1	1	4	5	5	7
--M-LEUKEMIA, MAST CELL		0	0	0	0	1	0	0	0
--M-LEUKEMIA, GRANULOCYTIC		0	0	0	0	1	0	0	0
SKIN, OTHER (SS)	NUMBER EXAMINED:	24	30	27	21	41	37	25	32
	NOT REMARKABLE:	23	28	26	17	39	37	25	30
--ACANTHOSIS		0	0	1	3	1	0	0	2
--INFLAMMATION, CHRONIC		1	1	0	2	0	0	0	0
--LYMPHOHISTIOCYTIC INFILTRATE		1	0	0	0	0	0	0	0
--ABSCESS		0	0	0	1	1	0	0	0
--FOCUS OF MAST CELLS		0	1	0	0	0	0	0	0
--NECROTIC CELL DEBRIS ON EPIDERMAL SURFACE		0	0	0	0	1	0	0	1
CAVITY, ABDOM (PC)	NUMBER EXAMINED:	1	1	3	1	6	1	0	3
	NOT REMARKABLE:	1	0	0	1	0	0	0	0
--INFLAMMATION, CHRONIC ACTIVE		0	1	1	0	1	0	0	0
--PERITONITIS		0	0	0	0	1	0	0	0
--N-FIBROSARCOMA		0	0	0	0	0	0	0	1
--ADHESION		0	0	1	0	0	0	0	1
--I-HEPATOCELLULAR CARCINOMA		0	0	1	0	0	0	0	0
--FAT NECROSIS		0	0	0	0	5	0	0	1
--PERIARTERITIS		0	0	0	0	1	0	0	1
--I-CARCINOMA, UTERUS		0	0	0	0	0	1	0	0
PREPUTIAL GLAND (PG)	NUMBER EXAMINED:	10	17	13	9	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0
--ABSCESS		6	8	2	2	0	0	0	0
--DUCT ECTASIA		7	12	13	8	0	0	0	0
--HYPERKERATOSIS		2	0	0	0	0	0	0	0
--INFLAMMATION, CHRONIC		1	1	1	1	0	0	0	0
LN, OTHER (LN)	NUMBER EXAMINED:	0	7	2	0	10	7	9	10
	NOT REMARKABLE:	0	5	1	0	2	2	4	4
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	0	2	2	3	5
--HYPERPLASIA, LYMPHOID		0	1	1	0	6	2	3	1
--N-CARCINOMA, UTERUS		0	0	0	0	0	1	0	0
SUBCUTANEOUS TIS (SQ)	NUMBER EXAMINED:	0	1	1	0	1	0	0	1
	NOT REMARKABLE:	0	0	0	0	0	0	0	0
--M-FIBROSARCOMA		0	1	1	0	0	0	0	1
--ABSCESS		0	0	0	0	1	0	0	0
CAVITY, THORACIC (TA)	NUMBER EXAMINED:	0	0	0	0	0	1	0	1
	NOT REMARKABLE:	0	0	0	0	0	0	0	1
--INFLAMMATION, CHRONIC		0	0	0	0	0	1	0	0
URETER (UE)	NUMBER EXAMINED:	0	0	0	1	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0
--INFLAMMATION, CHRONIC		0	0	0	1	0	0	0	0
--DILATATION		0	0	0	1	0	0	0	0
NERVE, OPTIC (ON)	NUMBER EXAMINED:	0	0	0	0	1	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0
--DEGENERATION		0	0	0	0	1	0	0	0

*** END OF LIST ***

Toxicokinetics:

- Plasma conivaptan concentrations were expressed as free base.
- T_{max} ranged between 2 and 4 hrs in mice
- The exposure increased in a dose proportional manner in mice
- The drug exposure 3 and 10 mg/kg/d were higher (23 and 159%) in female than male mice.

Table 2.6.6-80: Carcinogenicity study in mice – toxicokinetics [R087-TX-054]

Daily Dose (mg/kg)	1	3		10		30
Gender	F	M	F	M	F	M
Toxicokinetics: Week 53						
C_{max} (ng/mL)	32.9	157	191	771	1340	2880
AUC_{0-24} (ng·hr/mL)	117	509	628	3370	8725	21851

Drug exposure relative to clinical dose

Carci Doses	Dose, mg/kg/d	AUC_{0-24} ng.h/ml	Animal to human dose exposure ratio
104-WK mouse carci study	F: 1	F: 117	F: 0.03
	M: 3 F: 3	M: 509 F: 628	M: 0.14 F: 0.17
	M: 10 F: 10	M: 3370 F: 8725	M: 0.94 F: 2.5
	M: 30	M: 21851	M: 6
Clinical Dose: 20 mg bolus + 40 mg IV infusion for 4 days, average daily AUC		3580	

Study title: 104-Week carcinogenicity Gavage Study of YM087 in rats

Key study findings:
Sixty male an female CDF® (F-344) [redacted]BR rats in the main study and 20/dose in the toxicokinetic study were treated daily with oral gavage solution of conivaptan hydrochloride in 0.5% methylcellulose for 104 weeks and 53 weeks, respectively. Male rats were treated with 0.3, 1, 3, and 10 mg/kg/d (0.006, 0.03, 0.3 and 1.96 x human dose based on AUC)) and females with 1, 3, 10 and 30 mg/kg/d (0.05, 0.4, 2 and 7 x human dose based on $AUC_{0\text{-}24}$).
At the end of the study (WK 104), the survival rate in male rats were 39/60 (65%), 38/60 (63%), 44/60 (73%), 33/60 (53%) and 21/60 (35%) at 0, 0.3, 1, 3 and 10 mg/kg/d, respectively. The survival rate in female rats were 45/59 (76%), 44/60 (73%), 34/60 (57%), 29/60 (48%) and 18/59 (31%) at 0, 1, 3, 10 and 30 mg/kg/d, respectively. Conivaptan increased mortality in a dose-dependent manner in both male and female rats. Trend analysis found no significant dose-related increase in incidence of any neoplastic tumor in rats.

Adequacy of the carcinogenicity study and appropriateness of the test model:
The doses used in the rat carci study were not submitted for eCAC review. The MTD in the 13 and 26-WK rat toxicology studies were used in dose selection. In the 13-WK rat study, a significant decrease in BW gain was observed in males at 10 mg/kg/d with no change in females. However, in the 26-WK study, the BW gain of the females was decreased by 15% at 10 mg/kg/d. In the 26-WK study (1, 3, 10 and 100 mg/kg/d) a significant decrease in body weight at 3 (M: -7%, F: 8%), 10 (M: -16%, F: -8%) and 100 mg/kg/d (M: -32%, F: 9%) was observed. In addition, the number of deaths at 10 mg/kg/d (3/15 males and 4/15 female) and 100 mg/kg/d (4/15 males and 2/15 females), suggesting that 10 mg/kg/d is MTD. The dose-related increases in mortality rate in both males and females in the 2-year carci study suggest that the highest dose used had reached or exceeded the MTD. ECAC reviewed the results of this study on 8/3/04 and concluded that the study was adequate based on decreased survival at $\geqslant$ 3 mg/kg/day.

Evaluation of tumor findings:
There were no treatment related increases in neoplastic tumors in males or females in the 2-year rat carcinogenicity study.

Study no.: R087-TX-047 (20003910)
Volume #, and page #: 1-6, 1-2981
Conducting laboratory and location: [redacted]
Date of study initiation: May 15, 1997 (completed in Aug 28, 2003)
GLP compliance: yes
QA report: yes (x) no ( )
Drug, lot #, and % purity:

Lot No.	Date Received	Weeks Used	Purity
BC0874Z	April 28, 1997	Prestudy-47	[redacted]
BC0874Z	April 30, 1998	48-62	
08701	July 2, 1998	62-105	

CAC concurrence: No

Methods

Doses: males: 0.3, 1, 3 and 10 mg/kg/d and females: 1, 3, 10 and 30 mg/kg/d

Group	Dosage Level mg/kg/day	Concentration mg/mL	Number of Animals		Animal Numbers	
			Male	Female	Male	Female
Main Study						
1 (Control)	0	0.0	60	60	B90864-B90923	B90924-B90983
2 (Low)	0.3	0.06	60	-	B90984-B91043	-
3 (Mid-Low)	1	0.2	60	60	B91044-B91103	B91104-B91163
4 (Mid)	3	0.6	60	60	B91164-B91223	B91224-B91283
5 (Mid-High)	10	2.0	60	60	B91284-B91343	B91344-B91403
6 (High)	30	6.0	-	60	-	B91404-B91463
Satellite Study						
2 (Low)	0.3	0.06	20	-	B91464-B91483	-
3 (Mid-Low)	1	0.2	20	20	B91484-B91503	B91504-B91523
4 (Mid)	3	0.6	20	20	B91524-B91543	B91544-B91563
5 (Mid-High)	10	2.0	20	20	B91564-B91583	B91584-B91603
6 (High)	30	6.0	-	20	-	B91604-B91623

Basis of dose selection (MTD, MFD, AUC etc.): MTD
Species/strain: CDF® (F-344) BR rats
Number/sex/group (main study): 60/sex/dose
Route, formulation, volume: oral gavage solution, vehicle was 0.5% methylcellulose aqueous solution, 5 ml/kg/day, administered between 1000 and 1400 hrs
Frequency of dosing: once a day (dosing formulation was prepared weekly)
Satellite groups used for toxicokinetics or special groups: yes (20/sex/drug group)
Age: 22 to 24 days old, [redacted]
Animal housing: Stainless steel cages, housed in pairs
Restriction paradigm for dietary restriction studies: ad lib, pelleted rodent Diet #5002
Drug stability/homogeneity: stable for 2 years
Dual controls employed: single control group
Interim sacrifices: No
Deviations from original study protocol: The sponsor did not get the eCAC concurrence for the rat carci dose selection. The deviations from the protocol were not significantly different from the original protocol.

Observation times

Mortality: daily
Clinical signs: twice daily
Body weights: once a week
Food consumption: weekly
Histopathology: Peer review: yes (x), no ( )
Toxicokinetics: at 2, 4, 8 and 24 post dose during treatment week 53 from satellite group

Results

Mortality:

- Significant dose-dependent increase mortality in female rats at $\geq$ 3 mg/kg/d and males at 10 mg/kg/d suggest doses had exceeded MTD in the rat carci study

- The most common cause of death appeared to be foreign body pneumonia. Food particle associated pneumonia has been shown in other toxicology studies with this and other AVP antagonist.
- Survival in male rats was 65%, 63%, 73%, 53% and 35% at 0, 0.3, 1, 3 and 10 mg/kg/d, respectively.
- Survival in female rats was 76%, 73%, 57%, 48% and 31% at 0, 1, 3, 10 and 30 mg/kg/d, respectively.

Table 2.6.6-81: Carcinogenicity study in rats – survival data [R087-TX-047]

Daily Dose (mg/kg)	0		0.3	1		3		10		30
Gender	M	F	M	M	F	M	F	M	F	F
Animals Assigned	60	60	60	60	60	60	60	60	60	60
Week 26	60	59	60	60	60	60	60	59	60	60
Week 52	60	58	60	60	57	60	58	58	60	59
Week 78	58	57	57	58	56	55	54	45	52	49
Week 90	52	57	50	57	54	47	50	38	42	36
Terminal Sacrifice	39	45	38	42	44	32	34	19	29	17
Survival at Week 104 (%)	65	76	63	73	73	55	57††	35††	48††	31††

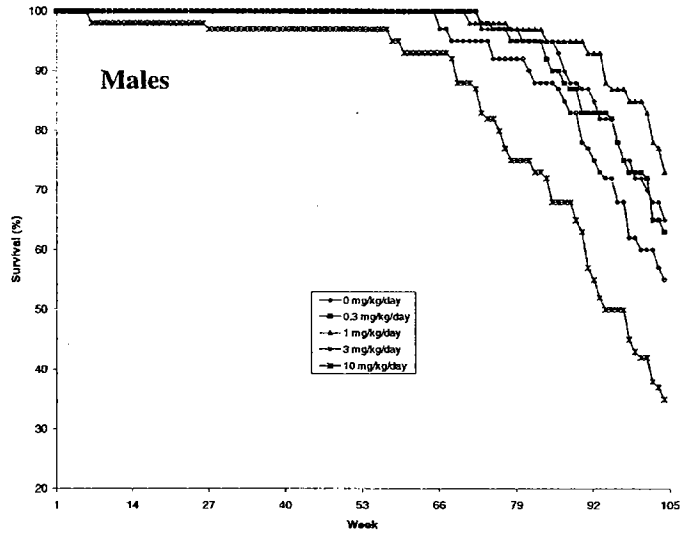
Cox-Tarone Binary Regression Methods and Gehan-Breslow Nonparametric Methods: †† - P<0.01

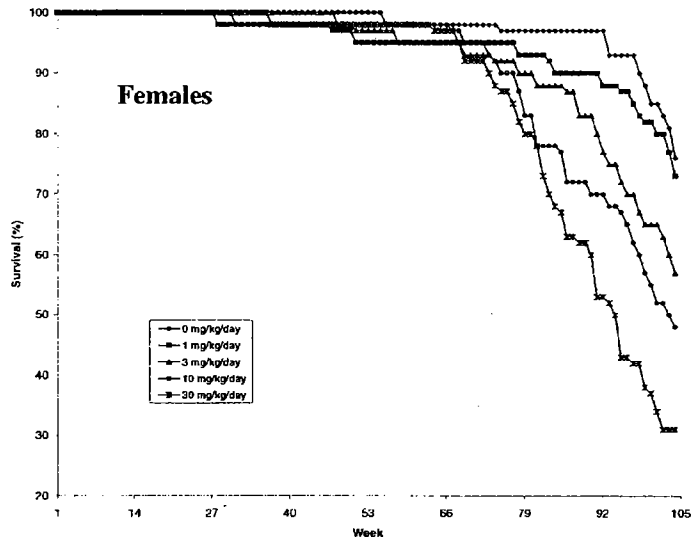
Mortality and Most Common Death Comments During 104 Week Course of Treatment

	MALE						FEMALE					
GROUP	1	2	3	4	5	6	1	2	3	4	5	6
TOTAL NO. EXAMINED	60	60	60	60	60	0	60	0	60	60	60	60
NO. DEAD/ MORIBUND	21	22	18	28	41	-	15	-	16	26	31	43
DEATH COMMENTS												
–Scheduled sacrifice	39	38	42	32	19	-	45	-	44	34	29	17
–Foreign-body pneumonia	1	1	2	17	30	-	0	-	0	12	20	30
–Hematopoietic neoplasia	7	8	8	2	4	-	3	-	7	9	3	2
–Pituitary neoplasia	8	2	1	5	1	-	4	-	2	2	5	3
–Total of other causes	5	8	3	2	5	-	6	-	9	1	4	3
–No determined cause	1	5	5	4	4	-	2	-	2	6	3	7

Note: Some animals had more than one lesion identified histologically as contributing to death; thus the numbers in the columns do not necessarily add up to the total numbers of animals examined.

Survival rate in rats treated with conivaptan for 2 years





Clinical signs:

- Hunched posture, thin appearance at $\geqslant$3 in males and $\geqslant$ 10 mg/kg/d in females
- Common observation were excessive urination and thirst related to drug

Body weights:

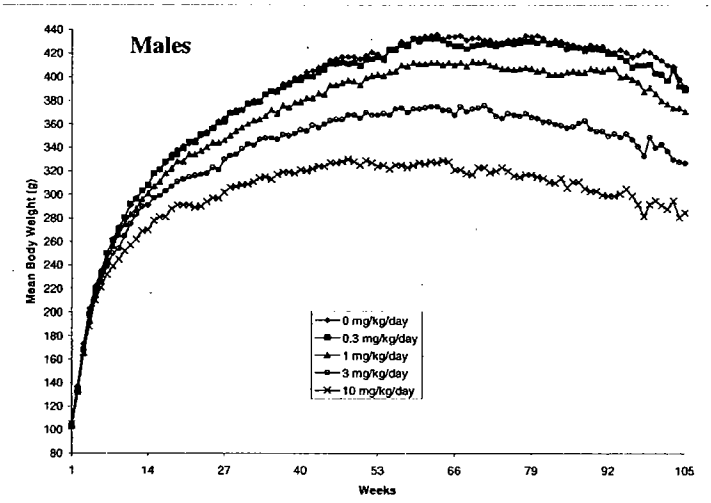
- Significant decrease in BW at 3 mg/kg/d (-15%), 10 mg/kg/d (-22%) and 30 mg/kg/d (-27%) in females and in males at 3 mg/kg/d (-17%) and 10 mg/kg/d (-29%)
- Significant decreases in BW gain (-7, -21, -32 and -41%) at 1, 3, 10 and 30 mg/kg/d in females and in males at 3 and 10 mg/kg/d (-22 and -36%, respectively)
- At start of the study the BW of males ranged from 103 to 106 g and in females from 88 to 89 g

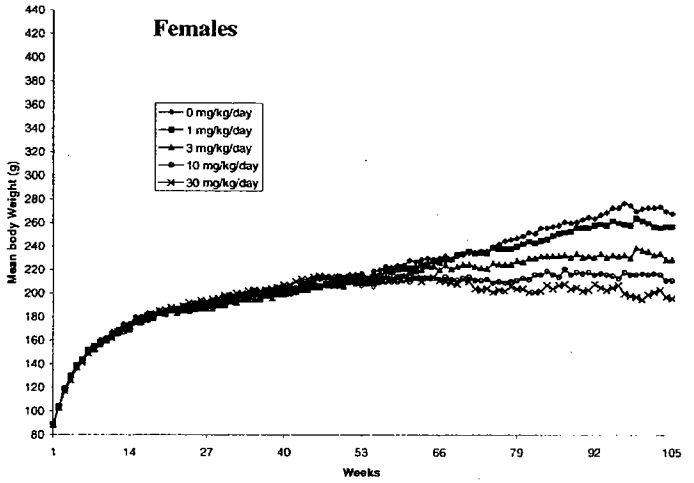
Table 2.6.6-82: Carcinogenicity study in rats – body weight [R087-TX-047]

Daily Dose (mg/kg)	0		0.3	1		3		10		30
Gender	M	F	M	M	F	M	F	M	F	F
Body Weight (g):										
Week 26	362	193	361	344*	189	321*	187*	297*	190	194
Week 52	421	216	415	401*	212	368*	209	327*	208*	213
Week 78	435	246	430	408*	238	369*	225*	317*	210*	206*
Week 104	398	270	392	374*	257	328*	229*	281*	211*	197*
Bodyweight Gain (Weeks 1-104):										
(g)	287	180	287	268	168*	223*	142*	183*	123*	107*
(% of Control)			100	93	93	78	79	64	68	59

Dunnett's Test: * - P<0.05

Body weight of male and female rats





Food consumption:

- There were sporadic changes in food intake at different time intervals particularly in the females. The decrease in food intake appeared to be associated with decrease in BW noted earlier.

Table 2.6.6-83: Carcinogenicity study in rats – food consumption [R087-TX-047]

Daily Dose (mg/kg)	0		0.3	1		3		10		30
Gender	M	F	M	M	F	M	F	M	F	F
Food Consumption (g/day):										
Week 25	19	12	19	19	13	19	13*	19	14*	14*
Week 53	19	12	20	20	13*	19	13*	19	14*	14*
Week 78	21	15	22*	22*	16*	21	16	20	15	15
Week 104	19	14	20	19	14	19	15	18	14	15

Dunnett's Test: * - P<0.05

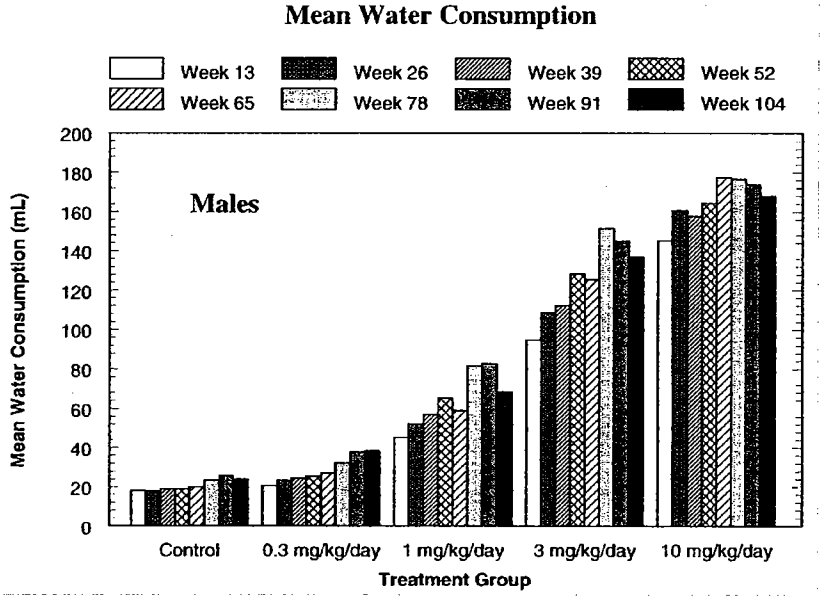
Water Consumption:

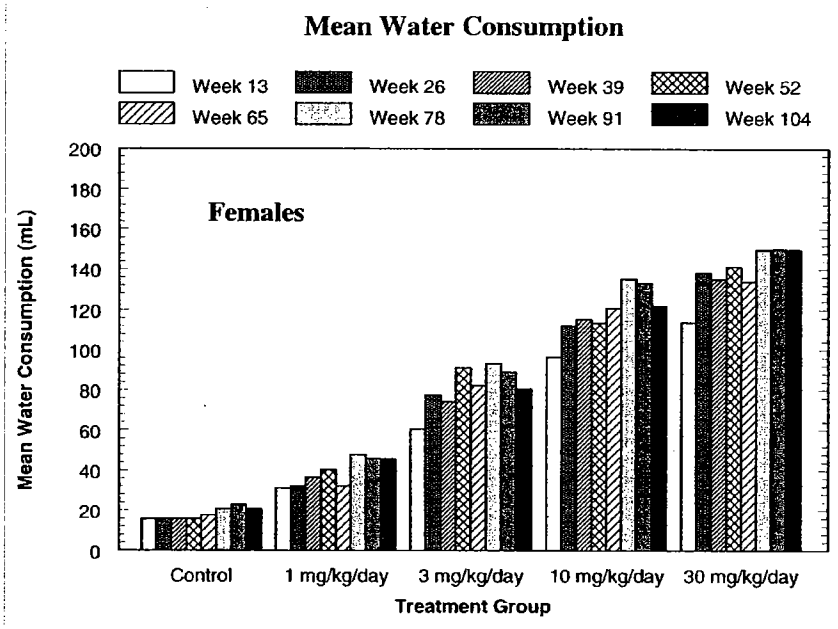
- Significant dose-dependent increase in water consumption (60% to 600%)
- The increase in water intake was consequence of powerful aquaresis produced by conivaptan

Table 2.6.6-84: Carcinogenicity study in rats – water consumption [R087-TX-047]

Daily Dose (mg/kg)	0		0.3	1		3		10		30
Gender	M	F	M	M	F	M	F	M	F	F
Water Consumption (g/day):										
Week 26	17.7	15.7	23.3*	52.1*	32.2*	108.7*	77.6*	160.6*	112.2*	138.5*
Week 52	18.8	15.7	25.4*	65.4*	40.2*	128.5*	91.2*	164.4*	113.4*	141.2*
Week 78	23.4	20.5	32.2*	81.6*	47.8*	151.4*	93.4*	176.7*	135.3*	149.7*
Week 104	23.9	20.5	38.3*	68.4*	45.5*	137.1*	80.7*	168.0*	122.1*	149.6*

Dunnett's Test: * - P<0.05





Gross pathology:

- Incidence of enlarged pituitary glands (primarily anterior) were noted in all groups, common to old F344 rats
- High incidence of abnormal testes (size and color) and associated interstitial cell tumors were observed in all males with greater incidence in survived rats
- Congestion /atelectasis in adrenal cortex in unscheduled necropsy rats at $\geqslant$10 mg/kg/d
- Increased splenic pigment in unscheduled necropsy rats at $\geqslant$10 mg/kg/d

Incidence of macroscopic findings in rats "unscheduled deaths"

Incidence of Macroscopic Observations - Unscheduled Deaths

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=UNSCHED;SUBSET=ALL		-- NUMBER-OF-ANIMALS-AFFECTED --											
	SEX:	----------MALE----------						----------FEMALE----------					
	GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
ORGAN AND KEYWORD(S) OR PHRASE	NUMBER:	21	22	18	28	41	0	15	0	16	26	31	43
*** TOP OF LIST ***													
BRAIN W/STEM (BR)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	15	19	15	26	40	0	11	0	13	25	29	37
SOFT		1	0	0	1	1	0	1	0	0	0	0	2
VENTRAL SURFACE, INDENTED		4	3	1	1	0	0	3	0	2	0	2	4
PALE		1	0	1	0	0	0	0	0	1	1	0	0
DARK		0	0	1	0	0	0	0	0	0	0	0	0
MASS		1	0	0	0	0	0	0	0	0	0	0	0
PITUITARY (PI)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	12	18	16	24	40	0	6	0	11	19	26	37
DARK		6	3	1	2	0	0	4	0	2	4	3	2
ENLARGED		7	3	2	4	0	0	6	0	3	5	5	4
MOTTLED		1	0	0	1	0	0	1	0	1	1	2	2
IRREGULARLY SHAPED		2	1	0	0	0	0	0	0	0	1	2	0
DARK AREA		1	1	0	0	1	0	3	0	2	1	0	2
PALE		1	0	0	0	0	0	0	0	0	1	0	0
ADRENAL, CORTEX (AC)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	21	21	17	27	41	0	15	0	16	24	31	41
UNEQUALLY SIZED		0	0	1	0	0	0	0	0	0	0	0	2
SMALL		0	1	0	0	0	0	0	0	0	0	0	0
DARK		0	0	0	1	0	0	0	0	0	1	0	0
SPECKLED		0	0	0	0	0	0	0	0	0	1	0	0
THYROID (TY)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	21	21	18	27	41	0	14	0	16	26	31	43
MASS		0	0	0	1	0	0	0	0	0	0	0	0
UNEQUALLY SIZED		0	1	0	0	0	0	1	0	0	0	0	0
ESOPHAGUS (ES)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	20	22	18	28	41	0	15	0	16	25	31	41
LUMEN, MATERIAL		1	0	0	0	0	0	0	0	0	1	0	1
PERFORATED		0	0	0	0	0	0	0	0	0	1	0	1
TRACHEA (TR)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	21	22	18	28	41	0	15	0	16	26	31	43
DARK		3	0	2	2	4	0	2	0	1	2	1	6
MASS		0	0	0	0	0	0	1	0	0	0	0	0
MOTTLED		4	1	1	4	14	0	0	0	1	6	10	15
PALE		0	0	0	0	0	0	0	0	0	1	1	0
DARK AREA		1	2	0	1	1	0	0	0	2	1	0	0
FAILURE TO COLLAPSE		0	0	0	1	0	0	1	0	0	0	0	0
HEART (HT)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	21	22	18	28	41	0	15	0	16	26	30	43
VENTRICLE, PALE AREA		0	0	0	0	0	0	0	0	0	0	1	0
SPLEEN (SP)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	13	14	11	20	25	0	11	0	8	14	23	33
SMALL		0	0	0	5	13	0	0	0	1	1	3	8
ENLARGED		8	8	7	3	3	0	4	0	7	10	5	2
MOTTLED		0	1	0	0	0	0	0	0	0	1	1	0
CONSTRICTED		0	0	0	0	0	0	0	0	1	0	1	0
PALE AREA		0	0	1	0	0	0	0	0	0	1	0	0
GRANULAR/PITTED/ROUGH		0	0	0	0	0	0	0	0	1	0	0	0
PALE		0	0	0	0	0	0	0	0	1	0	0	0
IRREGULARLY SHAPED		0	0	1	0	0	0	0	0	0	0	0	0
H-SMALL		0	0	0	0	0	0	0	0	0	1	0	0
LIVER (LI)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	11	15	11	22	24	0	11	0	9	19	23	34
DARK		0	0	1	0	1	0	0	0	1	0	1	2
SMALL		0	0	0	2	8	0	0	0	1	1	2	5
PALE		4	2	2	1	1	0	2	0	2	1	2	0
MOTTLED		0	1	1	1	3	0	1	0	1	2	1	1
GRANULAR/PITTED/ROUGH		5	4	4	1	1	0	2	0	4	3	0	0
PROTRUSION INTO DIAPHRAGM		0	0	1	0	1	0	0	0	0	0	1	0
LOBE, THICKENED		0	0	0	0	0	0	0	0	1	0	0	0
RAISED AREA		0	0	0	1	3	0	0	0	0	1	0	0
DARK AREA		1	2	0	0	0	0	1	0	0	0	0	0
PROMINENT RETICULAR PATTERN		1	2	0	0	0	0	1	0	0	0	0	0
FRIABLE		1	0	0	0	0	0	0	0	0	0	0	0
CYST		2	0	0	0	0	0	0	0	0	0	0	0
PALE AREA		0	0	1	0	1	0	0	0	0	1	0	0
IRREGULARLY SHAPED		0	0	0	0	0	0	0	0	0	1	0	0
ENLARGED		2	0	1	0	0	0	0	0	1	0	0	0
H-MASS		0	0	0	0	0	0	0	0	0	0	0	1
H-RAISED AREA		0	0	0	0	0	0	0	0	0	0	1	0

Incidence of macroscopic findings in rats "unscheduled deaths"

INCIDENCE OF MACROSCOPIC OBSERVATIONS - UNSCHEDULED DEATHS

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=UNSCHED;SUBSET=ALL

-- N U M B E R - O F - A N I M A L S - A F F E C T E D --

ORGAN AND KEYWORD(S) OR PHRASE		SEX:	MALE						FEMALE					
		GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
		NUMBER:	21	22	18	28	41	0	15	0	16	26	31	43
KIDNEY (KD)	NUMBER EXAMINED:		21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:		15	14	14	26	37	0	13	0	14	21	28	35
MASS			0	0	0	0	0	0	1	0	0	0	0	0
DARK			3	2	3	1	3	0	0	0	1	2	2	2
MOTTLED			0	0	0	0	1	0	1	0	0	2	0	3
PELVIS, DILATED			0	0	0	1	0	0	1	0	0	0	0	0
DARK AREA			0	0	0	0	0	0	0	0	1	0	1	0
SMALL			0	0	0	0	0	0	0	0	0	0	0	2
GRANULAR/PITTED/ROUGH			2	4	1	0	0	0	0	0	0	0	0	1
PALE AREA			0	1	0	0	0	0	0	0	0	1	0	0
ENLARGED			1	0	0	0	0	0	1	0	0	0	0	0
CYST			0	1	0	0	0	0	1	0	0	0	0	0
IRREGULARLY SHAPED			0	0	0	0	0	0	1	0	0	0	0	0
H-PELVIS, DILATED			0	1	0	0	0	0	0	0	0	0	0	0
STOMACH, NONGL (SU)	NUMBER EXAMINED:		21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:		19	22	18	28	41	0	14	0	16	26	30	42
MUCOSA, THICKENED			1	0	0	0	0	0	1	0	0	0	0	0
MUCOSA, ROUGH			1	0	0	0	0	0	0	0	0	0	0	0
PALE AREA			0	0	0	0	0	0	0	0	0	0	0	1
PERFORATED			1	0	0	0	0	0	0	0	0	0	0	0
MUCOSA, PITTED			0	0	0	0	0	0	1	0	0	0	0	0
H-PALE AREA			0	0	0	0	0	0	0	0	0	0	1	0
STOMACH, GL (ST)	NUMBER EXAMINED:		21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:		18	20	15	24	35	0	12	0	11	17	22	35
DEPRESSED AREA			0	0	0	0	1	0	0	0	0	0	0	0
DARK AREA			2	2	3	4	3	0	3	0	5	9	6	4
MUCOSA, DARK			0	0	0	0	2	0	0	0	0	0	0	1
RAISED AREA			0	0	0	0	0	0	0	0	0	0	2	0
PALE AREA			0	0	0	0	0	0	0	0	0	0	0	1
DISTENDED			0	0	0	0	0	0	0	0	0	0	1	3
LUMEN, GAS			0	0	0	0	0	0	0	0	0	0	1	3
MASS			1	0	0	0	0	0	0	0	0	0	0	0
MUCOSA, THICKENED			1	0	0	0	0	0	0	0	0	0	0	0
MUCOSA, ROUGH			1	0	0	0	0	0	0	0	0	0	0	0
MUCOSA, SMOOTH			0	0	0	0	0	0	0	0	0	0	1	0
DUODENUM (DU)	NUMBER EXAMINED:		21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:		21	22	18	28	41	0	15	0	16	26	31	42
DISTENDED			0	0	0	0	0	0	0	0	0	0	0	1
LUMEN, GAS			0	0	0	0	0	0	0	0	0	0	0	1
JEJUNUM (JE)	NUMBER EXAMINED:		21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:		21	21	18	27	39	0	15	0	16	25	30	40
SEROSA, DARK			0	0	0	1	1	0	0	0	0	0	0	2
DISTENDED			0	1	0	0	1	0	0	0	0	1	1	1
LUMEN, GAS			0	1	0	0	0	0	0	0	0	1	0	1
ILEUM (IL)	NUMBER EXAMINED:		21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:		21	21	18	28	39	0	15	0	16	26	31	41
DISTENDED			0	1	0	0	1	0	0	0	0	0	0	2
LUMEN, GAS			0	1	0	0	0	0	0	0	0	0	0	2
H-MASS			0	0	0	0	1	0	0	0	0	0	0	0
PANCREAS (PA)	NUMBER EXAMINED:		21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:		20	21	17	28	41	0	14	0	15	26	31	43
THICKENED			1	1	0	0	0	0	0	0	0	0	0	0
MOTTLED			1	0	0	0	0	0	0	0	0	0	0	0
MASS			0	0	1	0	0	0	1	0	1	0	0	0
CECUM (CE)	NUMBER EXAMINED:		21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:		21	22	18	28	39	0	15	0	15	26	31	41
LUMEN, GAS			0	0	0	0	1	0	0	0	0	0	0	2
DISTENDED			0	0	0	0	2	0	0	0	0	0	0	2
DARK AREA			0	0	0	0	0	0	0	0	1	0	0	0
COLON (CO)	NUMBER EXAMINED:		21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:		21	22	18	28	41	0	15	0	16	26	31	41
DISTENDED			0	0	0	0	0	0	0	0	0	0	0	2
LUMEN, GAS			0	0	0	0	0	0	0	0	0	0	0	2
RECTUM (RE)	NUMBER EXAMINED:		21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:		21	22	18	28	41	0	15	0	16	26	31	42
MASS			0	0	0	0	0	0	0	0	0	0	0	1
DISTENDED			0	0	0	0	0	0	0	0	0	0	0	1
LUMEN, GAS			0	0	0	0	0	0	0	0	0	0	0	1
LN, MESENTERIC (MS)	NUMBER EXAMINED:		21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:		20	20	17	27	39	0	13	0	15	24	30	41
DARK			0	0	0	0	2	0	1	0	0	1	0	2
ENLARGED			1	2	1	1	1	0	2	0	0	1	1	0
MOTTLED			1	0	0	0	0	0	0	0	0	0	0	0
H-ENLARGED			0	0	0	0	0	0	0	0	1	0	0	0
TESTIS (TE)	NUMBER EXAMINED:		21	22	18	28	41	0	0	0	0	0	0	0
	NOT REMARKABLE:		7	5	2	10	16	0	0	0	0	0	0	0
SMALL			4	4	3	5	11	0	0	0	0	0	0	0
DARK/PALE MATERIAL			13	12	13	12	16	0	0	0	0	0	0	0
MOTTLED			0	1	0	1	3	0	0	0	0	0	0	0

Incidence of macroscopic findings in rats "unscheduled deaths"

INCIDENCE OF MACROSCOPIC OBSERVATIONS - UNSCHEDULED DEATHS

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=UNSCHED;SUBSET=ALL

ORGAN AND KEYWORD(S) OR PHRASE		-- NUMBER-OF-ANIMALS-AFFECTED --											
SEX:		----------MALE----------						----------FEMALE----------					
GROUP:		-1-	-2-	-3-	-4-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
NUMBER:		21	22	18	28	41	0	15	0	16	26	31	43
*** FROM PREVIOUS PAGE ***													
TESTIS (TE)	NUMBER EXAMINED:	21	22	18	28	41	0	0	0	0	0	0	0
	NOT REMARKABLE:	7	5	2	10	16	0	0	0	0	0	0	0
DARK		0	0	1	0	1	0	0	0	0	0	0	0
SOFT		3	3	5	4	6	0	0	0	0	0	0	0
UNEQUALLY SIZED		1	4	2	5	3	0	0	0	0	0	0	0
TRANSLUCENT		0	1	0	2	0	0	0	0	0	0	0	0
RAISED AREA		1	0	0	0	0	0	0	0	0	0	0	0
ENLARGED		0	0	1	0	0	0	0	0	0	0	0	0
H-SOFT		0	1	0	0	0	0	0	0	0	0	0	0
H-DARK/PALE MATERIAL		0	1	0	0	0	0	0	0	0	0	0	0
EPIDIDYMIS (EP)	NUMBER EXAMINED:	21	22	18	28	41	0	0	0	0	0	0	0
	NOT REMARKABLE:	19	22	18	26	35	0	0	0	0	0	0	0
SMALL		1	0	0	2	6	0	0	0	0	0	0	0
RAISED AREA		1	0	0	0	0	0	0	0	0	0	0	0
PROSTATE (PR)	NUMBER EXAMINED:	21	22	18	28	41	0	0	0	0	0	0	0
	NOT REMARKABLE:	18	20	9	16	18	0	0	0	0	0	0	0
SMALL		3	2	9	11	23	0	0	0	0	0	0	0
H-SMALL		0	0	0	1	0	0	0	0	0	0	0	0
SEMINAL VESICLE (SV)	NUMBER EXAMINED:	21	22	18	28	41	0	0	0	0	0	0	0
	NOT REMARKABLE:	6	13	4	8	7	0	0	0	0	0	0	0
SMALL		13	9	13	18	34	0	0	0	0	0	0	0
TRANSLUCENT		2	0	1	3	2	0	0	0	0	0	0	0
DARK		0	0	0	0	2	0	0	0	0	0	0	0
H-SMALL		0	0	0	1	0	0	0	0	0	0	0	0
URINARY BLADDER (UB)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	20	22	17	28	41	0	15	0	15	25	31	41
DISTENDED		0	0	1	0	0	0	0	0	1	1	0	1
LUMEN, FLUID		0	0	1	0	0	0	0	0	1	1	0	1
SEROSA, DARK		1	0	0	0	0	0	0	0	0	0	0	0
H-DISTENDED		0	0	0	0	0	0	0	0	0	0	0	1
H-LUMEN, FLUID		0	0	0	0	0	0	0	0	0	0	0	1
OVARY (OV)	NUMBER EXAMINED:	0	0	0	0	0	0	15	0	16	26	31	43
	NOT REMARKABLE:	0	0	0	0	0	0	13	0	16	26	30	43
SMALL		0	0	0	0	0	0	0	0	0	0	1	0
DARK		0	0	0	0	0	0	1	0	0	0	0	0
H-CYST		0	0	0	0	0	0	1	0	0	0	0	0
UTERUS (UT)	NUMBER EXAMINED:	0	0	0	0	0	0	15	0	16	26	31	43
	NOT REMARKABLE:	0	0	0	0	0	0	12	0	11	18	28	32
SMALL		0	0	0	0	0	0	1	0	0	0	2	8
DISTENDED		0	0	0	0	0	0	1	0	2	4	0	0
LUMEN, FLUID		0	0	0	0	0	0	1	0	2	2	0	0
CYST		0	0	0	0	0	0	1	0	2	2	0	0
DARK		0	0	0	0	0	0	0	0	0	1	0	5
PALE		0	0	0	0	0	0	0	0	1	0	0	0
WALL, THICKENED		0	0	0	0	0	0	0	0	1	0	0	0
MASS		0	0	0	0	0	0	0	0	0	3	1	0
LUMEN, MATERIAL		0	0	0	0	0	0	0	0	0	1	0	0
UTERUS, CERVIX (CV)	NUMBER EXAMINED:	0	0	0	0	0	0	15	0	16	26	31	43
	NOT REMARKABLE:	0	0	0	0	0	0	14	0	13	26	31	42
PALE		0	0	0	0	0	0	0	0	1	0	0	0
MASS		0	0	0	0	0	0	1	0	1	0	0	0
WALL, THICKENED		0	0	0	0	0	0	0	0	1	0	0	0
H-THICKENED		0	0	0	0	0	0	0	0	0	0	0	1
VAGINA (VA)	NUMBER EXAMINED:	0	0	0	0	0	0	15	0	16	26	31	43
	NOT REMARKABLE:	0	0	0	0	0	0	14	0	15	26	31	42
PALE		0	0	0	0	0	0	0	0	1	0	0	0
MASS		0	0	0	0	0	0	1	0	0	0	0	0
H-CYST		0	0	0	0	0	0	0	0	0	0	0	1
LN, MANDIBULAR (MN)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	20	22	18	28	41	0	14	0	16	26	31	43
ENLARGED		1	0	0	0	0	0	0	0	0	0	0	0
DARK		0	0	0	0	0	0	1	0	0	0	0	0
MAND SALIVARY GL (SG)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	21	22	18	27	41	0	15	0	16	26	30	43
ENLARGED		0	0	0	0	0	0	0	0	0	0	1	0
MASS		0	0	0	1	0	0	0	0	0	0	0	0
THYMUS (TH)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	21	22	17	27	41	0	14	0	16	25	31	43
MASS		0	0	1	0	0	0	0	0	0	0	0	0
ENLARGED		0	0	0	0	0	0	1	0	0	1	0	0
DARK		0	0	0	1	0	0	0	0	0	0	0	0

Incidence of macroscopic findings in rats "unscheduled deaths"

INCIDENCE OF MACROSCOPIC OBSERVATIONS - UNSCHEDULED DEATHS

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=UNSCHED;SUBSET=ALL

ORGAN AND KEYWORD(S) OR PHRASE		-- NUMBER-OF-ANIMALS-AFFECTED --											
	SEX:	MALE						FEMALE					
	GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
	NUMBER:	21	22	18	28	41	0	15	0	16	26	31	43
EYE (EY)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	16	19	16	24	39	0	11	0	13	22	26	40
INTERNAL, OPAQUE		5	2	2	2	2	0	4	0	2	3	5	2
EXOPHTHALMUS		1	1	1	1	0	0	0	0	0	1	0	0
EXTERNAL, PALE MATERIAL		0	0	0	1	0	0	0	0	1	0	0	0
EXTERNAL, DARK MATERIAL		1	1	0	0	0	0	0	0	0	0	0	0
EXTERNAL, OPAQUE		0	0	0	1	0	0	0	0	0	0	0	1
SMALL		1	0	0	0	1	0	2	0	1	1	0	0
HARDERIAN GLAND (HG)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	21	22	18	28	41	0	15	0	16	26	31	43
MUSCLE, SKELETAL (SM)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	21	22	18	28	41	0	15	0	16	26	31	43
CAVITY, ORAL (OC)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	20	22	18	28	41	0	15	0	15	25	31	43
PALE MATERIAL		1	0	0	0	0	0	0	0	1	1	0	0
LARYNX (LA)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	21	22	18	28	41	0	15	0	15	26	31	43
LUMEN, MATERIAL		0	0	0	0	0	0	0	0	1	0	0	0
CAVITY, ABDOM (PC)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	18	21	17	28	39	0	13	0	15	26	29	42
MASS		0	0	1	0	0	0	1	0	0	0	0	0
ADIPOSE TISSUE, REDUCED		0	0	0	0	2	0	0	0	0	0	1	1
ADIPOSE TISSUE, THICKENED		2	1	0	0	0	0	0	0	0	0	0	0
FLUID		2	1	0	0	0	0	1	0	0	0	1	0
MOTTLED		1	0	0	0	0	0	0	0	0	0	0	0
PALE MATERIAL		0	0	0	0	0	0	0	0	1	0	0	0
RAISED AREA		1	0	0	0	0	0	0	0	0	0	0	0
SUBCUTANEOUS TIS (SQ)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	21	21	18	28	40	0	13	0	15	26	29	43
GELATINOUS		0	0	0	0	0	0	0	0	1	0	0	0
MASS-VHM		0	0	0	0	0	0	0	0	0	0	1	0
MASS-VFL		0	0	0	0	0	0	0	0	0	0	1	0
MASS-DFL		0	0	0	0	1	0	0	0	0	0	0	0
MASS-DPM		0	0	0	0	0	0	2	0	0	0	0	0
MASS-DHR		0	1	0	0	0	0	0	0	0	0	0	0
CAVITY, THORACIC (TA)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	20	20	18	28	41	0	14	0	14	26	31	43
FLUID		1	2	0	0	0	0	1	0	2	0	0	0
SKIN, OTHER (SS)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	17	15	12	20	39	0	15	0	14	23	30	38
SORE		3	4	4	4	1	0	0	0	0	3	0	3
ALOPECIA		0	0	0	0	0	0	0	0	1	0	1	1
MASS-DHL		0	1	0	0	0	0	0	0	0	0	0	0
DARK AREA		0	0	0	0	0	0	0	0	1	0	0	0
MASS-DHR		0	1	0	0	0	0	0	0	0	0	0	0
FOOT/PAW, SORE		1	0	1	3	1	0	0	0	0	0	0	1
MASS-VFR		0	0	1	1	0	0	0	0	0	0	0	0
FOOT/PAW, SWOLLEN		0	1	0	0	0	0	0	0	0	0	0	0
MASS-VHM		0	1	0	0	0	0	0	0	0	0	0	0
H-RAISED AREA		0	0	0	1	0	0	0	0	0	0	0	0
TAIL, SWOLLEN		0	0	1	0	0	0	0	0	0	0	0	0
H-SORE		0	0	1	0	0	0	0	0	0	0	0	0
HEAD, CORONAL (HC)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	21	20	18	28	41	0	15	0	16	25	31	43
MASS		0	2	0	0	0	0	0	0	0	1	0	0
CAVITY, CRANIAL (CC)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	20	22	18	28	41	0	15	0	16	26	31	43
TRIGEMINAL NERVE, ENLARGED		1	0	0	0	0	0	0	0	0	0	0	0
MAMMARY, FEMALE (MF)	NUMBER EXAMINED:	0	0	0	0	0	0	15	0	16	26	31	43
	NOT REMARKABLE:	0	0	0	0	0	0	12	0	14	25	28	43
THICKENED		0	0	0	0	0	0	1	0	0	0	2	0
MASS-VFL		0	0	0	0	0	0	1	0	1	0	0	0
MASS-VHL		0	0	0	0	0	0	1	0	0	0	1	0
MASS-VFR		0	0	0	0	0	0	0	0	1	1	0	0
MASS-VHR		0	0	0	0	0	0	0	0	0	1	0	0
LN, OTHER (LN)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	21	21	18	28	41	0	12	0	16	24	31	43
MULTIPLE, ENLARGED		0	1	0	0	0	0	2	0	0	1	0	0
DARK		0	0	0	0	0	0	2	0	0	1	0	0
ENLARGED		0	0	0	0	0	0	1	0	0	1	0	0

Incidence of macroscopic findings in rats "unscheduled deaths"

INCIDENCE OF MACROSCOPIC OBSERVATIONS - UNSCHEDULED DEATHS

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=UNSCHED;SUBSET=ALL

ORGAN AND KEYWORD(S) OR PHRASE		-- NUMBER-OF-ANIMALS-AFFECTED --											
	SEX:	MALE						FEMALE					
	GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
	NUMBER:	21	22	18	28	41	0	15	0	16	26	31	43
PENIS (PE)	NUMBER EXAMINED:	21	22	18	28	41	0	0	0	0	0	0	0
	NOT REMARKABLE:	19	21	18	28	40	0	0	0	0	0	0	0
PARAPHAMOSIS		2	1	0	0	1	0	0	0	0	0	0	0
MAMMARY, MALE (MM)	NUMBER EXAMINED:	21	22	18	28	41	0	0	0	0	0	0	0
	NOT REMARKABLE:	20	19	15	25	40	0	0	0	0	0	0	0
MASS-VFL		0	0	1	0	0	0	0	0	0	0	0	0
MASS-VFR		0	0	2	0	0	0	0	0	0	0	0	0
THICKENED		1	3	0	3	0	0	0	0	0	0	0	0
MASS-VHL		0	0	0	0	1	0	0	0	0	0	0	0
TAIL (TI)	NUMBER EXAMINED:	21	22	18	28	41	0	15	0	16	26	31	43
	NOT REMARKABLE:	21	21	18	28	41	0	15	0	16	26	31	43
MASS		0	1	0	0	0	0	0	0	0	0	0	0
PREPUTIAL GLAND (PG)	NUMBER EXAMINED:	21	22	18	28	41	0	0	0	0	0	0	0
	NOT REMARKABLE:	21	22	18	28	41	0	0	0	0	0	0	0

*** END OF LIST ***

Incidence of macroscopic findings in rats "Terminal sacrifice"

Incidence of Macroscopic Observations - Terminal Sacrifice

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

ORGAN AND KEYWORD(S) OR PHRASE		-- NUMBER-OF-ANIMALS-AFFECTED --											
SEX:		----------MALE----------						----------FEMALE----------					
GROUP:		-1-	-2-	-3-	-4-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
NUMBER:		39	38	42	32	19	0	45	0	44	34	29	17
*** TOP OF LIST ***													
BRAIN W/STEM (BR)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	39	35	37	31	19	0	43	0	40	32	26	13
SOFT		0	0	1	0	0	0	0	0	1	0	0	0
VENTRAL SURFACE, INDENTED		0	3	4	1	0	0	2	0	4	2	3	4
DARK AREA		0	0	1	0	0	0	0	0	0	0	0	0
PITUITARY (PI)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	29	23	34	25	17	0	27	0	27	22	17	8
DARK		3	5	5	2	0	0	4	0	5	5	5	5
ENLARGED		5	9	5	5	0	0	7	0	9	8	7	7
MOTTLED		2	4	1	3	0	0	6	0	3	1	1	2
DARK AREA		4	2	2	1	2	0	8	0	6	3	5	1
SMALL		0	1	0	1	2	0	2	0	1	1	1	0
RAISED AREA		1	2	0	0	0	0	0	0	1	0	0	0
H-DARK AREA		0	0	0	0	0	0	0	0	0	1	0	0
ADRENAL, CORTEX (AC)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	37	37	41	29	18	0	43	0	44	34	26	15
UNEQUALLY SIZED		2	0	1	2	1	0	1	0	0	0	0	1
SPECKLED		0	0	0	0	1	0	1	0	0	0	0	1
ENLARGED		0	0	0	0	0	0	0	0	0	0	3	1
DARK AREA		0	1	0	0	0	0	0	0	0	0	0	0
FIRM		0	0	0	1	0	0	0	0	0	0	0	0
THYROID (TY)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	37	37	38	32	19	0	45	0	43	33	28	17
MASS		1	1	1	0	0	0	0	0	1	1	0	0
UNEQUALLY SIZED		1	0	1	0	0	0	0	0	0	0	1	0
DARK AREA		0	0	1	0	0	0	0	0	0	0	0	0
PALE AREA		0	0	1	0	0	0	0	0	0	0	0	0
PARATHYROID (PT)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	39	38	42	32	19	0	45	0	43	34	29	17
UNEQUALLY SIZED		0	0	0	0	0	0	0	0	1	0	0	0
ESOPHAGUS (ES)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	39	38	42	31	18	0	45	0	44	32	27	16
LUMEN, MATERIAL		0	0	0	0	1	0	0	0	0	1	1	0
DISTENDED		0	0	0	1	1	0	0	0	0	2	2	1
LUNG (LU)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	39	38	39	30	18	0	44	0	44	33	27	17
DARK		0	0	1	1	0	0	0	0	0	0	0	0
MASS		0	0	1	0	0	0	1	0	0	0	0	0
MOTTLED		0	0	1	0	0	0	0	0	0	1	2	0
DARK AREA		0	0	0	1	0	0	0	0	0	0	0	0
FAILURE TO COLLAPSE		0	0	0	0	1	0	0	0	0	0	0	0
HEART (HT)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	38	38	42	32	19	0	45	0	44	34	29	17
ATRIUM, MOTTLED		1	0	0	0	0	0	0	0	0	0	0	0
SPLEEN (SP)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	24	27	31	26	19	0	38	0	42	33	27	16
SMALL		0	0	1	0	0	0	0	0	1	0	0	0
ENLARGED		14	11	10	6	0	0	7	0	1	1	2	1
PALE AREA		1	0	0	0	0	0	0	0	0	0	0	0
IRREGULARLY SHAPED		0	1	0	0	0	0	0	0	0	0	0	0
H-ENLARGED		1	0	0	0	0	0	0	0	0	0	0	0
LIVER (LI)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	29	31	36	28	16	0	41	0	41	31	27	15
DARK		0	0	0	1	0	0	1	0	0	0	0	0
PALE		1	1	0	0	0	0	0	0	0	0	0	0
GRANULAR/PITTED/ROUGH		4	1	1	0	0	0	1	0	1	0	0	1
PROTRUSION INTO DIAPHRAGM		1	0	0	0	2	0	0	0	1	0	1	0
RAISED AREA		3	0	2	1	1	0	1	0	1	2	0	1
DARK AREA		0	1	0	1	0	0	0	0	0	0	0	0
PROMINENT RETICULAR PATTERN		1	1	2	1	0	0	0	0	0	0	0	0
CYST		1	0	0	0	0	0	0	0	0	0	0	0
PALE AREA		3	0	1	0	0	0	0	0	0	0	1	0
IRREGULARLY SHAPED		0	1	0	0	0	0	1	0	0	1	0	0
ENLARGED		1	2	0	0	0	0	0	0	0	0	0	0
MASS		1	1	1	0	0	0	0	0	0	0	0	0
H-GRANULAR/PITTED/ROUGH		1	0	0	0	0	0	0	0	0	0	0	0
H-PALE AREA		0	1	0	0	0	0	0	0	0	0	0	0
KIDNEY (KD)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	30	31	37	29	19	0	42	0	43	33	28	14
MASS		0	0	0	0	0	0	0	0	0	1	0	0
DARK		4	1	1	0	0	0	3	0	0	0	0	1
MOTTLED		1	1	1	1	0	0	0	0	0	0	0	0
PELVIS, DILATED		0	0	0	0	0	0	0	0	0	0	1	0
GRANULAR/PITTED/ROUGH		6	5	2	2	0	0	0	0	0	0	0	2
PALE AREA		1	0	0	0	0	0	0	0	0	0	0	0
ENLARGED		0	1	0	0	0	0	0	0	0	0	0	0
CYST		0	0	2	1	0	0	0	0	1	0	0	0
PALE		0	2	0	0	0	0	0	0	0	0	0	0
PELVIS, GRANULAR MATERIAL		0	0	1	0	0	0	0	0	0	0	0	0

Incidence of macroscopic findings in rats "terminal sacrifice"

INCIDENCE OF MACROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

ORGAN AND KEYWORD(S) OR PHRASE		-- NUMBER-OF-ANIMALS-AFFECTED --											
SEX:		----------MALE----------						----------FEMALE----------					
GROUP:		-1-	-2-	-3-	-4-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
NUMBER:		39	38	42	32	19	0	45	0	44	34	29	17
STOMACH, NONGL (SU)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	39	38	42	30	18	0	45	0	44	34	28	17
RAISED AREA		0	0	0	1	1	0	0	0	0	0	1	0
MASS		0	0	0	1	0	0	0	0	0	0	0	0
STOMACH, GL (ST)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	37	36	40	30	15	0	44	0	44	32	24	16
DARK AREA		1	2	2	2	4	0	0	0	0	2	5	1
RAISED AREA		0	0	0	0	0	0	1	0	0	0	0	0
DISTENDED		1	0	0	0	0	0	0	0	0	0	0	0
LUMEN, GAS		1	0	0	0	0	0	0	0	0	0	0	0
DUODENUM (DU)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	38	38	42	32	19	0	45	0	44	34	29	17
DISTENDED		1	0	0	0	0	0	0	0	0	0	0	0
LUMEN, GAS		1	0	0	0	0	0	0	0	0	0	0	0
JEJUNUM (JE)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	38	38	42	32	19	0	45	0	44	34	29	17
DISTENDED		1	0	0	0	0	0	0	0	0	0	0	0
LUMEN, GAS		1	0	0	0	0	0	0	0	0	0	0	0
PANCREAS (PA)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	38	38	40	30	19	0	44	0	44	34	29	17
MASS		0	0	1	2	0	0	1	0	0	0	0	0
DARK		1	0	1	0	0	0	0	0	0	0	0	0
CECUM (CE)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	38	37	42	32	19	0	45	0	44	32	29	17
LUMEN, GAS		1	1	0	0	0	0	0	0	0	0	0	0
DISTENDED		1	0	0	0	0	0	0	0	0	1	0	0
DARK AREA		0	0	0	0	0	0	0	0	0	1	0	0
CYST		0	0	0	0	0	0	0	0	0	1	0	0
COLON (CO)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	38	37	42	32	19	0	45	0	44	34	29	17
DISTENDED		1	0	0	0	0	0	0	0	0	0	0	0
LUMEN, GAS		1	0	0	0	0	0	0	0	0	0	0	0
MASS		0	1	0	0	0	0	0	0	0	0	0	0
RECTUM (RE)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	39	38	42	32	19	0	45	0	44	34	29	17
LN, MESENTERIC (MS)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	38	37	41	32	19	0	44	0	44	33	29	17
ENLARGED		0	1	1	0	0	0	1	0	0	0	0	0
MOTTLED		0	0	0	0	0	0	1	0	0	0	0	0
MASS		0	0	0	0	0	0	0	0	0	1	0	0
CYST		1	0	0	0	0	0	0	0	0	0	0	0
TESTIS (TE)	NUMBER EXAMINED:	39	38	42	32	19	0	0	0	0	0	0	0
	NOT REMARKABLE:	3	3	2	2	3	0	0	0	0	0	0	0
SMALL		4	1	4	0	1	0	0	0	0	0	0	0
DARK/PALE MATERIAL		35	35	36	30	14	0	0	0	0	0	0	0
SOFT		2	4	5	1	1	0	0	0	0	0	0	0
UNEQUALLY SIZED		20	22	19	16	12	0	0	0	0	0	0	0
ENLARGED		3	1	9	1	0	0	0	0	0	0	0	0
H-DARK/PALE MATERIAL		0	0	1	0	2	0	0	0	0	0	0	0
EPIDIDYMIS (EP)	NUMBER EXAMINED:	39	38	42	32	19	0	0	0	0	0	0	0
	NOT REMARKABLE:	39	38	42	31	19	0	0	0	0	0	0	0
SMALL		0	0	0	1	0	0	0	0	0	0	0	0
PROSTATE (PR)	NUMBER EXAMINED:	39	38	42	32	19	0	0	0	0	0	0	0
	NOT REMARKABLE:	20	17	16	13	5	0	0	0	0	0	0	0
SMALL		19	21	26	18	14	0	0	0	0	0	0	0
MASS		0	0	0	1	0	0	0	0	0	0	0	0
SEMINAL VESICLE (SV)	NUMBER EXAMINED:	39	38	42	32	19	0	0	0	0	0	0	0
	NOT REMARKABLE:	10	7	6	5	2	0	0	0	0	0	0	0
SMALL		26	31	36	27	16	0	0	0	0	0	0	0
TRANSLUCENT		1	0	1	0	0	0	0	0	0	0	0	0
MASS		0	0	0	0	1	0	0	0	0	0	0	0
H-SMALL		2	0	0	0	0	0	0	0	0	0	0	0
URINARY BLADDER (UB)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	39	38	41	32	19	0	44	0	44	34	28	17
DISTENDED		0	0	0	0	0	0	0	0	0	0	1	0
LUMEN, FLUID		0	0	1	0	0	0	0	0	0	0	1	0
SEROSA, DARK		0	0	1	0	0	0	0	0	0	0	0	0
MASS		0	0	0	0	0	0	1	0	0	0	0	0
OVARY (OV)	NUMBER EXAMINED:	0	0	0	0	0	0	45	0	44	34	29	17
	NOT REMARKABLE:	0	0	0	0	0	0	42	0	40	32	27	17
DARK		0	0	0	0	0	0	0	0	1	0	0	0
CYST		0	0	0	0	0	0	3	0	4	2	2	0

Incidence of macroscopic findings in rats "terminal sacrifice"

INCIDENCE OF MACROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=T;SUBSET=ALL

ORGAN AND KEYWORD(S) OR PHRASE		-- NUMBER OF ANIMALS AFFECTED --											
	SEX:	MALE						FEMALE					
	GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
	NUMBER:	39	38	42	32	19	0	45	0	44	34	29	17
UTERUS (UT)	NUMBER EXAMINED:	0	0	0	0	0	0	45	0	44	34	29	17
	NOT REMARKABLE:	0	0	0	0	0	0	31	0	32	24	20	13
SMALL		0	0	0	0	0	0	0	0	0	0	6	3
DISTENDED		0	0	0	0	0	0	4	0	3	4	0	0
LUMEN, FLUID		0	0	0	0	0	0	2	0	0	3	0	0
CYST		0	0	0	0	0	0	5	0	4	5	2	1
WALL, THICKENED		0	0	0	0	0	0	0	0	1	1	0	0
MASS		0	0	0	0	0	0	5	0	5	3	1	0
H-DISTENDED		0	0	0	0	0	0	1	0	0	0	0	0
H-LUMEN FLUID		0	0	0	0	0	0	1	0	0	0	0	0
UTERUS, CERVIX (CV)	NUMBER EXAMINED:	0	0	0	0	0	0	45	0	44	34	29	17
	NOT REMARKABLE:	0	0	0	0	0	0	45	0	44	34	29	17
VAGINA (VA)	NUMBER EXAMINED:	0	0	0	0	0	0	45	0	44	34	29	17
	NOT REMARKABLE:	0	0	0	0	0	0	45	0	44	34	29	17
LN, MANDIBULAR (MN)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	39	38	41	32	19	0	44	0	44	34	28	17
ENLARGED		0	0	1	0	0	0	1	0	0	0	0	0
DARK		0	0	0	0	0	0	0	0	0	0	1	0
MAND SALIVARY GL (SG)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	38	38	41	32	19	0	44	0	44	33	29	17
MASS		0	0	1	0	0	0	1	0	0	1	0	0
CYST		1	0	0	0	0	0	0	0	0	0	0	0
THYMUS (TH)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	39	38	41	32	19	0	45	0	44	34	29	17
MASS		0	0	1	0	0	0	0	0	0	0	0	0
EYE (EY)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	33	33	36	29	13	0	39	0	30	28	21	14
INTERNAL, OPAQUE		4	4	6	3	5	0	4	0	10	4	6	2
EXOPHTHALMUS		1	0	1	0	1	0	1	0	0	1	2	0
EXTERNAL, PALE MATERIAL		1	0	0	0	0	0	0	0	0	1	0	0
EXTERNAL, OPAQUE		1	1	0	0	0	0	1	0	4	0	0	0
SMALL		0	2	2	1	2	0	1	0	4	4	3	1
GLOBE RUPTURED ANTE MORTEM		0	0	0	0	0	0	0	0	0	0	0	1
CAVITY, ABDOM (PC)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	37	37	40	31	19	0	45	0	43	34	29	17
MASS		0	1	0	0	0	0	0	0	0	0	0	0
ADIPOSE TISSUE, THICKENED		0	0	0	1	0	0	0	0	0	0	0	0
FLUID		2	0	0	0	0	0	0	0	0	0	0	0
MESENTERY, THICKENED		0	0	1	0	0	0	0	0	0	0	0	0
MESENTERY, MASS		1	0	0	0	0	0	0	0	0	0	0	0
ADIPOSE TISSUE, MASS		0	0	1	0	0	0	0	0	1	0	0	0
SUBCUTANEOUS TIS (SQ)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	36	38	41	32	19	0	45	0	44	34	29	17
MASS-DFL		1	0	1	0	0	0	0	0	0	0	0	0
MASS-DHR		1	0	0	0	0	0	0	0	0	0	0	0
MASS-DFR		1	0	0	0	0	0	0	0	0	0	0	0
SKIN, OTHER (SS)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	29	29	34	29	17	0	44	0	43	32	29	16
SORE		6	4	5	1	1	0	0	0	1	1	0	1
ALOPECIA		0	0	0	1	0	0	0	0	0	1	0	0
FOOT/PAW, SORE		5	6	3	1	1	0	1	0	0	0	0	0
FOOT/PAW, SWOLLEN		0	0	1	0	0	0	0	0	0	0	0	0
TAIL, SWOLLEN		1	0	0	0	0	0	0	0	0	0	0	0
FOOT/PAW, MASS		0	0	1	0	0	0	0	0	0	0	0	0
HEAD, CORONAL (HC)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	39	38	40	31	19	0	45	0	44	33	29	16
MASS		0	0	2	0	0	0	0	0	0	1	0	0
SORE		0	0	0	1	0	0	0	0	0	0	0	1
MAMMARY, FEMALE (MF)	NUMBER EXAMINED:	0	0	0	0	0	0	45	0	44	34	29	17
	NOT REMARKABLE:	0	0	0	0	0	0	36	0	38	33	29	15
THICKENED		0	0	0	0	0	0	1	0	4	1	0	1
MASS-VFL		0	0	0	0	0	0	5	0	1	0	0	0
MASS-VHL		0	0	0	0	0	0	0	0	1	0	0	0
MASS-VFR		0	0	0	0	0	0	1	0	1	0	0	0
MASS-VHM		0	0	0	0	0	0	0	0	0	0	0	1
MASS-VFM		0	0	0	0	0	0	1	0	0	0	0	0
H-MASS-VFR		0	0	0	0	0	0	1	0	0	0	0	0

Incidence of macroscopic findings in rats "terminal sacrifice"

INCIDENCE OF MACROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=T;SUBSET=ALL		-- NUMBER-OF-ANIMALS-AFFECTED --											
	SEX:	----------MALE----------						----------FEMALE----------					
	GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
ORGAN AND KEYWORD(S) OR PHRASE	NUMBER:	39	38	42	32	19	0	45	0	44	34	29	17
LN, OTHER (LN)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	39	36	39	32	19	0	45	0	44	34	28	17
MULTIPLE, ENLARGED		0	1	0	0	0	0	0	0	0	0	0	0
DARK		0	1	0	0	0	0	0	0	0	0	0	0
ENLARGED		0	0	1	0	0	0	0	0	0	0	1	0
MAJORITY, ENLARGED		0	0	1	0	0	0	0	0	0	0	0	0
UNEQUALLY SIZED		0	0	1	0	0	0	0	0	0	0	0	0
PENIS (PE)	NUMBER EXAMINED:	39	38	42	32	19	0	0	0	0	0	0	0
	NOT REMARKABLE:	39	38	42	32	19	0	0	0	0	0	0	0
MAMMARY, MALE (MM)	NUMBER EXAMINED:	39	38	42	32	19	0	0	0	0	0	0	0
	NOT REMARKABLE:	37	35	40	29	19	0	0	0	0	0	0	0
MASS-VFL		0	1	0	2	0	0	0	0	0	0	0	0
MASS-VFR		1	0	1	0	0	0	0	0	0	0	0	0
THICKENED		1	0	1	2	0	0	0	0	0	0	0	0
MASS-VFM		0	1	0	0	0	0	0	0	0	0	0	0
MASS-VHR		0	1	0	0	0	0	0	0	0	0	0	0
TAIL (TI)	NUMBER EXAMINED:	39	38	42	32	19	0	45	0	44	34	29	17
	NOT REMARKABLE:	39	38	42	32	19	0	45	0	44	33	29	17
NECROTIC		0	0	0	0	0	0	0	0	0	1	0	0
PREPUTIAL GLAND (PG)	NUMBER EXAMINED:	39	38	42	32	19	0	0	0	0	0	0	0
	NOT REMARKABLE:	38	38	42	32	19	0	0	0	0	0	0	0
ENLARGED		1	0	0	0	0	0	0	0	0	0	0	0

*** END OF LIST ***

Histopathology:

Statistical analysis was performed on non-neoplastic and neoplastic lesions only when there was an increase or decrease of at least two occurrences in one of the treatment groups over the control group.

Non-neoplastic:

- Significant drug-related increase in incidence of foreign body bronchopneumonia presumably caused by small plant material (food) in males (6, 3, 11, 36 and 49 at 0, 0.3, 1, 3 and 10 mg/kg/d) and females (0, 21, 37 and 48 at 0, 1, 3, 10 and 30 mg/kg/d) was likely cause of death. The sponsor has hypothesized that diuresis may have disrupted body water imbalance leading to swallowing difficulties resulting in dysphagia, dyspnea and aspiration of food material. Whether the food material was the cause is still unresolved, since similar findings have been noted in toxicology studies and as well with other AVP_2 antagonists.
- Significant dose-related decrease in renal pelvis calculi in males (48/60, 49/60, 12/60, 5/60 and 11/60 at 0, 0.3, 1, 3 and 10 mg/kg/d respectively) with corresponding decrease in renal pelvic epithelium hyperplasia. A similar trend but to a lesser degree was noted in females. The incidence of renal pelvic calculi in females was 57/60, 59/60, 46/60, 40/60 and 50/60 at 0, 1, 3, 10 and 30 mg/kg/d, respectively. A corresponding decrease renal pelvic epithelial hyperplasia was also noted in females. The reduced pelvic calculi were likely due to increased aquaresis produced by conivaptan.
- Significant increase in lymphoid depletion of spleen in males at 10 mg/kg/d. Higher incidence of lymphoid depletion in high dose in contrast to higher incidence of leukemia in control and low dose group appear to be related to greater survival rate (greater leukemia in older animals).

- Significant dose-related increase in incidence of nonglandular stomach muscularis mineralization in both male and female rats. Since the clinical route of conivaptan is by IV route, the significance or whether the increased mineralization is due to direct impact of conivaptan in stomach is not clear

The incidence and severity of non-neoplastic histopath finding in rats

Selected Histologic Changes Related to Treatment

		MALE						FEMALE					
	GROUP	1	2	3	4	5	6	1	2	3	4	5	6
LUNGS	NO. EXAMINED	60	60	60	60	60	0	60	0	60	60	60	60
–Pneumonia, foreign body	Minimal (Grade 1)	2	0	2	10	5	-	0	-	2	2	4	2
	Mild (Grade 2)	3	2	6	7	7	-	0	-	0	3	9	14
	Moderate (Grade 3)	1	0	2	17	24	-	0	-	0	11	17	17
	Mod Severe (Grade 4)	0	1	1	1	12	-	0	-	0	5	7	15
	Severe (Grade 5)	0	0	0	1	1	-	0	-	0	0	0	0
	Total Affected	**6**	**3**	**11**	**36**	**49**	-	**0**	-	**2**	**21**	**37**	**48**
	Mean Severity Grade	1.8	2.7	2.2	2.3	2.9	-	0.0	-	1.0	2.9	2.7	2.9
TRACHEA	NO. EXAMINED	60	60	60	60	60	-	60	-	60	60	60	59
–Ingesta in lumen	**Total Affected**	**2**	**1**	**1**	**3**	**3**	-	**0**	-	**1**	**2**	**4**	**8**
ESOPHAGUS	NO. EXAMINED	60	60	60	60	60	-	60		59	60	60	60
-- Distended/ingesta	**Total affected**	**1**	**1**	**2**	**4**	**4**	-	**0**	-	**1**	**6**	**5**	**6**
KIDNEYS	NO. EXAMINED	60	60	60	60	60	-	60	-	60	60	60	60
–Pelvic calculi	Minimal (Grade 1)	40	41	12	4	7	-	36	-	36	35	23	35
	Mild (Grade 2)	8	8	0	1	3	-	18	-	20	11	17	13
	Moderate (Grade 3)	0	0	0	0	1	-	3	-	3	0	0	2
	Total Affected	**48**	**49**	**12**	**5**	**11**	-	**57**	-	**59**	**46**	**40**	**50**
	Mean Severity Grade	1.2	1.2	1.0	1.2	1.5	-	1.4	-	1.4	1.2	1.4	1.3
							-		-				
–Hyperplasia, pelvic epithelium	Minimal (Grade 1)	18	24	17	1	2	-	26	-	30	23	10	12
	Mild (Grade 2)	31	29	6	1	2	-	18	-	23	4	5	3
	Moderate (Grade 3)	1	1	0	0	0	-	1	-	2	0	0	0
	Mod Severe (Grade 4)	1	0	1	0	0	-	0	-	0	0	0	0
	Total Affected	**51**	**54**	**24**	**2**	**4**	-	**45**	-	**55**	**27**	**15**	**15**
	Mean Severity Grade	1.7	1.6	1.4	1.5	1.5	-	1.4	-	1.5	1.1	1.3	1.2
FORESTOMACH	NO. EXAMINED	59	60	60	60	60	0	60	0	60	60	60	60
–Mineralization of muscularis	Minimal (Grade 1)	0	0	1	1	3	-	0	-	0	1	1	2
	Mild (Grade 2)	0	1	4	6	12	-	0	-	0	0	0	4
	Moderate (Grade 3)	0	0	3	1	3	-	0	-	0	2	1	1
	Mod Severe (Grade 4)	0	0	0	0	1	-	0	-	0	0	0	1
	Total Affected	**0**	**1**	**8**	**8**	**19**	-	**0**	-	**0**	**3**	**2**	**8**
	Mean Severity Grade	0.0	2.0	2.3	2.0	2.1	-	0.0	-	0.0	2.3	2.0	2.1

The incidence of all drug-related positive non-neoplastic histopath findings in rats (n=60/sex/dose)

Histopath findings	Male, mg/kg/d					Female, mg/kg/d				
	0	0.3	1	3	10	0	1	3	10	30
Lungs, Pneumonia, foreign body	6	3	11	36	49	0	2	21	37	48
Kidney, Pelvic calculi	48	49	12	5	11	57	59	46	40	50
Kidney, Hyperplasia, pelvic epithelium	81	54	24	2	4	45	55	27	15	15
Kidney, Nephropathy	19	22	13	26	32	10	5	13	6	7
Forestomach, Mineralization of muscularis	0	1	8	8	19	0	0	3	2	8
Adrenal cortex, Congestion/angiectasis	9	5	4	14	20	12	3	15	21	37
Spleen, Pigmentation	3	1	2	17	29	2	6	18	20	36
Spleen, Lymphoid depletion	2	1	0	6	15	22	2	4	14	15
Liver, biliary hyperplasia, fibrosis	21	22	17	28	35	9	10	14	10	15

Non-neoplastic findings summarized by the sponsor

Table 2.6.6-86: Carcinogenicity study in rats – non-neoplastic lesions [R087-TX-047]

Daily Dose (mg/kg)	**0**		**0.3**	**1**		**3**		**10**		**30**
Gender	**M**	**F**	**M**	**M**	**F**	**M**	**F**	**M**	**F**	**F**
Lung: N	60	60	60	60	60	60	60	60	60	60
Foreign Body Pneumonia	6	0	3	11	2	36**	21**	49**	37**	48**
Esophagus: N	60	60	60	60	59	60	60	60	60	60
Distended with Ingesta	1	0	1	2	1	4	6*	4	5*	6*
Trachea: N	60	60	60	60	60	60	60	60	60	59
Foreign Material (Ingesta)	2	0	1	1	1	3	2	3	4	8**
Kidney: N	60	60	60	60	60	60	60	60	60	60
Calculi, pelvis	48	57	49	12**	59	5**	46**	11**	40**	50*
Hyperplasia, Pelvic Epithelium	51	45	54	24**	55*	2**	27**	4**	15**	15**
Stomach, Nonglandular: N	59	60	60	60	60	60	60	60	60	60
Mineralization, Muscularis	0	0	1	8**	0	8**	3	19**	2	8**

N = Number of animals examined.
Cochran-Armitage Test and Fisher-Irwin Exact Test: * - P<0.05, ** - P<0.01.

Neoplastic:

- There were no significant dose-dependent increase incidence of neoplastic lesions in conivaptan treated male or female rats.
- The significant decrease in thyroid c-cell carcinoma (3 mg/kg/d) and leukemia (3 and 10 mg/kg/d) observed in male was unlikely to be drug-related.

The incidence of neoplastic lesions in rats died before terminal necropsy and at rats at the terminal necropsy are shown in table below

Table 2.6.6-85: Carcinogenicity study in rats – neoplastic lesions [R087-TX-047]

Daily Dose (mg/kg)	0		0.3	1		3		10		30
Gender	M	F	M	M	F	M	F	M	F	F
Adrenal, medulla: N	60	59	60	60	59	60	59	60	60	60
Pheochromocytoma	5	0	2	4	0	1	0	3	0	0
Complex Pheochromocytoma	1	0	0	1	0	0	0	0	0	0
Malignant Pheochromocytoma	0	1	0	2	0	0	0	1	0	1
Hematopoietic Neoplasia: N	60	60	60	60	60	60	60	60	60	60
Leukemia, Large Granular Lymphocytic	16	12	15	15	11	7*	13	4**	5	4
Lymphoma	0	0	0	0	1	1	1	0	0	0
Sarcoma, Histiocytic	1	0	0	0	0	0	1	0	0	0
Liver: N	60	60	60	60	60	60	60	60	60	60
Adenoma, Hepatocellular	4	1	2	5	1	0*	1	3	1	0
Carcinoma, Hepatocellular	0	0	1	0	0	0	0	0	0	0
Mammary, Caudal: N		49			49		54		50	50
Fibroadenoma		1			0		0		0	0
Mammary, Cranial: N		52			47		43		48	50
Carcinoma		0			1		0		0	0
Mammary, Other: N		8			6		1		2	1
Fibroadenoma		5			4		1		1	0
Pancreas: N	60	60	60	58	60	60	60	60	60	60
Adenoma, Islet Cell	3	1	4	1	0	0	0	0	0	0
Carcinoma, Islet Cell	2	0	1	1	0	2	0	0	0	0
Pituitary: N	59	60	59	60	60	60	60	60	59	59
Adenoma, Anterior Lobe	24	26	29	22	29	21	23	8	19	17
Adenoma, Intermediate Lobe	0	0	0	0	0	0	1	0	0	0
Carcinoma, Anterior Lobe	0	0	0	1	0	1	0	0	2	0
Testis: N	60		60	60		60		60		
Benign Interstitial Cell Tumor	53		53	57		53		43		
Thyroid: N	60	58	60	60	60	60	60	60	60	60
Follicular Cell Adenoma	0	0	1	1	0	1	0	0	0	0
"C" Cell Adenoma	2	3	4	7*	3	0	4	4	2	1
"C" Cell Carcinoma	9	3	7	7	3	2*	7	4	5	0
Uterus: N		60			60		60		60	60
Endometrial Stromal Polyp		8			6		10		2	2
Endometrial Stromal Sarcoma		1			0		0		1	0
Sarcoma		0			0		1		0	0
Carcinoma		1			3		0		0	0
Uterine, Cervix: N		60			60		60		60	60
Granular Cell Tumor		0			0		1		0	0
Endometrial Stromal Polyp		0			1		1		1	0
Endometrial Stromal Sarcoma		0			1		0		0	1
Schwannoma		0			1		0		0	0

N = Number of animals examined.

Dinse and Lagakos Logistic Prevalence Methods and Cox-Tarone Binary Regression Methods:

* - P<0.05, ** - P<0.01.

Incidence of microscopic findings in rats "unscheduled deaths"

Incidence of Microscopic Observations - Unscheduled Deaths

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=UNSCHED;FIND=ALL;SUBSET=ALL

		-- NUMBER-OF-ANIMALS-AFFECTED --									
	SEX:	----------MALE----------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-3-	-4-	-5-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	21	22	18	28	41	15	16	26	31	43
*** TOP OF LIST ***											
BRAIN W/STEM (BR)	NUMBER EXAMINED:	21	22	18	28	41	15	16	26	31	43
	NOT REMARKABLE:	12	15	15	26	41	12	14	23	29	38
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	2	1	1	0	0	0	1	0	1
--M-ASTROCYTOMA		1	2	0	0	0	0	0	0	0	0
--VENTRAL DISTORTION (PITUITARY TUMOR)		6	3	1	1	0	3	2	1	2	4
--VENTRICULAR DILATATION (PITUITARY NEOPLASM)		3	1	0	0	0	2	1	0	0	1
--ABSCESS		0	0	1	0	0	0	0	0	0	0
--HEMORRHAGE, HYPOTHALAMUS (PITUITARY TUMOR)		0	0	0	0	0	0	0	1	0	0
CORD, CERVICAL (CS)	NUMBER EXAMINED:	21	22	18	28	40	15	16	26	31	43
	NOT REMARKABLE:	19	20	17	28	40	15	16	25	31	42
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	2	1	0	0	0	0	1	0	0
--INCLUSION CYST		0	0	0	0	0	0	0	0	0	1
CORD, LUMBAR (LC)	NUMBER EXAMINED:	21	22	18	28	40	15	16	26	31	43
	NOT REMARKABLE:	19	20	18	28	40	15	16	25	31	43
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	2	0	0	0	0	0	1	0	0
CORD, THORACIC (TC)	NUMBER EXAMINED:	21	22	18	28	40	15	16	26	31	43
	NOT REMARKABLE:	19	22	18	28	40	15	16	26	31	43
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	0	0	0	0	0	0	0	0	0
PITUITARY (PI)	NUMBER EXAMINED:	21	21	18	28	41	15	16	26	30	42
	NOT REMARKABLE:	7	7	8	11	28	5	5	15	15	24
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	1	1	0	1	1	1	1	0
--B-ADENOMA, ANTERIOR LOBE		9	8	6	10	2	6	5	9	6	9
--M-CARCINOMA, ANTERIOR LOBE		0	0	0	1	0	0	0	0	0	0
--HYPERPLASIA, FOCAL		5	2	2	4	7	3	3	1	2	4
--CYST(S), ANTERIOR LOBE		0	1	1	1	3	1	2	2	4	6
--CYST(S), INTERMEDIATE LOBE		0	2	0	0	1	0	0	0	0	0
--CYST(S), NEUROHYPOPHYSIS		0	0	0	0	0	0	1	0	0	0
--ANGIECTASIS		0	1	1	0	1	2	1	0	4	2
--HEMATOCYST		0	0	0	0	0	1	0	0	0	0
--GLIOSIS, FOCAL, NEUROHYPOPHYSIS		0	0	1	0	0	0	0	0	0	0
--ABSCESS		0	1	0	0	0	0	0	0	0	0
ADRENAL, CORTEX (AC)	NUMBER EXAMINED:	21	22	18	28	41	15	16	25	31	43
	NOT REMARKABLE:	1	7	2	7	12	5	6	5	10	8
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		3	5	4	1	1	1	3	5	1	1
--HYPERPLASIA, FOCAL		4	1	2	4	0	0	0	3	1	1
--HYPERTROPHY, FOCAL		0	0	1	0	2	0	0	0	1	2
--LIPOIDOSIS, FOCAL		7	5	4	9	17	6	5	7	9	10
--LIPOIDOSIS, DIFFUSE		8	7	2	0	3	1	0	1	0	2
--CONGESTION/ANGIECTASIS		7	5	4	14	17	4	2	13	15	28
--CYSTIC DEGENERATION		0	0	1	0	0	0	1	1	1	0
--NECROSIS, FOCAL		0	0	0	0	0	0	0	0	1	0
--THROMBUS		0	0	0	0	0	0	1	0	0	2
ADRENAL, MEDULLA (AM)	NUMBER EXAMINED:	21	22	18	28	41	14	15	25	31	43
	NOT REMARKABLE:	19	17	13	25	35	13	13	21	31	42
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	2	1	1	0	1	0	3	0	1
--B-PHEOCHROMOCYTOMA		1	1	3	1	3	0	0	0	0	0
--B-COMPLEX PHEOCHROMOCYTOMA		0	0	1	0	0	0	0	0	0	0
--M-MALIGNANT PHEOCHROMOCYTOMA		0	0	1	0	0	0	0	0	0	0
--HYPERPLASIA, FOCAL		0	2	0	1	4	0	2	1	0	0
THYROID (TY)	NUMBER EXAMINED:	21	22	18	28	41	13	16	26	31	43
	NOT REMARKABLE:	16	19	15	25	36	10	16	23	28	41
--B-FOLLICULAR CELL ADENOMA		0	0	0	1	0	0	0	0	0	0
--B-"C" CELL ADENOMA		2	0	2	0	3	0	0	1	0	0
--M-"C" CELL CARCINOMA		1	1	1	0	2	2	0	2	2	0
--HYPERPLASIA, FOLLICULAR CELL		1	0	0	1	0	0	0	0	0	0
--HYPERPLASIA, "C" CELL		1	2	0	1	0	1	0	0	0	2
--CYSTS(S), ULTIMOBRANCHIAL		0	0	0	0	0	0	0	0	1	0
--CYSTIC FOLLICLE(S)		1	0	0	0	0	1	0	0	0	0
PARATHYROID (PT)	NUMBER EXAMINED:	21	22	17	23	38	13	15	25	29	40
	NOT REMARKABLE:	21	22	16	23	38	12	15	24	28	40
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	1	0	0	0	0
--B-ADENOMA		0	0	0	0	0	0	0	0	1	0
--HYPERPLASIA, FOCAL		0	0	0	0	0	0	0	1	0	0
--HYPERTROPHY		0	0	1	0	0	0	0	0	0	0
ESOPHAGUS (ES)	NUMBER EXAMINED:	21	22	18	28	41	15	15	26	31	43
	NOT REMARKABLE:	19	21	16	24	37	15	14	19	26	37
--DISTENDED WITH INGESTA		1	1	2	4	4	0	1	6	5	6
--INFLAMMATION, CHRONIC		1	0	0	0	0	0	0	1	0	0
TRACHEA (TR)	NUMBER EXAMINED:	21	22	18	28	41	15	16	26	31	42
	NOT REMARKABLE:	18	21	17	23	37	15	16	23	26	31
--EXUDATE/FOREIGN MATERIAL (INGESTA)		2	1	1	3	3	0	0	2	4	8
--HYPERPLASIA, GLANDS		0	0	0	5	2	0	0	1	0	4
--INFLAMMATION, CHRONIC		2	0	0	0	0	0	0	0	0	0
--FIBROSIS, SUBMUCOSA		0	0	0	0	0	0	0	0	1	0
--ABSCESS, GLANDS		0	0	0	0	0	0	0	1	0	2

Incidence of microscopic findings in rats "unscheduled deaths"

INCIDENCE OF MICROSCOPIC OBSERVATIONS - UNSCHEDULED DEATHS

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=UNSCHED;FIND=ALL;SUBSET=ALL

-- N U M B E R - O F - A N I M A L S - A F F E C T E D --

ORGAN AND FINDING DESCRIPTION	NUMBER:	SEX:	-MALE-					-FEMALE-			
		GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-3-	-4-	-5-	-6-
			21	22	18	28	41	15	16	26	31	43
LUNG (LU)	NUMBER EXAMINED:		21	22	18	28	41	15	16	26	31	43
	NOT REMARKABLE:		0	1	1	0	0	0	1	0	1	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			5	7	5	2	4	3	5	7	2	1
--N-THYMOMA, METASTATIC			0	0	1	0	0	0	0	0	0	0
--N-NEPHROBLASTOMA, METASTATIC			0	0	0	0	0	1	0	0	0	0
--BRONCHIOLAR ASSOCIATED LYMPHOID TISSUE			18	20	15	24	34	12	14	21	26	34
--FOREIGN BODY PNEUMONIA			1	2	5	19	35	0	1	13	23	35
--CONGESTION/HEMORRHAGE, AGONAL			4	0	0	1	2	2	2	2	0	2
--INFLAMMATION, CHRONIC, FOCAL			1	2	1	0	0	1	0	3	1	0
--ALVEOLAR HISTIOCYTOSIS			2	1	1	2	0	2	1	0	1	1
--HYPERPLASIA, GOBLET CELLS			0	0	0	0	0	0	0	0	0	1
--THROMBUS			0	0	0	0	1	0	0	0	0	0
--INFLAMMATION, ACUTE, PLEURA			0	0	0	0	0	1	1	0	0	0
--NECROSIS, FOCAL			0	1	0	0	0	0	0	0	0	0
--MICROTHROMBI			2	0	0	0	0	0	0	0	0	0
--EDEMA, PERIVASCULAR			0	0	1	0	0	0	0	0	0	0
HEART (HT)	NUMBER EXAMINED:		21	22	18	28	41	15	16	26	31	43
	NOT REMARKABLE:		2	1	1	3	5	2	5	8	8	11
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			2	3	3	2	2	1	0	5	1	1
--CARDIOMYOPATHY, DEGENERATIVE			16	17	16	17	16	9	6	8	9	12
--DEGENERATION, MYOCARDIUM			1	2	0	4	0	0	1	1	1	2
--MINERALIZATION, GREAT VESSELS/CORONARY VESSELS			10	15	13	20	35	8	5	10	22	24
--THROMBUS, ATRIUM			2	1	1	1	0	1	2	0	1	0
--MINERALIZATION, MYOCARDIUM			0	0	0	0	2	0	1	0	1	1
--MYXOID DEGENERATION, MYOCARDIUM, FOCAL			0	0	0	0	0	0	0	0	1	0
--INFLAMMATION, CHRONIC, CORONARY GROOVE			0	0	0	1	0	0	0	0	0	0
--ABSCESS, MYOCARDIUM			0	0	1	0	0	0	1	0	0	0
--INFLAMMATION, ACUTE, PERICARDIUM			0	0	0	0	0	1	1	0	0	0
--INFLAMMATION, ACUTE, MYOCARDIUM			0	0	0	0	0	1	0	0	0	0
SPLEEN (SP)	NUMBER EXAMINED:		21	22	18	28	41	14	16	26	31	42
	NOT REMARKABLE:		8	12	7	8	6	2	2	4	5	4
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			6	8	8	3	4	3	6	9	3	2
--X-MESOTHELIOMA			0	1	0	0	0	0	0	0	0	0
--M-SARCOMA			0	0	1	0	0	0	0	0	0	0
--INCREASED PIGMENT			3	1	1	16	29	2	4	12	15	34
--INCREASED EXTRAMEDULLARY HEMATOPOIESIS			3	0	2	1	0	6	4	2	3	1
--LYMPHOID DEPLETION			2	0	0	6	15	1	2	3	13	15
--FIBROSIS			0	0	0	0	0	0	1	0	1	0
--NECROSIS, LYMPHOID			0	0	0	0	0	0	0	0	1	0
--HISTIOCYTOSIS			1	0	0	0	0	0	0	0	0	0
--FIBROSIS, CAPSULE			0	0	0	0	0	0	1	0	0	0
LIVER (LI)	NUMBER EXAMINED:		21	22	18	28	41	15	16	26	31	43
	NOT REMARKABLE:		0	0	0	0	6	1	1	6	14	22
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			7	8	8	3	3	4	6	9	3	3
--X-MESOTHELIOMA			1	1	0	0	0	0	0	0	0	0
--B-ADENOMA, HEPATOCELLULAR			2	0	0	0	2	0	1	1	0	0
--CHRONIC BILIARY DISEASE (HYPERPLASIA, FIBROSIS, INFLAMMATION)			21	22	17	28	35	9	10	14	10	16
--INFLAMMATION, CHRONIC, FOCAL			2	4	1	4	0	3	0	3	4	4
--NECROSIS, FOCAL			1	0	0	0	1	1	1	1	0	0
--NECROSIS, CENTRILOBULAR			0	0	0	0	0	0	1	0	0	0
--CELLULAR ALTERATION, BASOPHILIC			2	1	3	3	0	2	2	1	5	2
--CELLULAR ALTERATION, EOSINOPHILIC			1	0	2	0	0	0	0	0	0	0
--CELLULAR ALTERATION, CLEAR			1	2	1	0	0	0	1	1	0	0
--CELLULAR ALTERATION, MIXED			0	0	0	0	0	0	0	0	0	1
--LIPOIDOSIS, NONZONAL			0	0	0	0	0	1	0	0	0	0
--LIPOIDOSIS, FOCAL			1	0	1	0	0	0	0	0	0	0
--LIPOIDOSIS, CENTRILOBULAR			0	0	0	0	0	0	1	1	0	0
--LIPOIDOSIS, PERIPORTAL			0	0	0	0	0	2	1	0	0	1
--LIPOIDOSIS, MIDZONAL			0	0	1	0	0	1	0	0	0	0
--EXTRAMEDULLARY HEMATOPOIESIS			0	0	0	0	0	1	0	0	2	0
--DEGENERATION/NECROSIS, CENTRILOBULAR (TUMOR RELATED)			2	1	0	0	0	1	2	0	1	0
--ANGIECTASIS, FOCAL			1	0	0	0	1	2	0	0	0	0
--HISTIOCYTOSIS, SINUSOIDAL			0	0	0	0	0	0	1	1	0	0
--HEPATOCYTOMEGALY, CENTRILOBULAR			0	0	0	0	0	0	0	0	1	0
--CYSTIC DEGENERATION			2	3	0	0	0	0	0	0	0	0
--HEPATODIAPHRAGMATIC NODULE			0	0	1	1	1	0	0	0	1	0
--BILE PIGMENT			0	0	0	0	0	0	1	0	2	0
--INCREASED MITOSIS, HEPATOCYTES			0	1	0	0	0	1	1	0	0	0
--HEPATOCELLULAR PLEOMORPHISM			0	0	0	0	0	1	1	0	0	0
--APOPTOSIS, INCREASED			0	0	0	0	0	0	1	0	0	0
--REGENERATIVE HYPERPLASIA			1	0	0	0	0	0	0	0	0	0
--ATROPHY, HEPATOCELLULAR, PERIPORTAL			0	1	0	0	0	0	0	0	0	0
--DISTENDED EXTRAHEPATIC BILE DUCTS			1	0	0	0	0	0	0	0	0	0

Incidence of microscopic findings in rats "unscheduled deaths"

INCIDENCE OF MICROSCOPIC OBSERVATIONS - UNSCHEDULED DEATHS

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=UNSCHED;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		-- NUMBER-OF-ANIMALS-AFFECTED --									
SEX:		----------MALE----------					---------FEMALE--------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-3-	-4-	-5-	-6-
NUMBER:		21	22	18	28	41	15	16	26	31	43
KIDNEY (KD)	NUMBER EXAMINED:	21	22	18	28	41	15	16	26	31	43
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	3	1	2	1	2	1	2	0	1
--X-MESOTHELIOMA		0	1	0	0	0	0	0	0	0	0
--B-PAPILLOMA, TRANSITIONAL CELL		0	0	0	0	0	0	0	1	0	0
--M-NEPHROBLASTOMA		0	0	0	0	0	1	0	0	0	0
--CALCULI, PELVIS		18	16	5	4	9	13	15	20	19	35
--HYPERPLASIA, PELVIC EPITHELIUM		19	17	5	1	3	11	15	9	4	13
--MICROCALCULI, MEDULLA		19	22	18	24	38	15	16	25	30	43
--MICROCONCRETIONS/MINERALIZATION, CORTEX		21	22	18	28	41	15	15	26	31	43
--NEPHROPATHY, CHRONIC PROGRESSIVE		19	22	13	26	32	10	5	13	6	17
--PIGMENT, TUBULES		21	20	16	26	35	14	15	25	29	39
--PELVIS, DILATATION, UNILATERAL		1	1	0	2	1	0	0	0	0	0
--PELVIS, DILATATION, BILATERAL		0	0	0	1	0	0	0	0	0	1
--TUBULES, HYALINE DROPLET DEGENERATION		0	0	1	0	0	0	1	2	0	0
--MINERALIZATION, BASEMENT MEMBRANES		0	0	0	0	1	0	0	0	0	1
--PROTEINURIA		0	0	0	0	1	0	0	0	0	0
--TUBULES, DEGENERATION, HYALINE		0	0	0	0	0	0	0	1	0	0
--DEGENERATION/NECROSIS, TUBULES		0	0	0	0	0	0	0	0	1	0
--TUBULES, DILATATION		0	1	0	0	0	0	0	0	0	1
--MINERALIZATION, PAPILLA		0	0	0	0	0	0	0	0	0	1
--INFLAMMATION, SUBACUTE CORTEX		0	0	0	0	0	0	1	0	0	0
--INFARCT		0	0	0	0	0	0	0	1	0	0
--NECROSIS, TUBULES, PAPILLA		0	0	0	0	0	0	1	0	0	0
--ATROPHY, CORTICAL		0	1	0	0	0	0	0	0	0	0
--CYST(S)		0	1	0	0	0	0	0	0	0	1
STOMACH, NONGL (SU)	NUMBER EXAMINED:	20	22	18	28	41	15	16	26	31	43
	NOT REMARKABLE:	17	20	15	24	29	14	12	24	27	40
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	2	0	0	0	0	2	0	0	0
--B-PAPILLOMA		0	0	0	1	0	0	0	0	0	0
--ULCER		2	1	1	1	0	1	2	1	1	0
--MINERALIZATION, MUSCULARIS		0	0	2	3	11	0	0	1	2	3
--KERATIN CYST		0	0	0	0	0	0	0	0	1	0
--HYPERKERATOSIS		1	0	0	0	1	1	0	0	0	1
--ACANTHOSIS		1	0	0	0	1	1	0	0	1	1
--EDEMA, SUBMUCOSA		0	0	0	1	0	0	0	0	0	0
--INFLAMMATION, SUBACUTE		0	0	0	1	0	0	0	0	0	0
STOMACH, GL (ST)	NUMBER EXAMINED:	20	22	18	28	40	15	16	26	30	43
	NOT REMARKABLE:	17	19	17	22	36	13	13	24	23	37
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	1	0	1	1	0	0	0
--EROSION, MUCOSA		2	0	1	2	4	0	0	2	5	5
--FIBROSIS, LAMINA PROPRIA		0	2	0	2	0	0	0	0	1	0
--ULCER		1	0	0	1	0	0	3	0	0	0
--DILATED GLANDS		0	0	0	0	0	1	0	0	0	0
--HYPERPLASIA		0	0	0	0	0	0	0	0	1	0
--MINERALIZATION, SUBMUCOSA		0	0	0	0	0	0	0	0	0	1
DUODENUM (DU)	NUMBER EXAMINED:	18	20	14	25	33	13	14	22	29	36
	NOT REMARKABLE:	18	18	14	24	33	13	14	22	29	36
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	1	0	0	0	0	0	0
--X-MESOTHELIOMA		0	1	0	0	0	0	0	0	0	0
JEJUNUM (JE)	NUMBER EXAMINED:	16	19	11	23	26	11	12	21	24	32
	NOT REMARKABLE:	15	17	11	22	26	11	12	21	24	32
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	1	0	1	0	0	0	0	0	0
--X-MESOTHELIOMA		0	1	0	0	0	0	0	0	0	0
ILEUM (IL)	NUMBER EXAMINED:	15	20	11	21	27	11	12	21	21	33
	NOT REMARKABLE:	15	18	11	20	25	11	12	21	21	33
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	1	0	0	0	0	0	0
--X-MESOTHELIOMA		0	1	0	0	0	0	0	0	0	0
--M-ADENOCARCINOMA		0	0	0	0	1	0	0	0	0	0
--PARASITISM		0	0	0	0	1	0	0	0	0	0
PANCREAS (PA)	NUMBER EXAMINED:	21	22	16	28	41	15	16	26	31	43
	NOT REMARKABLE:	15	16	14	26	36	13	14	25	31	43
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	1	0	1	1	2	1	1	0	0
--X-MESOTHELIOMA		0	1	0	0	0	0	0	0	0	0
--B-ADENOMA, ISLET CELL		1	0	0	0	0	0	0	0	0	0
--M-CARCINOMA, ISLET CELL		1	0	0	0	0	0	0	0	0	0
--EOSINOPHILIC FOCI		0	0	0	0	1	0	1	0	0	0
--ACINAR ATROPHY		1	3	1	0	1	0	0	0	0	0
--HYPERPLASIA, ISLET CELL		1	1	1	1	2	0	0	0	0	0
CECUM (CE)	NUMBER EXAMINED:	14	18	10	21	25	12	12	18	22	29
	NOT REMARKABLE:	13	17	9	21	25	12	12	18	22	27
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	0	0	0	0	0	0	0
--PARASITISM		0	0	1	0	0	0	0	0	0	2
--EDEMA		1	0	0	0	0	0	0	0	0	0
COLON (CO)	NUMBER EXAMINED:	18	20	15	27	35	13	16	24	29	39
	NOT REMARKABLE:	17	18	15	22	29	11	15	22	23	31
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	1	0	1	0	0	0	0	0	0
--X-MESOTHELIOMA		0	1	0	0	0	0	0	0	0	0
--PARASITISM		0	0	0	4	5	2	1	2	6	8
--ULCER		0	0	0	0	1	0	0	0	0	0
RECTUM (RE)	NUMBER EXAMINED:	18	22	16	27	39	13	15	23	29	39
	NOT REMARKABLE:	16	22	16	24	38	13	15	23	28	38
--PARASITISM		2	0	0	3	1	0	0	0	1	1

Incidence of microscopic findings in rats "unscheduled deaths"

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104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=UNSCHED;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		-- NUMBER-OF-ANIMALS-AFFE									
SEX:		----------MALE---------					---------FEMALE--------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-3-	-4-	-5-	-6-
NUMBER:		21	22	18	28	41	15	16	26	31	43
LN, MESENTERIC (MS)	NUMBER EXAMINED:	21	22	18	28	39	15	15	26	31	42
	NOT REMARKABLE:	17	19	16	27	38	12	12	23	29	42
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		4	3	2	1	1	3	2	2	2	0
--HYPERPLASIA, LYMPHOID		0	0	0	0	0	0	0	1	0	0
--NECROSIS		0	0	0	0	0	0	1	0	0	0
MAND SALIVARY GL (SG)	NUMBER EXAMINED:	21	22	18	27	41	14	16	26	31	43
	NOT REMARKABLE:	21	22	18	25	41	12	15	26	31	43
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	1	0	1	1	0	0	0
--M-CARCINOMA		0	0	0	1	0	0	0	0	0	0
--VACUOLIZATION, MUCOUS CELLS		0	0	0	0	0	1	0	0	0	0
PAROTID SAL GL. (SG0)	NUMBER EXAMINED:	20	22	18	27	38	15	15	25	29	43
	NOT REMARKABLE:	20	20	17	27	38	14	15	25	28	43
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	0	0	1	0	0	0	0
--SIALOCYST		0	0	1	0	0	0	0	0	0	0
--INFLAMMATION, SUBACUTE		0	0	0	0	0	0	0	0	1	0
--INFLAMMATION, ACUTE		0	1	0	0	0	0	0	0	0	0
LN, MANDIBULAR (MN)	NUMBER EXAMINED:	21	22	17	27	40	14	16	25	31	42
	NOT REMARKABLE:	19	21	17	25	39	12	14	24	30	42
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	1	0	1	1	2	1	1	1	0
--N-SALIVARY GLAND CARCINOMA, METASTATIC		0	0	0	1	0	0	0	0	0	0
--NECROSIS		0	0	0	0	0	0	1	0	0	0
THYMUS (TH)	NUMBER EXAMINED:	20	19	16	22	22	15	15	19	23	27
	NOT REMARKABLE:	4	6	3	11	11	7	3	6	8	7
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		3	1	0	1	0	2	3	2	1	0
--M-THYMOMA		0	0	1	0	0	0	0	0	0	0
--LYMPHOID DEPLETION		13	12	11	10	11	6	10	10	14	20
--HYPERPLASIA, EPITHELIAL		0	1	0	0	0	0	1	1	0	0
--NECROSIS		0	0	0	0	0	0	1	0	0	0
--ECTOPIC PARATHYROID		0	0	1	0	0	0	0	0	0	0
AORTA, THORACIC (AO)	NUMBER EXAMINED:	21	22	18	28	41	15	16	26	31	43
	NOT REMARKABLE:	21	20	17	28	39	15	16	26	28	41
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	0	0	0	0	0	0	0
--MINERALIZATION		0	1	1	0	2	0	0	0	3	2
EYE (EY)	NUMBER EXAMINED:	21	22	18	28	41	14	16	25	31	43
	NOT REMARKABLE:	0	0	0	0	1	0	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	1	0	0	0	0	0	0
--CORNEAL DYSTROPHY		21	21	17	28	39	14	16	24	30	41
--CALCIFIC BODIES, LIMBUS		10	13	10	17	17	6	7	10	11	17
--ULCER, CORNEA		1	0	0	2	0	0	1	0	0	2
--CATARACT		1	1	1	2	2	2	2	1	0	3
--RETINAL DEGENERATION		1	2	1	3	3	3	2	1	2	3
--OSSEOUS METAPLASIA, SCLERA		10	9	3	9	7	4	3	8	11	10
--INFLAMMATION, CHRONIC, CORNEA		0	1	2	0	0	0	0	0	0	2
--INFLAMMATION, ACUTE, CORNEA		0	2	1	2	0	1	1	1	1	1
--VASCULARIZATION, CORNEA		1	1	0	2	0	3	2	2	1	1
--HYPERPLASIA, CORNEAL EPITHELIUM		0	1	0	0	0	1	1	1	1	0
--HYPERKERATOSIS, CORNEA		0	0	0	1	0	0	0	0	0	0
--INFLAMMATION, ACUTE, ANTERIOR CHAMBER		1	0	1	1	0	0	1	1	1	1
--PANOPHTHALMITIS, ACUTE		0	1	0	0	0	0	0	1	0	0
--INFLAMMATION, CHRONIC, CHOROID		0	1	0	0	0	0	0	0	0	0
--INFLAMMATION, CHRONIC, RETROBULBAR		0	0	0	1	0	0	0	0	0	0
--HEMORRHAGE, ANTERIOR CHAMBER		0	0	0	0	0	0	0	0	0	1
HARDERIAN GLAND (HG)	NUMBER EXAMINED:	21	22	18	28	41	15	16	26	31	43
	NOT REMARKABLE:	20	21	18	26	41	14	14	25	31	43
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	0	0	1	0	1	0	0
--M-SARCOMA		0	0	0	1	0	0	0	0	0	0
--N-SALIVARY GLAND CARCINOMA, METASTATIC		0	0	0	1	0	0	0	0	0	0
--INFLAMMATION, ACUTE		1	0	0	0	0	0	0	0	0	0
--HYPERPLASIA		0	0	0	0	0	0	1	0	0	0
--EMBRYONAL EPITHELIAL CYST(S)		0	0	0	0	0	0	1	0	0	0
MUSCLE, SKELETAL (SM)	NUMBER EXAMINED:	21	22	18	28	41	15	16	26	31	43
	NOT REMARKABLE:	20	20	16	27	41	15	16	26	30	43
--DEGENERATION		1	2	2	1	0	0	0	0	1	0
NERVE, SCIATIC (SN)	NUMBER EXAMINED:	21	22	18	28	41	15	16	26	30	41
	NOT REMARKABLE:	15	12	5	19	24	13	13	22	20	30
--AXONAL DEGENERATION		6	10	13	9	17	2	3	4	10	11
TONGUE (TO)	NUMBER EXAMINED:	21	22	18	28	41	15	16	26	31	43
	NOT REMARKABLE:	2	4	2	4	4	2	3	3	7	7
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	0	0	0	0	0	0	0
--DEGENERATION/MINERALIZATION, ARTERIOLE		17	18	16	24	37	13	13	23	24	36
--INFLAMMATION, SUBACUTE/CHRONIC		1	1	0	0	0	0	0	0	1	0
--EROSION, EPITHELIUM		0	0	0	0	1	0	0	0	0	0
--ACANTHOSIS, FOCAL		0	0	0	0	1	0	0	0	0	0

Incidence of microscopic findings in rats "unscheduled deaths"

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104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=UNSCHED;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		- NUMBER-OF-ANIMALS-AFFECTED -									
SEX:		----------MALE----------					----------FEMALE----------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-3-	-4-	-5-	-6-
	NUMBER:	21	22	18	28	41	15	16	26	31	43
TESTIS (TE)	NUMBER EXAMINED:	21	22	18	28	41	0	0	0	0	0
	NOT REMARKABLE:	1	2	0	5	8	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA"	FOR TYPE)	1	0	1	1	0	0	0	0	0	0
--X-MESOTHELIOMA		2	1	0	0	1	0	0	0	0	0
--B-BENIGN INTERSTITIAL CELL TUMOR		16	19	17	22	25	0	0	0	0	0
--HYPERPLASIA, INTERSTITIAL CELL		2	1	0	1	5	0	0	0	0	0
--DEGENERATION, SEMINIFEROUS TUBULES		16	18	15	19	21	0	0	0	0	0
EPIDIDYMIS (EP)	NUMBER EXAMINED:	21	22	18	28	41	0	0	0	0	0
	NOT REMARKABLE:	10	8	5	15	21	0	0	0	0	0
--X-MESOTHELIOMA		2	1	0	0	1	0	0	0	0	0
--HYPOSPERMIA		11	14	13	13	19	0	0	0	0	0
PROSTATE (PR)	NUMBER EXAMINED:	21	22	18	28	41	0	0	0	0	0
	NOT REMARKABLE:	3	3	4	12	23	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA"	FOR TYPE)	1	1	0	1	0	0	0	0	0	0
--X-MESOTHELIOMA		0	1	0	0	0	0	0	0	0	0
--ABSCESS		1	4	4	4	3	0	0	0	0	0
--INFLAMMATION, SUBACUTE/CHRONIC		15	12	8	11	14	0	0	0	0	0
--HYPERPLASIA		2	4	3	3	6	0	0	0	0	0
--MUCOID CYST(S)		1	0	0	0	2	0	0	0	0	0
--FIBROSIS		0	1	3	2	0	0	0	0	0	0
SEMINAL VESICLE (SV)	NUMBER EXAMINED:	21	22	18	28	39	0	0	0	0	0
	NOT REMARKABLE:	20	19	17	27	38	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA"	FOR TYPE)	1	1	0	1	1	0	0	0	0	0
--X-MESOTHELIOMA		0	1	0	0	0	0	0	0	0	0
--EPITHELIAL HYPERPLASIA		0	0	0	0	1	0	0	0	0	0
--ABSCESS		0	1	1	0	0	0	0	0	0	0
OVARY (OV)	NUMBER EXAMINED:	0	0	0	0	0	15	16	26	31	43
	NOT REMARKABLE:	0	0	0	0	0	12	15	26	31	43
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA"	FOR TYPE)	0	0	0	0	0	2	1	0	0	0
--INFLAMMATION, ACUTE, BURSA		0	0	0	0	0	1	0	0	0	0
UTERUS (UT)	NUMBER EXAMINED:	0	0	0	0	0	15	16	26	31	43
	NOT REMARKABLE:	0	0	0	0	0	8	10	14	27	38
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA"	FOR TYPE)	0	0	0	0	0	2	1	0	0	0
--B-ENDOMETRIAL STROMAL POLYP		0	0	0	0	0	1	1	3	0	0
--M-ENDOMETRIAL STROMAL SARCOMA		0	0	0	0	0	1	0	0	1	0
--M-CARCINOMA		0	0	0	0	0	0	1	0	0	0
--M-SARCOMA		0	0	0	0	0	0	0	1	0	0
--ENDOMETRIAL FIBROSIS		0	0	0	0	0	3	1	0	1	4
--ENDOMETRIAL CYSTIC HYPERPLASIA		0	0	0	0	0	2	2	4	2	0
--DILATATION		0	0	0	0	0	1	1	4	1	0
--ENDOMETRIAL HYPERPLASIA		0	0	0	0	0	0	0	0	0	1
--ENDOMETRIAL CYST		0	0	0	0	0	1	1	1	1	0
UTERUS, CERVIX (CV)	NUMBER EXAMINED:	0	0	0	0	0	15	16	26	31	43
	NOT REMARKABLE:	0	0	0	0	0	12	12	24	30	42
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA"	FOR TYPE)	0	0	0	0	0	2	2	1	0	0
--B-POLYP, ENDOMETRIAL STROMAL		0	0	0	0	0	0	1	1	1	0
--M-SARCOMA, ENDOMETRIAL STROMAL		0	0	0	0	0	0	1	0	0	1
--ENDOCERVICAL CYST		0	0	0	0	0	1	0	0	0	0
VAGINA (VA)	NUMBER EXAMINED:	0	0	0	0	0	15	16	26	31	43
	NOT REMARKABLE:	0	0	0	0	0	14	16	26	31	43
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA"	FOR TYPE)	0	0	0	0	0	1	0	0	0	0
URINARY BLADDER (UB)	NUMBER EXAMINED:	21	22	18	28	40	14	16	26	31	43
	NOT REMARKABLE:	19	19	16	28	40	13	16	26	31	43
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA"	FOR TYPE)	0	1	0	0	0	1	0	0	0	0
--X-MESOTHELIOMA		1	1	0	0	0	0	0	0	0	0
--INTRAEPITHELIAL ABSCESS		0	0	1	0	0	0	0	0	0	0
--HYPERPLASIA, EPITHELIAL		1	0	1	0	0	0	0	0	0	0
--HEMORRHAGE		1	1	0	0	0	0	0	0	0	0
--INFLAMMATION, SUBACUTE		1	0	0	0	0	0	0	0	0	0
--INFLAMMATION, CHRONIC		0	1	1	0	0	0	0	0	0	0
SKIN (SK)	NUMBER EXAMINED:	21	22	18	28	41	15	16	26	31	43
	NOT REMARKABLE:	21	21	17	27	41	14	15	25	31	41
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA"	FOR TYPE)	0	1	0	0	0	0	0	0	0	0
--EPIDERMAL CYST		0	0	1	0	0	1	1	1	0	1
--BASAL CELL HYPERPLASIA, FOCAL		0	0	0	0	0	0	0	0	0	1
--INFLAMMATION, GRANULOMATOUS, SUBCUTANEOUS LYMPH NODE		0	0	0	1	0	0	0	0	0	0

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TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=UNSCHED;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		- NUMBER - OF - ANIMALS - AFFECTED --									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-3-	-4-	-5-	-6-
	NUMBER:	21	22	18	28	41	15	16	26	31	43
MAMMARY,CRANIAL (MF0)	NUMBER EXAMINED:	0	0	0	0	0	13	15	20	24	34
	NOT REMARKABLE:	0	0	0	0	0	2	2	7	13	19
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	1	0	0	0	0
--M-CARCINOMA		0	0	0	0	0	0	1	0	0	0
--LACTATION		0	0	0	0	0	9	13	10	7	5
--MAMMARY DYSPLASIA		0	0	0	0	0	5	7	9	7	6
--MASCULINIZATION		0	0	0	0	0	0	0	0	1	7
--HYPERPLASIA		0	0	0	0	0	1	0	0	0	0
MAMMARY,CAUDAL (MF1)	NUMBER EXAMINED:	0	0	0	0	0	12	12	21	23	36
	NOT REMARKABLE:	0	0	0	0	0	2	4	9	11	21
--B-FIBROADENOMA		0	0	0	0	0	1	0	0	0	0
--LACTATION		0	0	0	0	0	8	8	11	7	8
--MAMMARY DYSPLASIA		0	0	0	0	0	5	3	9	5	5
--MASCULINIZATION		0	0	0	0	0	0	0	0	4	6
--HYPERPLASIA		0	0	0	0	0	1	0	0	0	0
MARROW, STERNUM (SE)	NUMBER EXAMINED:	21	22	18	28	40	14	16	26	31	43
	NOT REMARKABLE:	17	19	16	27	38	13	14	25	29	35
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	3	1	1	0	0	0	0	0	1
--HYPERPLASIA		0	0	0	0	1	1	0	1	0	0
--FIBROSIS		0	0	1	0	0	0	0	0	1	1
--HYPOCELLULAR		0	0	0	0	0	0	0	0	1	0
--HYPERPLASIA, GRANULOCYTIC		2	0	0	0	0	0	1	0	0	6
--DEPLETION		0	0	0	0	1	0	1	0	0	0
BONE, STERNUM (SB)	NUMBER EXAMINED:	21	22	18	28	41	15	16	26	31	43
	NOT REMARKABLE:	21	20	17	22	38	14	16	24	29	40
--X-HEMATOPOIETIC NEOPLASIA		0	1	0	0	0	0	0	0	0	0
--OSTEOPETROSIS		0	1	0	0	1	1	0	2	2	1
--OSTEOLYSIS, FOCAL		0	0	0	6	2	0	0	0	0	1
--OSTEOID CYST		0	0	0	0	0	0	0	0	0	1
--FIBROUS OSTEODYSTROPHY, RENAL		0	0	1	0	0	0	0	0	0	0
MARROW, FEMUR (FM)	NUMBER EXAMINED:	21	22	18	28	40	15	16	26	31	41
	NOT REMARKABLE:	18	18	15	26	31	14	9	22	26	37
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	4	2	2	1	0	0	2	1	1
--HYPERPLASIA		0	0	0	0	2	1	3	2	1	0
--HYPOCELLULAR		0	0	0	0	4	0	0	0	3	1
--FIBROSIS		0	0	1	0	1	0	0	0	1	0
--OSSEOUS METAPLASIA		0	0	0	0	0	0	0	0	1	0
--HYPERPLASIA, GRANULOCYTIC		2	0	0	0	0	0	3	0	0	2
--DEPLETION		0	0	1	0	1	0	1	0	0	0
BONE, FEMUR (FE)	NUMBER EXAMINED:	21	22	18	28	41	15	16	26	31	42
	NOT REMARKABLE:	21	22	17	28	40	12	14	24	28	41
--OSTEOPETROSIS		0	0	0	0	1	3	2	2	3	1
--FIBROUS OSTEODYSTROPHY, RENAL		0	0	1	0	0	0	0	0	0	0
VER,LUMBAR,1ST (OB0)	NUMBER EXAMINED:	21	22	18	28	40	15	16	26	31	43
	NOT REMARKABLE:	21	19	18	28	40	15	16	24	30	43
--X-HEMATOPOIETIC NEOPLASIA		0	1	0	0	0	0	0	0	0	0
--OSTEOPETROSIS		0	2	0	0	0	0	0	1	1	0
--MARROW FIBROSIS		0	0	0	0	0	0	0	1	0	0
VER,LUMBAR,2ND (OB1)	NUMBER EXAMINED:	21	22	18	28	40	15	16	26	31	43
	NOT REMARKABLE:	21	19	18	27	40	15	16	25	30	43
--X-HEMATOPOIETIC NEOPLASIA		0	1	0	0	0	0	0	0	0	0
--OSTEOPETROSIS		0	2	0	0	0	0	0	0	1	0
--MARROW FIBROSIS		0	0	0	0	0	0	0	1	0	0
--NECROSIS, ADJACENT MUSCLE		0	0	0	1	0	0	0	0	0	0
--NECROSIS BONE MARROW		0	0	0	1	0	0	0	0	0	0
HEMATO NEOPLASIA (HN)	NUMBER EXAMINED:	21	22	18	28	41	15	16	26	31	43
	NOT REMARKABLE:	14	14	10	25	37	11	9	17	28	40
--M-LEUKEMIA, LARGE GRANULAR LYMPHOCYTIC		6	8	8	2	4	4	6	9	3	3
--M-SARCOMA, HISTIOCYTIC		1	0	0	0	0	0	0	0	0	0
--M-LYMPHOMA		0	0	0	1	0	0	1	0	0	0

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TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=UNSCHED;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		-- NUMBER OF ANIMALS AFFECTED --									
SEX:		MALE					FEMALE				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-3-	-4-	-5-	-6-
NUMBER:		21	22	18	28	41	15	16	26	31	43
^DEATH COMMENT (DC)	NUMBER EXAMINED:	21	22	18	28	41	15	16	26	31	43
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
--UNDETERMINED HISTOLOGICALLY		1	5	5	4	4	2	2	6	3	7
--HEMATOPOIETIC NEOPLASIA		7	8	8	2	4	3	7	9	3	2
--PITUITARY NEOPLASIA		8	2	1	5	1	4	2	2	5	3
--FOREIGN BODY PNEUMONIA		1	1	2	17	30	0	0	12	20	30
--MYOCARDIAL DEGENERATION		0	0	0	0	1	0	1	0	0	1
--ATRIAL THROMBOSIS		1	1	0	1	0	1	1	0	0	0
--NEPHROBLASTOMA		0	0	0	0	0	1	0	0	0	0
--BASAL CELL CARCINOMA		0	1	0	0	0	0	0	0	0	0
--THYMOMA		0	0	1	0	0	0	0	0	0	0
--NEPHROCALCINOSIS		0	0	0	0	1	0	0	0	0	0
--ZYMBAL'S GLAND TUMOR		0	1	0	0	0	0	0	0	0	0
--RHABDOMYOSARCOMA		0	0	0	0	1	0	0	0	0	0
--MESOTHELIOMA		1	1	0	0	0	0	0	0	0	0
--ASTROCYTOMA		1	2	0	0	0	0	0	0	0	0
--MAMMARY GLAND ADENOMA/FIBROADENOMA		0	0	0	0	0	1	0	0	1	0
--MAMMARY GLAND CARCINOMA		0	0	0	0	0	0	1	0	0	0
--PERITONITIS		0	0	0	0	0	0	1	0	0	0
--FIBROSARCOMA		0	0	0	0	1	1	0	0	1	0
--HEPATORENAL DEGENERATION		0	0	0	0	0	0	0	0	1	0
--SEPSIS		0	1	1	0	0	0	1	0	0	0
--SEROUSITIS		0	0	0	0	0	1	1	0	0	0
--ENDOMETRIAL POLYP OR SARCOMA		0	0	0	0	0	0	2	0	1	1
--CHRONIC PROGRESSIVE NEPHROPATHY		1	1	1	0	0	0	0	0	0	1
--UTERINE CARCINOMA		0	0	0	0	0	0	1	0	0	0
--LEIOMYOSARCOMA		0	0	0	0	0	0	0	1	0	0
--ILEAL CARCINOMA		0	0	0	0	1	0	0	0	0	0
--SALIVARY GLAND CARCINOMA		0	0	0	1	0	0	0	0	0	0
--FIBROMA		0	0	0	0	0	1	0	0	0	0
--SQUAMOUS CELL CARCINOMA		1	0	0	0	0	0	0	0	0	0
LARYNX (LA)	NUMBER EXAMINED:	0	0	0	0	0	0	1	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	1	0	0	0
CAVITY, ABDOM (PC)	NUMBER EXAMINED:	3	1	0	1	0	2	2	0	0	1
	NOT REMARKABLE:	0	0	0	0	0	0	1	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA"	FOR TYPE)	1	0	0	1	0	0	0	0	0	0
--N-NEPHROBLASTOMA, METASTATIC		0	0	0	0	0	1	0	0	0	0
--M-MESOTHELIOMA		2	1	0	0	0	0	0	0	0	0
--INFLAMMATION, ACUTE		0	0	0	0	0	1	1	0	0	0
--HEMORRHAGE		0	0	0	0	0	0	0	0	0	1
SKIN, OTHER (SS)	NUMBER EXAMINED:	4	8	5	6	2	1	0	3	2	4
	NOT REMARKABLE:	0	0	0	0	0	0	0	1	1	1
--B-SQUAMOUS CELL PAPILLOMA		0	2	0	0	1	0	0	0	1	0
--B-KERATOACANTHOMA		0	1	2	0	0	1	0	0	0	0
--NECROSIS, TAIL		0	1	1	1	0	0	0	1	0	2
--ABSCESS, FOOT		1	1	1	2	0	0	0	0	0	0
--ESCHAR, TAIL		1	0	0	0	0	0	0	0	0	0
--INFLAMMATION, CHRONIC WITH HYPERKERATOSIS, TAIL		1	1	0	0	0	0	0	1	0	0
--EPIDERMAL CYST		1	1	1	0	0	0	0	0	0	0
--ULCER		0	0	0	1	0	0	0	0	0	0
--ABSCESS, TAIL		0	0	0	1	0	0	0	0	0	0
--ULCER, FOOT		0	0	0	2	1	0	0	0	0	1
--UNIDENTIFIABLE NECROTIC TISSUE		0	1	0	0	0	0	0	0	0	0
--ABSCESS, SUBCUTANEOUS		0	1	0	0	0	0	0	0	0	0
--HYPERKERATOSIS, FOCAL, TAIL		0	0	1	0	0	0	0	0	0	0
--INFLAMMATION, SUBACUTE, FOOT		0	0	1	0	0	0	0	0	0	0
--HYPERKERATOSIS, TAIL		0	1	0	0	0	0	0	0	0	0
HEAD, CORONAL (HC)	NUMBER EXAMINED:	1	2	0	0	0	0	0	0	0	0
	NOT REMARKABLE:	1	0	0	0	0	0	0	0	0	0
--M-BASAL CELL CARCINOMA		0	1	0	0	0	0	0	0	0	0
--M-CARCINOMA, ZYMBAL'S GLAND		0	1	0	0	0	0	0	0	0	0
LN, OTHER (LN)	NUMBER EXAMINED:	0	1	0	0	0	4	1	1	0	0
	NOT REMARKABLE:	0	0	0	0	0	2	1	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA"	FOR TYPE)	0	1	0	0	0	2	0	1	0	0
SUBCUTANEOUS TIS (SQ)	NUMBER EXAMINED:	0	1	0	2	2	3	0	0	1	1
	NOT REMARKABLE:	0	0	0	0	0	1	0	0	0	0
--M-RHABDOMYOSARCOMA		0	0	0	0	1	0	0	0	0	0
--B-FIBROMA		0	1	0	2	0	1	0	0	0	0
--M-FIBROSARCOMA		0	0	0	0	1	1	0	0	1	1
PENIS (PE)	NUMBER EXAMINED:	2	1	0	0	1	0	0	0	0	0
	NOT REMARKABLE:	1	1	0	0	0	0	0	0	0	0
--INFLAMMATION, CHRONIC		1	0	0	0	0	0	0	0	0	0
--NECROSIS		0	0	0	0	1	0	0	0	0	0
PREPUTIAL GLAND (PG)	NUMBER EXAMINED:	0	0	0	1	0	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
--B-ADENOMA		0	0	0	1	0	0	0	0	0	0

Incidence of microscopic findings in rats "unscheduled deaths"

INCIDENCE OF MICROSCOPIC OBSERVATIONS - UNSCHEDULED DEATHS

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

		NUMBER-OF-ANIMALS-AFFECTED--									
TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=1-106 DEATH=UNSCHED;FIND=ALL;SUBSET=ALL	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-3-	-4-	-5-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	21	22	18	28	41	15	16	26	31	43
MAMMARY, MALE (MM)	NUMBER EXAMINED:	1	2	1	2	0	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	1	0	0	0	0	0	0
--B-FIBROADENOMA		0	0	1	0	0	0	0	0	0	0
--LACTATION		1	1	0	1	0	0	0	0	0	0
--MAMMARY DYSPLASIA		1	2	0	0	0	0	0	0	0	0
CAVITY, THORACIC (TA)	NUMBER EXAMINED:	0	0	0	0	0	1	1	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
--INFLAMMATION, ACUTE, MEDIASTINAL TISSUES		0	0	0	0	0	1	1	0	0	0
MAMMARY, OTHER (MG)	NUMBER EXAMINED:	0	0	0	0	0	0	1	1	2	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
--B-FIBROADENOMA		0	0	0	0	0	0	1	1	1	0
--GALACTOCELE(S)		0	0	0	0	0	0	1	1	0	0
--LACTATION		0	0	0	0	0	0	0	0	1	0
--MAMMARY DYSPLASIA		0	0	0	0	0	0	0	1	1	0
CLITORAL GLAND (CL)	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
TAIL (TI)	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
CAVITY, CRANIAL (CC)	NUMBER EXAMINED:	1	0	0	0	0	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
--I-CARCINOMA, SQUAMOUS CELL, TRIGEMINAL NERVE, INVASIVE		1	0	0	0	0	0	0	0	0	0

*** END OF LIST ***

Incidence of microscopic findings in rats "terminal Sacrifice"

Incidence of Microscopic Observations - Terminal Sacrifice

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		-- NUMBER-OF-ANIMALS-AFFECTED --									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-3-	-4-	-5-	-6-
	NUMBER:	39	38	42	32	19	45	44	34	29	17
*** TOP OF LIST ***											
BRAIN W/STEM (BR)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	39	34	36	31	19	44	40	31	24	12
--M-ASTROCYTOMA		0	0	1	0	0	0	0	0	0	0
--I-PITUITARY CARCINOMA, INVASIVE		0	0	1	0	0	0	0	0	2	0
--VENTRAL DISTORTION (PITUITARY TUMOR)		0	4	4	1	0	1	4	2	5	5
--VENTRICULAR DILATATION (PITUITARY NEOPLASM)		0	1	1	0	0	0	2	0	3	2
--SUPPURATIVE MENINGITIS		0	0	0	0	0	0	0	1	0	0
CORD, CERVICAL (CS)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	39	38	42	32	19	45	44	33	29	17
--SUPPURATIVE MENINGITIS		0	0	0	0	0	0	0	1	0	0
CORD, LUMBAR (LC)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	39	38	42	32	19	45	44	34	29	17
CORD, THORACIC (TC)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	39	38	42	32	19	45	44	33	29	17
--SUPPURATIVE MENINGITIS		0	0	0	0	0	0	0	1	0	0
PITUITARY (PI)	NUMBER EXAMINED:	38	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	17	11	9	12	7	8	7	12	6	8
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	0	1	0	0	0	0
--B-ADENOMA, ANTERIOR LOBE		15	21	16	11	6	20	24	14	13	8
--B-ADENOMA, INTERMEDIATE LOBE		0	0	0	0	0	0	0	1	0	0
--M-CARCINOMA, ANTERIOR LOBE		0	0	1	0	0	0	0	0	2	0
--HYPERPLASIA, FOCAL		2	7	17	11	5	10	9	5	8	1
--CYST(S), ANTERIOR LOBE		4	1	2	2	0	9	12	4	6	0
--CYST(S), INTERMEDIATE LOBE		1	0	0	0	0	0	0	0	0	0
--ANGIECTASIS		1	1	2	2	1	0	1	3	0	0
--HEMATOCYST		0	0	0	0	1	3	2	0	2	0
--FIBROSIS, FOCAL, ANTERIOR LOBE		0	0	1	0	0	0	0	0	0	0
--ATROPHY		0	1	0	0	0	0	0	0	0	0
ADRENAL, CORTEX (AC)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	8	18	23	17	9	9	13	7	11	4
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		5	2	3	0	0	3	2	0	0	0
--B-ADENOMA		0	0	1	1	0	0	0	0	0	0
--M-CARCINOMA		0	0	0	0	0	0	1	0	0	0
--HYPERPLASIA, FOCAL		13	5	8	6	1	13	5	8	5	1
--HYPERTROPHY, FOCAL		2	1	0	0	0	2	1	2	1	1
--LIPOIDOSIS, FOCAL		17	13	14	10	7	21	28	21	13	7
--LIPOIDOSIS, DIFFUSE		2	2	0	0	0	0	0	1	0	0
--CONGESTION/ANGIECTASIS		2	0	0	0	3	8	1	2	6	9
--CYSTIC DEGENERATION		0	0	0	0	3	0	0	0	0	2
--NECROSIS, FOCAL		1	0	0	0	0	0	0	0	0	0
--THROMBUS		0	0	0	0	0	0	0	0	0	1
--FIBROSIS, GLOMERULOSA		0	0	0	1	0	0	0	0	0	0
--CYST(S)		0	1	0	0	0	0	0	0	0	0
--EXTRAMEDULLARY HEMATOPOIESIS		0	0	0	0	0	0	1	0	0	0
--ATROPHY, DEGENERATION, MINERALIZATION		0	0	0	0	0	0	1	0	0	0
ADRENAL, MEDULLA (AM)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	28	31	37	32	18	43	43	34	28	16
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		3	0	1	0	0	1	0	0	0	0
--B-PHEOCHROMOCYTOMA		4	1	1	0	0	0	0	0	0	0
--B-COMPLEX PHEOCHROMOCYTOMA		1	0	0	0	0	0	0	0	0	0
--M-MALIGNANT PHEOCHROMOCYTOMA		0	0	1	0	1	1	0	0	0	1
--HYPERPLASIA, FOCAL		3	6	4	0	0	0	0	0	1	0
--VENOUS THROMBUS		0	0	0	0	0	0	1	0	0	0
THYROID (TY)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	27	25	25	26	15	34	31	25	21	16
--B-FOLLICULAR CELL ADENOMA		0	1	1	0	0	0	0	0	0	0
--B-"C" CELL ADENOMA		0	4	5	0	1	3	3	3	2	1
--M-"C" CELL CARCINOMA		8	6	6	2	2	1	3	5	3	0
--HYPERPLASIA, FOLLICULAR CELL		1	0	0	0	0	1	0	0	0	0
--HYPERPLASIA, "C" CELL		3	2	4	2	1	6	6	1	3	0
--CYSTS(S), ULTIMOBRANCHIAL		0	0	0	0	0	0	2	0	0	0
--CYSTIC FOLLICLE(S)		0	0	3	2	0	0	0	0	0	0
PARATHYROID (PT)	NUMBER EXAMINED:	35	36	40	32	19	41	42	34	28	17
	NOT REMARKABLE:	35	36	40	32	19	41	42	34	28	17
ESOPHAGUS (ES)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	39	38	42	32	19	45	44	34	29	17
TRACHEA (TR)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	39	38	42	32	19	45	43	34	29	17
--EXUDATE/FOREIGN MATERIAL (INGESTA)		0	0	0	0	0	0	1	0	0	0

Incidence of microscopic findings in rats "terminal"

INCIDENCE OF MICROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		- NUMBER - OF - ANIMALS - AFFECTED -									
SEX:		----------MALE---------					---------FEMALE--------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-3-	-4-	-5-	-6-
	NUMBER:	39	38	42	32	19	45	44	34	29	17
LUNG (LU)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	0	3	0	1	0	2	11	2	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		5	2	1	0	0	4	2	0	0	1
--M-CARCINOMA, BRONCHIOLAR-ALVEOLAR		0	0	1	0	0	1	0	0	0	0
--BRONCHIOLAR ASSOCIATED LYMPHOID TISSUE		38	35	42	31	19	43	32	30	28	17
--FOREIGN BODY PNEUMONIA		5	1	6	17	14	0	1	8	14	13
--INFLAMMATION, CHRONIC, FOCAL		2	1	2	1	0	4	1	0	1	0
--ALVEOLAR HISTIOCYTOSIS		2	2	3	5	2	2	0	3	1	3
--THROMBUS		0	1	0	0	0	1	0	0	0	0
--SEPTIC THROMBUS		0	0	0	0	0	0	0	1	0	0
--HYPERPLASIA, ALVEOLAR CELL		1	1	0	0	0	0	0	0	0	0
--INFARCT		0	1	0	0	0	0	0	0	0	0
--ABSCESS		0	0	0	0	0	0	0	0	1	0
--FIBROSIS, FOCAL, PLEURA		0	0	0	0	0	0	1	1	0	0
HEART (HT)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	2	0	0	1	1	2	0	0	1	2
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	1	0	0	0	1	0	0	0	0
--M-SCHWANNOMA		0	1	1	0	0	0	0	0	0	0
--CARDIOMYOPATHY, DEGENERATIVE		35	38	42	28	13	40	43	34	21	11
--MINERALIZATION, GREAT VESSELS/CORONARY VESSELS		31	22	34	29	17	25	24	22	24	12
--THROMBUS, ATRIUM		2	0	0	0	0	0	0	0	0	0
--MINERALIZATION, MYOCARDIUM		0	0	2	0	0	0	0	0	0	1
--INFLAMMATION, CHRONIC, CORONARY GROOVE		0	1	0	0	0	1	1	2	0	1
--INFLAMMATION, CHRONIC, SUBEPICARDIAL		0	0	1	0	0	0	0	0	0	0
--INFLAMMATION, CHRONIC, MYOCARDIUM		0	1	0	0	0	0	1	2	0	0
--INFLAMMATION, CHRONIC, ENDOCARDIUM		0	1	0	0	0	0	0	0	0	0
--THROMBUS, VENTRICLE		0	0	1	0	0	0	0	0	0	0
--ARTERITIS		0	0	0	0	0	0	1	0	0	0
SPLEEN (SP)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	28	28	34	26	19	36	33	21	19	14
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		10	7	7	5	0	8	5	5	2	1
--X-MESOTHELIOMA		1	0	0	0	0	0	0	0	0	0
--INCREASED PIGMENT		0	0	1	1	0	0	2	6	5	2
--INCREASED EXTRAMEDULLARY HEMATOPOIESIS		0	1	0	0	0	0	4	1	2	0
--LYMPHOID DEPLETION		0	1	0	0	0	1	0	1	1	0
--FIBROSIS		1	1	0	0	0	0	0	0	0	0
--HYPERPLASIA, RETICULOENDOTHELIAL CELL		0	2	0	0	0	0	0	0	0	0
--INFARCT		0	1	0	0	0	0	0	0	0	0
LIVER (LI)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	0	0	0	0	0	0	0	1	1	2
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		10	7	6	4	0	8	5	5	2	1
--X-MESOTHELIOMA		1	0	0	0	0	0	0	0	0	0
--B-ADENOMA, HEPATOCELLULAR		2	2	5	0	1	1	0	0	1	0
--M-CARCINOMA, HEPATOCELLULAR		0	1	0	0	0	0	0	0	0	0
--CHRONIC BILIARY DISEASE (HYPERPLASIA, FIBROSIS, INFLAMMATION)		39	38	42	31	19	42	37	27	18	13
--INFLAMMATION, CHRONIC, FOCAL		5	8	5	2	2	32	35	24	13	10
--NECROSIS, FOCAL		0	1	0	0	0	2	0	3	0	0
--CELLULAR ALTERATION, BASOPHILIC		17	22	36	16	5	27	20	17	20	11
--CELLULAR ALTERATION, EOSINOPHILIC		4	2	2	0	0	1	1	2	0	1
--CELLULAR ALTERATION, CLEAR		1	5	7	2	0	3	1	0	2	0
--CELLULAR ALTERATION, MIXED		0	3	1	0	0	2	0	1	0	0
--LIPOIDOSIS, NONZONAL		0	0	0	2	0	2	0	0	0	0
--LIPOIDOSIS, PERIPORTAL		0	5	0	1	0	0	0	0	0	0
--LIPOIDOSIS, MIDZONAL		0	0	1	0	0	0	0	0	0	0
--EXTRAMEDULLARY HEMATOPOIESIS		0	0	0	0	0	0	1	0	2	0
--ANGIECTASIS, FOCAL		8	4	3	2	1	1	3	0	0	0
--CYSTIC DEGENERATION		5	5	7	0	0	0	0	0	0	0
--HEPATODIAPHRAGMATIC NODULE		2	1	0	0	2	0	2	1	1	0
--REGENERATIVE HYPERPLASIA		1	0	0	0	0	0	0	0	0	0
--MUCINOUS CYST		0	0	0	0	0	0	0	1	0	0
--FIBROUS NODULE, CAPSULE		0	0	0	0	0	0	1	0	0	0
KIDNEY (KD)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	1	0	0	0	0	1	0	0
--X-MESOTHELIOMA		1	0	1	0	0	0	0	0	0	0
--B-ADENOMA, TUBULAR CELL		0	1	0	0	0	0	0	0	0	0
--B-LIPOMA		1	0	0	0	0	0	1	0	0	0
--M-LIPOSARCOMA		0	0	1	0	0	0	0	0	0	0
--M-MESENCHYMAL TUMOR (OSTEOGENIC)		0	0	0	0	0	0	0	1	0	0
--CALCULI, PELVIS		30	33	7	1	2	44	44	26	21	15
--HYPERPLASIA, PELVIC EPITHELIUM		32	37	19	1	1	34	40	18	11	2
--MICROCALCULI, MEDULLA		38	36	38	32	19	45	44	33	29	17
--MICROCONCRETIONS/MINERALIZATION, CORTEX		39	38	42	32	19	45	44	34	29	17
--NEPHROPATHY, CHRONIC PROGRESSIVE		39	38	41	32	19	39	42	28	21	16
--PIGMENT, TUBULES		38	38	41	32	19	44	44	34	27	17
--PELVIS, DILATATION, UNILATERAL		2	0	1	0	0	0	0	1	0	1
--TUBULES, HYALINE DROPLET DEGENERATION		1	0	0	0	0	0	0	0	0	0
--INFARCT		1	0	0	0	0	0	0	0	0	0
--ATROPHY, CORTICAL		0	0	0	0	0	0	0	0	1	0
--CYST(S)		1	0	0	1	0	0	2	0	0	0

Incidence of microscopic findings in rats "terminal sacrifice"

INCIDENCE OF MICROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		-- NUMBER-OF-ANIMALS-AFFECTED --									
SEX:		----------MALE----------					---------FEMALE--------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-3-	-4-	-5-	-6-
NUMBER:		39	38	42	32	19	45	44	34	29	17
STOMACH, NONGL (SU)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	38	37	35	25	9	44	44	32	27	12
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	1	0	0	0	0
--B-PAPILLOMA		0	0	0	1	0	0	0	0	0	0
--M-SQUAMOUS CELL CARCINOMA		0	0	0	0	1	0	0	0	0	0
--MINERALIZATION, MUSCULARIS		0	1	6	5	8	0	0	2	0	5
--HYPERKERATOSIS		0	0	1	0	0	0	0	0	2	0
--ACANTHOSIS		1	0	1	0	0	0	0	0	2	0
--EDEMA, SUBMUCOSA		0	0	1	0	0	0	0	0	0	0
--INFLAMMATION, SUBACUTE		0	0	1	0	0	0	0	0	0	0
--INFLAMMATION, CHRONIC		0	0	0	0	1	0	0	0	0	0
--BALLOONING DEGENERATION, EPITHELIUM		0	0	0	1	0	0	0	0	0	0
STOMACH, GL (ST)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	38	36	42	32	16	44	42	32	28	16
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	0	0	1	0	0
--EROSION, MUCOSA		1	0	0	0	3	0	0	0	0	0
--ULCER		0	1	0	0	0	0	0	0	0	0
--DILATED GLANDS		0	0	0	0	0	1	2	1	0	1
--MINERALIZATION, MUCOSA		0	1	0	0	0	0	0	0	0	0
--INFLAMMATION, ACUTE, FOCAL, MUCOSA		0	1	0	0	0	0	0	0	0	0
--HYPERPLASIA, ATYPICAL		0	0	0	0	0	0	0	0	1	0
DUODENUM (DU)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	39	38	42	32	19	45	44	34	29	17
JEJUNUM (JE)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	39	38	42	32	19	45	44	33	29	17
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	0	0	1	0	0
ILEUM (IL)	NUMBER EXAMINED:	38	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	38	38	42	32	19	45	44	33	29	17
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	0	0	1	0	0
PANCREAS (PA)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	29	25	31	25	16	39	41	32	27	14
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	0	0	1	0	1	0	0
--X-MESOTHELIOMA		1	0	0	0	0	0	0	0	0	0
--B-ADENOMA, ISLET CELL		2	4	1	0	0	1	0	0	0	0
--M-CARCINOMA, ISLET CELL		1	1	1	2	0	0	0	0	0	0
--ACINAR ATROPHY		6	7	8	4	1	3	3	1	2	3
--HYPERPLASIA, ISLET CELL		0	0	0	0	1	1	0	0	0	0
--HYPERPLASIA, ACINAR CELL		0	0	1	0	0	0	0	0	0	0
--HYPERPLASIA, MIXED ISLET-ACINAR		0	0	0	1	1	0	0	0	0	0
--NECROSIS, ACINAR		0	0	0	0	0	0	0	1	0	0
--FIBROSIS		0	0	0	0	0	0	0	1	0	0
CECUM (CE)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	39	38	42	32	19	45	44	33	29	16
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	0	0	1	0	0
--PARASITISM		0	0	0	0	0	0	0	0	0	1
--ULCER		0	0	0	0	0	0	0	1	0	0
COLON (CO)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	34	36	36	30	18	45	43	33	29	17
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	0	0	0	0	1	0	0
--X-MESOTHELIOMA		0	0	1	0	0	0	0	0	0	0
--M-LEIOMYOSARCOMA		0	1	0	0	0	0	0	0	0	0
--PARASITISM		5	1	5	2	1	0	1	0	0	0
RECTUM (RE)	NUMBER EXAMINED:	39	38	42	32	19	45	44	33	29	17
	NOT REMARKABLE:	27	32	32	28	14	36	40	31	19	13
--X-MESOTHELIOMA		1	0	0	0	0	0	0	0	0	0
--PARASITISM		11	6	10	4	5	9	4	2	10	4
LN, MESENTERIC (MS)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	38	35	40	32	19	44	43	32	29	17
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	2	0	0	1	1	2	0	0
--LYMPHANGIECTASIS		1	2	0	0	0	0	0	0	0	0
MAND SALIVARY GL (SG)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	39	37	41	32	19	44	44	33	29	17
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	0	0	0	0	1	0	0
--M-SCHWANNOMA		0	0	1	0	0	1	0	0	0	0
PAROTID SAL GL. (SG0)	NUMBER EXAMINED:	38	38	42	32	19	43	43	34	29	17
	NOT REMARKABLE:	38	38	42	32	19	42	43	34	29	17
--I-SARCOMA, INVASIVE		0	0	0	0	0	1	0	0	0	0
LN, MANDIBULAR (MN)	NUMBER EXAMINED:	39	38	42	31	19	45	44	34	28	17
	NOT REMARKABLE:	38	33	39	31	19	44	44	33	28	17
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	1	2	0	0	1	0	1	0	0
--N-THYROID C-CELL CARCINOMA, METASTATIC		0	1	0	0	0	0	0	0	0	0
--HYPERPLASIA, LYMPHOID		0	0	1	0	0	0	0	0	0	0
--LYMPHECTASIA		0	3	0	0	0	0	0	0	0	0

Incidence of microscopic findings in rats "terminal sacrifice"

INCIDENCE OF MICROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		-- NUMBER-OF-ANIMALS-AFFECTED --									
SEX:		----------MALE---------					---------FEMALE--------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-3-	-4-	-5-	-6-
NUMBER:		39	38	42	32	19	45	44	34	29	17
THYMUS (TH)	NUMBER EXAMINED:	36	38	40	30	16	41	42	32	27	16
	NOT REMARKABLE:	20	4	11	8	7	20	10	2	7	6
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	1	0	0	1	0	1	0	0
--LYMPHOID DEPLETION		16	33	28	22	8	19	32	27	19	10
--HYPERPLASIA, EPITHELIAL		0	0	0	0	0	2	0	0	0	0
--CYST(S)		0	0	0	0	1	1	1	4	2	0
AORTA, THORACIC (AO)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	39	37	42	31	18	45	44	34	29	17
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	0	0	0	0	0	0	0
--MINERALIZATION		0	0	0	0	1	0	0	0	0	0
--OSSEOUS METAPLASIA		0	0	0	1	0	0	0	0	0	0
EYE (EY)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	0	0	1	0	0	0	0	1	0	0
--M-MELANOMA, IRIS		0	1	0	0	0	0	0	0	0	0
--CORNEAL DYSTROPHY		37	38	40	31	18	40	43	33	27	17
--CALCIFIC BODIES, LIMBUS		20	21	27	19	6	22	25	14	12	2
--ULCER, CORNEA		1	0	1	0	0	0	0	0	0	0
--CATARACT		4	5	6	3	5	4	6	4	4	2
--RETINAL DEGENERATION		4	5	7	4	6	4	6	5	5	1
--OSSEOUS METAPLASIA, SCLERA		24	24	23	18	7	16	22	12	12	4
--INFLAMMATION, CHRONIC, CORNEA		3	2	1	1	0	4	3	1	0	0
--INFLAMMATION, ACUTE, CORNEA		2	0	0	0	0	0	0	1	0	0
--INFLAMMATION, SUBACUTE, CORNEA		0	0	1	0	0	0	0	0	0	0
--VASCULARIZATION, CORNEA		10	8	3	1	2	4	9	4	4	1
--HYPERPLASIA, CORNEAL EPITHELIUM		2	1	1	0	1	4	5	2	1	0
--HYPERKERATOSIS, CORNEA		1	0	1	0	1	1	2	1	0	0
--INFLAMMATION, ACUTE, ANTERIOR CHAMBER		1	0	0	0	1	0	0	0	0	0
--PANOPHTHALMITIS, ACUTE		0	0	0	1	0	0	0	1	1	0
--HEMORRHAGE, ANTERIOR CHAMBER		0	0	0	0	0	1	0	0	0	0
--INFLAMMATION, GRANULOMATOUS, CHOROID		0	0	0	0	1	0	0	0	0	0
--RUPTURED GLOBE		0	0	0	0	0	0	0	0	0	1
--PARAKERATOSIS, CORNEA		0	1	0	0	0	0	0	0	0	0
--ABSCESS		0	0	0	0	0	0	0	0	1	0
--INFLAMMATION, GRANULOMATOUS		0	0	0	0	0	0	0	1	0	0
HARDERIAN GLAND (HG)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	38	36	42	32	18	43	44	34	29	17
--CYST(S)		0	0	0	0	1	0	0	0	0	0
--HYPERPLASIA		1	0	0	0	0	1	0	0	0	0
--FIBROSIS		0	1	0	0	0	1	0	0	0	0
--SQUAMOUS METAPLASIA		0	1	0	0	0	0	0	0	0	0
MUSCLE, SKELETAL (SM)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	37	37	40	32	19	45	44	34	29	16
--DEGENERATION		2	0	2	0	0	0	0	0	0	1
--INFLAMMATION, CHRONIC, FOCAL		0	1	0	0	0	0	0	0	0	0
NERVE, SCIATIC (SN)	NUMBER EXAMINED:	39	37	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	21	9	19	13	13	24	29	14	13	11
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	1	0	0	0	0
--AXONAL DEGENERATION		18	28	23	19	6	20	15	19	16	6
--SUPPURATIVE NEURITIS		0	0	0	0	0	0	0	1	0	0
TONGUE (TO)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	4	0	1	7	0	3	2	2	0	3
--DEGENERATION/MINERALIZATION, ARTERIOLE		35	38	41	25	19	42	42	31	29	14
--INFLAMMATION, SUBACUTE/CHRONIC		1	2	1	0	0	3	0	0	0	0
--SQUAMOUS REST		0	0	0	0	0	1	0	0	0	0
--DEGENERATION, MUSCLE, FOCAL		0	1	0	0	0	0	0	0	0	0
--PERIARTERITIS		0	0	0	0	0	0	0	1	0	0
TESTIS (TE)	NUMBER EXAMINED:	39	38	42	32	19	0	0	0	0	0
	NOT REMARKABLE:	0	1	1	0	0	0	0	0	0	0
--X-MESOTHELIOMA		2	0	1	0	0	0	0	0	0	0
--B-BENIGN INTERSTITIAL CELL TUMOR		37	34	40	31	18	0	0	0	0	0
--HYPERPLASIA, INTERSTITIAL CELL		0	3	0	0	1	0	0	0	0	0
--DEGENERATION, SEMINIFEROUS TUBULES		38	35	39	29	16	0	0	0	0	0
--PERIARTERITIS		1	0	0	0	0	0	0	0	0	0
--INFARCT		0	1	0	0	0	0	0	0	0	0
EPIDIDYMIS (EP)	NUMBER EXAMINED:	39	38	42	32	19	0	0	0	0	0
	NOT REMARKABLE:	7	5	3	8	6	0	0	0	0	0
--X-MESOTHELIOMA		2	0	1	0	0	0	0	0	0	0
--HYPOSPERMIA		31	33	38	24	13	0	0	0	0	0
--INFLAMMATION, CHRONIC		0	1	0	0	0	0	0	0	0	0
PROSTATE (PR)	NUMBER EXAMINED:	39	38	42	32	19	0	0	0	0	0
	NOT REMARKABLE:	8	7	10	8	7	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	0	0	0	0	0	0
--X-MESOTHELIOMA		1	0	0	0	0	0	0	0	0	0
--ABSCESS		2	2	2	0	0	0	0	0	0	0
--INFLAMMATION, SUBACUTE/CHRONIC		27	26	27	22	12	0	0	0	0	0

*** CONTINUED ON NEXT PAGE ***

Incidence of microscopic findings in rats "terminal sacrifice"

INCIDENCE OF MICROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		-- NUMBER-OF-ANIMALS-AFFECTED --									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-3-	-4-	-5-	-6-
	NUMBER:	39	38	42	32	19	45	44	34	29	17
*** FROM PREVIOUS PAGE ***											
PROSTATE (PR)	NUMBER EXAMINED:	39	38	42	32	19	0	0	0	0	0
	NOT REMARKABLE:	8	7	10	8	7	0	0	0	0	0
--HYPERPLASIA		4	0	2	1	2	0	0	0	0	0
--MUCOID CYST(S)		0	2	1	1	0	0	0	0	0	0
--FIBROSIS		2	7	9	3	5	0	0	0	0	0
--KERATIN CYST		0	0	0	1	0	0	0	0	0	0
SEMINAL VESICLE (SV)	NUMBER EXAMINED:	39	38	42	32	19	0	0	0	0	0
	NOT REMARKABLE:	39	38	41	31	18	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	0	0	0	0	0	0
--FAT NECROSIS		0	0	0	0	1	0	0	0	0	0
--INFLAMMATION, ACUTE		0	0	0	1	0	0	0	0	0	0
OVARY (OV)	NUMBER EXAMINED:	0	0	0	0	0	45	44	34	29	17
	NOT REMARKABLE:	0	0	0	0	0	41	38	32	26	17
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	1	0	0	0	0
--B-GRANULOSA/THECA CELL TUMOR		0	0	0	0	0	0	1	1	1	0
--CYST(S), BURSA		0	0	0	0	0	3	2	1	0	0
--CYST(S)		0	0	0	0	0	0	3	0	1	0
--CYST(S), PAROVARIAN		0	0	0	0	0	0	0	0	1	0
UTERUS (UT)	NUMBER EXAMINED:	0	0	0	0	0	45	44	34	29	17
	NOT REMARKABLE:	0	0	0	0	0	23	28	19	18	13
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	1	0	1	0	0
--B-ENDOMETRIAL STROMAL POLYP		0	0	0	0	0	7	5	7	2	2
--M-CARCINOMA		0	0	0	0	0	1	2	0	0	0
--ENDOMETRIAL FIBROSIS		0	0	0	0	0	5	1	2	5	0
--ENDOMETRIAL CYSTIC HYPERPLASIA		0	0	0	0	0	5	4	2	3	2
--DILATATION		0	0	0	0	0	4	7	8	1	1
--ENDOMETRIAL HYPERPLASIA		0	0	0	0	0	0	0	1	0	0
--ENDOMETRIAL CYST		0	0	0	0	0	1	1	1	0	0
UTERUS, CERVIX (CV)	NUMBER EXAMINED:	0	0	0	0	0	45	44	34	29	17
	NOT REMARKABLE:	0	0	0	0	0	44	42	33	29	17
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	1	0	0	0	0
--B-GRANULAR CELL TUMOR		0	0	0	0	0	0	0	1	0	0
--M-SCHWANNOMA		0	0	0	0	0	0	1	0	0	0
--KERATIN CYST		0	0	0	0	0	0	1	0	0	0
VAGINA (VA)	NUMBER EXAMINED:	0	0	0	0	0	45	44	34	29	16
	NOT REMARKABLE:	0	0	0	0	0	45	44	34	28	16
--KERATIN CYST		0	0	0	0	0	0	0	0	1	0
URINARY BLADDER (UB)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	37	36	40	32	19	44	44	34	29	17
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	0	0	1	0	0	0	0
--X-MESOTHELIOMA		1	0	1	0	0	0	0	0	0	0
--B-TRANSITIONAL CELL PAPILLOMA		0	0	1	0	0	0	0	0	0	0
--HYPERPLASIA, EPITHELIAL		1	0	0	0	0	0	0	0	0	0
--INFLAMMATION, CHRONIC		0	1	1	0	0	0	0	0	0	0
SKIN (SK)	NUMBER EXAMINED:	39	37	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	39	37	40	32	19	45	43	33	29	17
--EPIDERMAL CYST		0	0	0	0	0	0	1	0	0	0
--HYPERKERATOSIS		0	0	1	0	0	0	0	0	0	0
--INFLAMMATION, CHRONIC, SUBCUTANEOUS		0	0	1	0	0	0	0	0	0	0
--INFLAMMATION, CHRONIC, DERMIS		0	0	0	0	0	0	0	1	0	0
MAMMARY,CRANIAL (MF0)	NUMBER EXAMINED:	0	0	0	0	0	39	32	23	24	16
	NOT REMARKABLE:	0	0	0	0	0	5	0	3	11	6
--LACTATION		0	0	0	0	0	30	28	16	12	10
--MAMMARY DYSPLASIA		0	0	0	0	0	22	24	10	6	7
--GALACTOCELE(S)		0	0	0	0	0	1	0	0	0	0
--HYPERPLASIA		0	0	0	0	0	3	4	5	0	0
MAMMARY,CAUDAL (MF1)	NUMBER EXAMINED:	0	0	0	0	0	37	37	33	27	14
	NOT REMARKABLE:	0	0	0	0	0	6	3	5	8	8
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	0	1	0	0	0	0
--LACTATION		0	0	0	0	0	22	27	21	15	6
--MAMMARY DYSPLASIA		0	0	0	0	0	11	21	10	7	5
--GALACTOCELE(S)		0	0	0	0	0	0	0	1	1	0
--HYPERPLASIA		0	0	0	0	0	4	7	7	3	0
MARROW, STERNUM (SE)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	39	38	42	31	19	45	44	34	29	17
--HYPERPLASIA		0	0	0	1	0	0	0	0	0	0
BONE, STERNUM (SB)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	39	36	41	32	19	42	44	32	29	17
--OSTEOPETROSIS		0	2	1	0	0	3	0	2	0	0

Incidence of microscopic findings in rats "terminal sacrifice"

INCIDENCE OF MICROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		-- NUMBER-OF-ANIMALS-AFFECTED --									
SEX:		----------MALE----------					---------FEMALE---------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-3-	-4-	-5-	-6-
NUMBER:		39	38	42	32	19	45	44	34	29	17
MARROW, FEMUR (FM)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	36	36	41	31	19	45	43	33	29	15
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	0	1	0	0	0	0	1	0	0
--HYPERPLASIA		1	2	0	0	0	0	0	0	0	0
--FIBROSIS		0	0	0	0	0	0	0	0	0	1
--HYPERPLASIA, GRANULOCYTIC		0	0	0	1	0	0	0	0	0	0
--HYPERPLASIA, RETICULOENDOTHELIAL CELL		0	0	0	0	0	0	1	0	0	1
BONE, FEMUR (FE)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	38	36	39	32	19	38	42	32	28	17
--OSTEOPETROSIS		1	1	3	0	0	7	2	2	1	0
--FIBROUS OSTEODYSTROPHY, RENAL		0	1	0	0	0	0	0	0	0	0
VER,LUMBAR,1ST (OB0)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	39	38	41	32	19	45	44	34	29	17
--OSTEOPETROSIS		0	0	1	0	0	0	0	0	0	0
VER,LUMBAR,2ND (OB1)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	39	38	42	32	19	45	44	34	29	17
HEMATO NEOPLASIA (HN)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	29	31	35	27	19	37	39	28	27	16
--M-LEUKEMIA, LARGE GRANULAR LYMPHOCYTIC		10	7	7	5	0	8	5	4	2	1
--M-SARCOMA, HISTIOCYTIC		0	0	0	0	0	0	0	1	0	0
--M-LYMPHOMA		0	0	0	0	0	0	0	1	0	0
^DEATH COMMENT (DC)	NUMBER EXAMINED:	39	38	42	32	19	45	44	34	29	17
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
--SCHEDULED SACRIFICE		39	38	42	32	19	45	44	34	29	17
LARYNX (LA)	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
CAVITY, ABDOM (PC)	NUMBER EXAMINED:	2	1	2	1	0	0	1	1	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	1	0	0
--M-MESOTHELIOMA		2	0	1	0	0	0	0	0	0	0
--FAT NECROSIS, FOCAL		0	1	1	1	0	0	1	0	0	0
SKIN, OTHER (SS)	NUMBER EXAMINED:	11	8	10	3	2	1	1	3	0	1
	NOT REMARKABLE:	1	0	0	0	0	0	0	1	0	1
--B-SQUAMOUS CELL PAPILLOMA		1	1	0	0	0	0	0	0	0	0
--B-KERATOACANTHOMA		3	4	3	1	1	0	0	0	0	0
--B-ADENOMA, ZYMBAL'S GLAND		1	0	0	0	0	0	0	0	0	0
--B-PAPILLOMA		0	0	2	0	0	0	0	0	0	0
--B-BASAL CELL ADENOMA		0	0	0	0	0	0	0	1	0	0
--M-BASAL CELL CARCINOMA		1	0	0	0	0	0	0	0	0	0
--NECROSIS, TAIL		0	0	0	0	1	0	0	0	0	0
--ABSCESS, FOOT		1	3	2	0	0	0	0	0	0	0
--EPIDERMAL CYST		3	1	1	0	0	0	0	0	0	0
--ABSCESS, TAIL		1	1	2	0	0	0	0	0	0	0
--ULCER, FOOT		1	0	0	1	0	0	0	0	0	0
--HYPERKERATOSIS, FOCAL, TAIL		1	0	1	0	0	0	0	0	0	0
--HYPERKERATOSIS, TAIL		0	0	0	0	0	0	0	1	0	0
--INFLAMMATION, ACUTE, FOCAL		1	0	0	0	0	0	0	0	0	0
--HYPERKERATOSIS, FOOT		0	1	0	0	0	1	0	0	0	0
--MINERALIZATION, FOCAL, DERMIS		0	0	0	1	0	0	0	0	0	0
--INFLAMMATION, CHRONIC, TAIL		0	0	1	0	0	0	0	0	0	0
--INFLAMMATION, CHRONIC, FOOT		0	1	0	0	0	0	0	0	0	0
--ACANTHOSIS, FOOT		0	1	0	0	0	0	0	0	0	0
--HYPERKERATOSIS, FOCAL		0	1	0	0	0	0	0	0	0	0
--INFLAMMATION, CHRONIC		0	0	0	0	0	0	1	0	0	0
--ESCHAR		0	0	0	0	0	0	1	0	0	0
HEAD, CORONAL (HC)	NUMBER EXAMINED:	0	0	2	1	0	0	0	0	0	1
	NOT REMARKABLE:	0	0	1	0	0	0	0	0	0	1
--B-TRICHOEPITHELIOMA		0	0	1	0	0	0	0	0	0	0
--GRANULOMA, SUBCUTANEOUS		0	0	0	1	0	0	0	0	0	0
LN, OTHER (LN)	NUMBER EXAMINED:	4	4	6	3	1	10	6	2	1	1
	NOT REMARKABLE:	4	3	3	3	1	9	6	2	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	1	0	0	1	0	0	0	0
--HYPERPLASIA, LYMPHOID		0	0	2	0	0	0	0	0	0	0
--MICROGRANULOMAS		0	0	1	0	0	0	0	0	1	0
SUBCUTANEOUS TIS (SQ)	NUMBER EXAMINED:	2	1	0	0	0	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
--B-FIBROMA		2	0	0	0	0	0	0	0	0	0
--FAT NECROSIS		0	1	0	0	0	0	0	0	0	0
PENIS (PE)	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0

Incidence of microscopic findings in rats "terminal sacrifice"

INCIDENCE OF MICROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

104-WEEK CARCINOGENICITY GAVAGE STUDY OF YM087 IN RATS

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-106
DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		-- NUMBER-OF-ANIMALS-AFFECTED --									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-3-	-4-	-5-	-6-
	NUMBER:	39	38	42	32	19	45	44	34	29	17
PREPUTIAL GLAND (PG)	NUMBER EXAMINED:	2	0	0	0	0	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
--B-ADENOMA		1	0	0	0	0	0	0	0	0	0
--DILATATION		1	0	0	0	0	0	0	0	0	0
MAMMARY, MALE (MM)	NUMBER EXAMINED:	1	2	1	1	0	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
--B-FIBROADENOMA		0	1	0	0	0	0	0	0	0	0
--LACTATION		1	0	0	0	0	0	0	0	0	0
--MAMMARY DYSPLASIA		1	1	0	0	0	0	0	0	0	0
--CYST(S)		0	0	0	1	0	0	0	0	0	0
--GALACTOCELE(S)		0	1	1	0	0	0	0	0	0	0
--VENOUS ECTASIA		0	1	0	0	0	0	0	0	0	0
CAVITY, THORACIC (TA)	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
MAMMARY, OTHER (MG)	NUMBER EXAMINED:	0	0	0	0	0	8	5	0	0	1
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA		0	0	0	0	0	1	0	0	0	0
--B-FIBROADENOMA		0	0	0	0	0	5	3	0	0	0
--LACTATION		0	0	0	0	0	2	2	0	0	1
--MAMMARY DYSPLASIA		0	0	0	0	0	2	2	0	0	1
--HYPERPLASIA		0	0	0	0	0	0	1	0	0	0
CLITORAL GLAND (CL)	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0	3
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	1
--B-ADENOMA		0	0	0	0	0	0	0	0	0	1
--HYPERPLASIA		0	0	0	0	0	0	0	0	0	1
TAIL (TI)	NUMBER EXAMINED:	0	0	0	0	0	0	0	1	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	1	0	0
CAVITY, CRANIAL (CC)	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0	0	0

*** END OF LIST ***

Toxicokinetics:

- t_{max} ranged between 2 to 4 hrs except for high dose females (30 mkd) where t_{max} was 8 hrs
- Cmax and AUC increased in a dose-dependent manner. AUC exposure was higher in females than males at 1, 3 and 10 mg/kg/d by 87, 26 and 6%, respectively.

Table 2.6.6-87: Carcinogenicity study in rats – toxicokinetics [R087-TX-047]

Daily Dose (mg/kg)	0.3	1		3		10		30
Gender	M	M	F	M	F	M	F	F
Toxicokinetics: Week 53								
C_{max} (ng/mL)	2.43	17.1	28.7	125	183	557	752	2080
AUC_{0-24} (ng·hr/mL)	22.3	103	193	956	1202	7017	7424	25546

Drug exposure relative to clinical dose

Carci Doses	Dose, mg/kg/d	AUC_{0-24} ng.h/ml	Animal to human dose exposure ratio
104-WK rat carci study	M: 0.3	M: 22.3	M: 0.006
	M: 1 F: 1	M: 103 F: 193	M: 0.03 F: 0.05
	M: 3 F: 3	M: 956 F: 1202	M: 0.3 F: 0.4
	M: 10 F: 10	M: 7017 F: 7424	M: 1.96 F: 2
	F: 30	F: 25546	F: 7
Clinical Dose: 20 mg bolus + 40 mg IV infusion for 4 days, average daily AUC		3580	

2.6.6.6 Reproductive and developmental toxicology

The reprotoxicity studies include both oral and IV bolus administration. The sponsor had performed nearly 36 reprotoxicity studies. The preliminary and dose ranging studies were reviewed but only a brief summary of the studies are reported in the review (see appendix B). The studies previously reviewed are listed below. Since the sponsor had changed the study title and the study number, both old and new study numbers are shown in table below for clarity:

Study title	Old Study #	New Study #
Fertility study (segment I) of YM087 administered orally to male rats (Effect on fertility in male rats with oral treatment, 1, 10 and 100 mg/kg/d)	RR-745-02725	R087-TX-009
Effect of YM087 on the estrous cycle and fertility in rats (Effects on fertility and estrous cycle in female rats with oral treatment, exploratory study)	RR-745-02785	R087-TX-116
Female fertility study (segment I study) of YM087 in rats by oral administration (Effects of fertility and early embryonic development in female rats with oral treatment, 1, 3, 10 and 100 mg/kg/d)	RR-745-02735	R087-TX-010
Additional female fertility study (segment I study) of YM087 in rats by oral administration, reassessment of NOAEL (Effects on fertility and early embryonic development in female rats with oral treatment, additional study, 1, 3, 10 and 100 mg/kg/d)	RR-745-02749	R087-TX-041
Teratology study of YM087 by oral administration to rats: effect on fetuses (Embryo-fetal development in rats with oral treatment, effect on fetuses, 1, 10 and 100 mg/kg/d)	RR-745-02751	R087-TX-012
Teratology study of YM087 by oral administration to rats: assessment of the effects on offspring (Embryo-fetal development in rats with oral treatment, assessment of the effects on offspring, 1, 10 and 100 mg/kg/d)	RR-745-02745	R087-TX-013
Teratology study of YM087 in rabbits by oral administration (Embryo-fetal development in rabbits with oral treatment, 0.2, 1 and 6 mg/kg/d)	RR-745-02723	R087-TX-014
Preliminary study on oral administration of YM087 during the lactation period (Effects on maternal function during lactation period in rats with oral treatment, preliminary study)	RR-745-02746	R087-TX-017
Single oral dose toxicity study of YM087 during estrous cycle and pregnancy, and after parturition in rats	RR-745-02748	R087-TX-016

Reproductive Toxicity Summary:

Series of IV and oral gavage reproductive studies have been performed in rats (fertility, early embryo thru postnatal development) and rabbit (early development). The oral studies have been reviewed in detail in INDC [redacted]
The effect of conivaptan on male fertility was examined after 4 WKs of treatment with IV bolus conivaptan at 0.5, 1.25 and 2.5 mg/kg/d. The treated males were mated with untreated female rats. Fertility parameters were unaffected by the largest dose used in this study in males. There were no adverse effects on pre- or post-implantation, on the numbers of implantations or on the numbers of live embryos. Conivaptan, however, did decrease food consumption and body weight gain in male rats. After intravenous administration, the NOEL for general toxicity in males was considered to be 0.5 mg/kg. The NOAEL for male fertility was considered to be greater than 2.5 mg/kg.

In the fertility and early embryonic development study in female rats, similar doses of conivaptan (0.5, 1.25 and 2.5 mg/kg/d) were administered IV beginning 15 days before cohabitation through gestation day (GD) 7. Females were sacrificed on GD13. There was no change in BW and only a transient decrease in food intake was noted at 1.25 and 2.5 mg/kg/d. The 2.5 mg/kg/d dose reduced the number of estrous cycles and increased the number of rats with 6 or more days of diestrus. None of the litter parameters were affected by 1.25 mg/kg/d dose. The 2.5 mg/kg/d dose significantly reduced the number of corpora luteas and viable embryos and increased the number of dams with nonviable embryos, the number of nonviable embryos per liter and postimplantation loss. The percent nonviable embryos per litter were increased in HD females. All placentas appeared to be normal. Exposure comparison could not be made since TK analysis was not performed. However distribution studies in pregnant animals (IV) suggest mammary and placental exposures 2-3 X > than plasma fetal/amniotic concentration were <10% maternal plasma but accumulation occurred in the fetus because of slower clearance.

Embryofetal Development Studies Using IV Formulation
Conivaptan was injected via tail vein to rats (n=25/dose) at 0.5, 1.25 and 2.5 mg/kg/d (0.1, 0.5 and 1x clinical dose based on AUC_{0-24} of 3580 ng.h/ml), from GD 7 to GD17 (c-section on GD 21). No changes in maternal BW or any notable clinical signs. One female at 2.5 mg/kg/d delivered before C-section on GD21. There were no gross external, visceral or skeletal alterations in fetuses at any dose level. Live fetal weight was reduced at 1.25 mg/kg/d. None of the litter parameters were affected by any of the doses. The NOAEL was 2.5 mg/kg/d for fetal development (AUC_{0-24} =3803 ng.h/ml).

In embryofetal development study in rabbits (n=20/dose), conivaptan IV doses of 3, 6 and 12 mg/kg/d (1, 1.6 and 7.6 x clinical dose based on AUC_{0-24}) were administered from GD 6 to 18. Consistent with previous IV doses of conivaptan, injection site findings such as abrasions and purple, swollen ear at the injection sites were dose-related and observed at 6 and 12 mg/kg/day. There were no treatment related deaths. No effect on BW gain at 6 mg/kg/d, however, the 12 mg/kg/d dose reduced maternal BW gain during GD 6 to 18 by 66.7% relative to control. The food intake at 12 mg/kg/d was reduced transiently on GD 6 to 8. Pregnancy occurred in 18 to 20 rabbits per group (C:19, LD:18, MD:20 and HD:18). There were no changes related to C-section or litter parameters. There were no dead fetus and all placentas appeared normal. No

dose-related or significant change in litter or fetal incidence of gross external, soft tissue or skeletal abnormalities. A few non-dose-related malformations that were observed occurred in control as well as treated animals. The maternal reproductive NOAEL and developmental NOAEL were >12 mg/kg/d. The maternal NOAEL was 3 mg/kg/d (AUC_{0-24} = 3458 ng.h/ml) due to incidence of injection site findings at 6 mg/kg/d (AUC_{0-24} =5645 ng.h/ml).

Prenatal and Postnatal Development Using IV Formulation

In the dose ranging study, rats (n=10/dose) were treated with 0.1, 0.5, 1.25 ad 2.5 mg/kg/d conivaptan from GD 7 to GD24 or lactation Day (DL) 6. Conivaptan had no notable effect on pregnant rats at doses up to 2.5 mg/kg/d except for small decrease in BW gain during the gestation period with accompanying decrease in food consumption at 2.5 mg/kg/d. Conivaptan had no effect on any pre- and postnatal development at any dose or any effect on BW at 0.5 or 1.25 mg/kg/d. The maternal and littler toxicity NOEL was 0.5 mg/kg/d. Based on this study, the sponsor chose 0.5, 1.25 and 2.5 mg/kg/d for the definitive intravenous formulation of Conivaptan. Previous embryofetal development studies using doses up to 2.5 mg/kg/d have not produced significant toxicity in pregnant rats.
Based on dose-ranging study, the same doses (0.5, 1.25 and 2.5 mg/kg/d, 0.06, 0.15 and 0.44x clinical dose based on AUC_{0-24} of 3580 ng.h/ml) were administered to pregnant rats (n=25/goup) from GD 7 to DL20. No treatment related death in dams. Food intake was decreased in early gestation and lactation phase in 1.25 and 2.5 mg/kg. BW and BW gain was not significantly altered by the highest dose (2.5m/) in the study. There were no treatment related changes in clinical signs, gross pathology, maintenance of pregnancy, parturition or lactation. Viability, weaning indices and pup weight per litter were reduced at 2.5 mg/kg. Pups had increased mortality, decreased viability, decreased weaning indices, decreased body weight and delayed reflex development at 2.5 mg/kg/d.
There was however, a delayed development of several reflexes in pups at 2.5 mg/kg (surface righting, acoustic startle, turning on an inclined plane and air righting) which may have correlated with lower BW of F1 pups. Body weights in F1 pups of dams treated with 2.5 mg/kg/d were lower than controls but recovered during post weaning period. No clinical or necropsy changes of F1 rats. Sexual maturity was delayed at 2.5 mg/kg but this delay was also likely due to lower BW of F1 rats. No abnormalities were observed in mating or fertility of F1 rats or findings in Caesarian section. The 0.5 mg/kg/d dose was considered NOAEL for maternal function (0.06 x clinical dose based on AUC). For F1 and F2 generation, the NOAEL was 1.25 mg/kg (0.16 x clinical dose, based on AUC). Drug exposure increased in a dose-proportional manner but tend to be lower with repeated drug administration as AUC values were lower on LD 20 relative to GD7.

Fertility and early embryonic development

Study title: Effect on Fertility in Male Rats with Bolus Intravenous Treatment with PG/EtOH formulation (Study of fertility in Male rats by intravenous injection of YM087)

Key study findings: Male rat appear to tolerate 2.5 mg/kg/d dose IV well. There were no reproductive abnormalities in non-treated female mated with males treated with conivaptan PG/EtOH for 4 weeks.

Study no.: R087-TX-088 (20030331)
Volume #, and page #: not applicable (electronic document)
Conducting laboratory and location: [redacted]

Date of study initiation: March 15, 2000
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: 08701 and [redacted] purity

Methods

Conivaptan hydrochloride dissolved in the PG/EtOH (clinical formulation) was administered for 4 WKs to 10 to 11-WK old males SD (IGS)rats (22/dose). Conivaptan was administered via tail vein. Males were mated with non-treated females (21/group). The vehicle was [redacted]propylene glycol/ [redacted]ethanol in sterile water for injection. The dose solution was diluted with 5% dextrose. Food and water was available ad lib. Drug solutions were prepared weekly.

Doses: 0.5, 1.25 and 2.5 mg/kg/d a
Species/strain: [redacted]CD ®SD (IGS) BR VAF/Plus male rats, [redacted]
Number/sex/group: 22/group
Route, formulation, volume, and infusion rate: 10 ml/kg at a rate of 1 ml/min, Lot #08701
Satellite groups used for toxicokinetics: no TK
Study design:
Parameters and endpoints evaluated: Male rats were sacrificed and thoracic, abdominal and pelvic viscera was evaluated. The injection site lesions were also examined. The reproductive organs such as epididymides, prostate, testes and seminal vesicle were evaluated histologically. In females, C-section was performed on gestation day 13 for evaluations of implantation sites, live and dead embryos were observed during uterine examination. Ovaries were evaluated for the number of corpora lutea present on each. A necropsy was then performed on the male rats.

Results

Mortality: no mortality
Clinical signs: Rats treated with 1.25 and 2.5 mg/kg, had swollen tails. Since the total number of swollen tails (10, 12, 15 and 19 rats at 0, 0.5, 1.25 and 2.5 mg/kg/d, respectively) increased with dose, suggests additional irritation by Conivaptan PG/EtOH. There were no other clinical signs related to the treatment.
Body weight: There was no change in BW, however, a decreased in BW gain (-15%) was observed at 2.5 mg/kg/day on day 1 through 4. This was likely due to drug-related water loss.
Food consumption: Food consumption was lower in the 2.5 mg/kg/d dosed group on Day 1-8

Necropsy: No treatment-related necropsy findings were observed even at the highest dose of 2.5 mg/kg except for moderate renal pelvis dilation in one HD male rat.

The summary table IV conivaptan in males is presented in table below:

Design similar to ICH 4.1.1.: Yes
Species/Strain: SD (IGS) Rats
Initial Age: 10-11 Weeks
Date of First Dose: 28 Mar, 2000
Special Features: None
No Observed Adverse Effect Level:
F_0 Males: 0.5 mg/kg
F_1 Litters: 2.5 mg/kg

Duration of Dosing: M: 4 weeks prior to mating until sacrifice (59 days)
Day of Mating: Day 0
Day of C-Section: GD13
Method of Administration: Intravenous, bolus at 10 mL/kg
Vehicle/Formulation: Vehicle: 30% propylene glycol, 10% ethanol, and lactic acid sufficient to adjust pH to 3.3 ± 0.2. Diluent: 5% dextrose solution

Study No. R087-TX-088
GLP Compliance: Yes

Daily Dose (mg/kg)		0 (control)	0.5	1.25	2.5
Males	No. Evaluated	22	22	22	22
	No. Died or Sacrificed Moribund	0	0	0	0
	Clinical Observations				
	Swollen tail	10	12	15+	19++
	Necropsy Observations	-	-	-	-
	Body weight: Day 28[a]	444.4	447.4	444.1	431.6
	Body weight gain: Day 1-4	9.4	13.3	10.5	2.8*
	Day 1-60	152.2	156.0	153.7	130.1
	Food Consumption: Day 1-8	26.9	27.0	26.6	24.0**
	Food Consumption: Day 1-57	27.2	27.1	27.3	26.0
	Mean No. Days Prior to Mating	2.8	4.0	3.4	3.4
	No. of Males that Mated (%)	22 (100)	22 (100)	22 (100)	22 (100)
	No. of Fertile Males (%)	20 (90.9)	21 (95.4)	19 (86.4)	21 (95.4)
Female (untreated)	No. of Pregnant Females	20	21	19	21
	No. Died or Sacrificed Moribund	0	0	0	0
	Clinical Observations	-	-	-	-
	Localized alopecia (limbs)	0	0	3	1
	Necropsy Observations	-	-	-	-
	Dilation of renal pelvis (right)	1	0	0	1
	Gestation Body Weight: GD 13	329.4	327.0	330.8	326.7
	Gestation Body Weight gain: GD0-7	39.0	33.0	36.8	30.5**
	GD0-13	70.8	64.0	70.3	64.1
	Gestation Food Consumption: GD0-13	26.3	25.0	26.0	25.8
	No. Aborted or with Total Resorption of Litter	0	0	0	0
	Mean No. Corpora Lutea	19.2	18.8	19.0	18.7
	Mean No. Implantations	16.8	16.7	17.0	16.2
	% Preimplantation Loss[a]	12.5	11.4	10.5	13.0
	Mean No. Live Conceptuses	15.9	16.1	16.4	15.4
	Mean No. Resorption	1.0	0.6	0.6	0.8
	No. Dead Conceptuses	19	12	12	17
	% Postimplantaion Loss[d]	5.6	3.4	3.7	5.0

- No noteworthy findings. GD = Gestation day.
Dunnett's Test: * - P<0.05 ** - p<0.01
a - Totaled value per group.

Fertility parameters (mating/fertility index, corpora lutea, preimplantation loss, etc.):
All mating and fertility parameters such as numbers of days in cohabitation, the copulation and fertility indices, rats with confirmed mating dates during the first, second and third week of cohabitation, and the number of pregnancies per number of rats in cohabitation were unaffected by the treatment even at the highest dose of 2.5 mg/kg. There were no adverse effects on pre- or post-implantation, on the numbers of implantations or on the numbers of live embryos. After intravenous administration, the NOEL for general toxicity in males was considered to be 0.5 mg/kg. The NOAEL for reproductive function in males and for embryos was considered to be greater than 2.5 mg/kg.

Study title: Effects on Fertility and Early Embryonic Development to Implantation in Female Rats with Bolus Intravenous Treatment with PG/EtOH Formulation (Study of Fertility and Early Embryonic Development to Implantation in Female Rats by Intravenous Injection of YM087)

Key study findings: No deaths at any dose. At 2.5 mg/kg/day, a significant decrease in the number of estrous cycles, the numbers of corpora lutea and viable embryos, and an increase the number of dams with nonviable embryos, the number of nonviable embryos per litter, the percentage of nonviable embryos per litter and postimplantation loss was noted. Doses of YM087 as high as 1.25 mg/kg/day did not affect the reproductive performance of the female rat.

Study no.: R087-TX-089 (20030320)
Volume #, and page #: not applicable (electronic document)
Conducting laboratory and location: [redacted]
Date of study initiation: March 15, 2000
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: 08701 and [redacted] purity
Methods: Conivaptan hydrochloride dissolved in the PG/EtOH (clinical formulation) was administered via tail vein to female rats (22/dose) beginning 15 days before cohabitation and continuing through gestation day 7 (GD7). The vehicle was [redacted]propylene glycol [redacted]ethanol in sterile water for injection. The dose solution was diluted with 5% dextrose. Food and water was available ad lib. Drug solutions were prepared weekly. Estrous cycle was evaluated before and after drug administration. Male mates of non-pregnant females were also sacrificed and evaluated.

Dosage Group	Dosage[a] (mg/kg/day)	Concentration (mg/mL)	Injection Rate (mL/min)	Dosage Volume (mL/kg)	Number of Rats	Assigned Rat Numbers
I	0 (Vehicle/ Diluent)[b]	0	1	10	22	2601-2622
II	0.5	0.05	1	10	22	2623-2644
III	1.25	0.125	1	10	22	2645-2666
IV	2.5	0.25	1	10	22	2667-2688

a. The test article (assay value of [redacted] was considered [redacted] active for the purpose of dosage calculations.
b. The control group was given the vehicle diluted in the same proportion as the high dose solution.

Doses: 0 (vehicle control), 0.5 (LD), 1.25 (MD) and 2.5 mg/kg/d (HD)
Species/strain: [redacted]CD ®SD (IGS) BR VAF/Plus female rats, [redacted]
Number/sex/group: 22/group
Route, formulation, volume, and infusion rate: 10 ml/kg at a rate of 1ml/min,Lot#08701
Satellite groups used for toxicokinetics: no TK

Study design: Parameters and endpoints evaluated: Female rats were sacrificed on GD 13 female rats were sacrificed and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed. The injection sites from all female rats were examined. Uteri from nonpregnant rats and ovaries from all female rats were examined. The number and distribution of corpora lutea in each ovary, number and distribution of

implantation sites, and viable and nonviable embryos and other reproductive parameters were recorded.

Results

Mortality: No mortality

Clinical signs: No adverse effect or notable gross lesions at any dose. The 2.5 mg/kg/d dose appeared to reduce the number of estrous cycles and increased the number of rats with six or more days of diestrus during the 2WKs before cohabitation compared to pre-treatment cycles.

Body weight: No notable change in mean BW at the end of study.

Food consumption: Transient decreased in food intake was reduced in MD and HD on pre-gestation days 1-8. No change in food intake during gestation days. 8.

Necropsy: 5 male rats failed to produce pregnancy in females appeared to be normal at gross necropsy.

Fertility parameters (mating/fertility index, corpora lutea, preimplantation loss, etc.):

- None of the litter parameters were affected by 1.25 mg/kg/d dose. The significant reduction in number of implantation and preimplantation loss in the 0.5 mg/kg/d were unlikely to be drug related.
- 2.5 mg/kg/d dose significantly reduced the number of corpora lutes and viable embryo
- 2.5 mg/kg/d dose significantly increased the number of dams with nonviable embryos, the number of nonviable embryos per liter and postimplantation loss
- The percent nonviable embryos per litter was increased in HD females
- All placenta appeared to be normal

PROTOCOL 125-011: STUDY OF FERTILITY AND EARLY EMBRYONIC DEVELOPMENT TO IMPLANTATION IN FEMALE RATS BY INTRAVENOUS INJECTION OF YM087

MATING AND FERTILITY, ESTROUS STAGES AND DAYS IN COHABITATION - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE GROUP (MG/KG/DAY)a		0 (VEHICLE/DILUENT)	0.5	1.25	2.5
MATING OBSERVATIONS					
RATS IN COHABITATION	N	22	22	22	22
DAYS IN COHABITATION	MEAN±S.D.	2.2 ± 1.1	2.1 ± 1.2	1.9 ± 0.9	2.0 ± 1.2
RATS THAT MATED	N(%)	22(100.0)	22(100.0)	22(100.0)	22(100.0)
COPULATION INDEX b	N/N	22/ 22	22/ 22	22/ 22	22/ 22
	(%)	(100.0)	(100.0)	(100.0)	(100.0)
FERTILITY INDEX c	N/N	21/ 22	22/ 22	19/ 22	21/ 22
	(%)	(95.4)	(100.0)	(86.4)	(95.4)
RATS WITH CONFIRMED MATING DATES	N	22	22	22	22
MATED BY FIRST MALE DAYS 1-4	N(%)	22(100.0)	22(100.0)	22(100.0)	22(100.0)
RATS PREGNANT/RATS IN COHABITATION	N/N	21/ 22	22/ 22	19/ 22	21/ 22
	(%)	(95.4)	(100.0)	(86.4)	(95.4)

a. Dosage occurred on day 1 of study through day 7 of presumed gestation.
b. Number of female rats with evidence of copulation/Number of female rats cohabited with male rats.
c. Number of pregnancies/number of rats that mated.

CAESAREAN-SECTIONING AND LITTER OBSERVATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE GROUP (MG/KG/DAY)a		0 (VEHICLE/DILUENT)	0.5	1.25	2.5
RATS TESTED	N	22	22	22	22
PREGNANT	N(%)	21(95.4)	22(100.0)	19(86.4)	21(95.4)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 13 OF GESTATION	N	21	22	19	21
CORPORA LUTEA	MEAN±S.D.	18.0 ± 2.8	16.2 ± 2.4	16.0 ± 2.6	15.0 ± 2.6**
IMPLANTATIONS	MEAN±S.D.	15.8 ± 1.9	13.6 ± 3.7*	14.7 ± 2.0	13.6 ± 4.0
VIABLE EMBRYOS	N	321	291	264	249
	MEAN±S.D.	15.3 ± 1.8	13.2 ± 4.0	13.9 ± 2.2	11.8 ± 4.1**
NONVIABLE EMBRYOS	N	11	9	15	37
	MEAN±S.D.	0.5 ± 0.7	0.4 ± 0.7	0.8 ± 0.9	1.8 ± 1.8*
DAMS WITH ANY NONVIABLE EMBRYOS	N(%)	8(38.1)	7(31.8)	10(52.6)	17(81.0)**
DAMS WITH ALL NONVIABLE EMBRYOS	N(%)	0(0.0)	1(4.5)	0(0.0)	1(4.8)
DAMS WITH VIABLE EMBRYOS	N(%)	21(100.0)	21(95.4)	19(100.0)	20(95.2)
PLACENTAE APPEARED NORMAL	N(%)	21(100.0)	21(100.0)	19(100.0)	20(100.0)
% NONVIABLE EMBRYOS/LITTER	MEAN±S.D.	3.2 ± 4.6	2.2 ± 3.7	5.6 ± 6.5	12.6 ± 13.1

a. Dosage occurred on day 1 of study through day 7 of gestation.
* Significantly different from the vehicle control group value ($p \leq 0.05$).
** Significantly different from the vehicle control group value ($p \leq 0.01$).

CAESAREAN-SECTIONING AND LITTER OBSERVATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE GROUP (MG/KG/DAY)a		0 (VEHICLE/DILUENT)	0.5	1.25	2.5
RATS TESTED	N	22	22	22	22
PREGNANT	N(%)	21(95.4)	22(100.0)	19(86.4)	21(95.4)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 13 OF GESTATION	N	21	22	19	21
PREIMPLANTATION LOSS b	N/N	45/377	57/357*	26/305	29/315
	(%)	(11.9)	(16.0)	(8.5)	(9.2)
PREIMPLANTATION LOSS c	MEAN±S.D.	10.8 ± 11.2	16.1 ± 20.9	7.9 ± 6.8	11.2 ± 22.0
POSTIMPLANTATION LOSS b	N/N	11/332	9/300	15/279	37/286**
	(%)	(3.3)	(3.0)	(5.4)	(12.9)
POSTIMPLANTATION LOSS c	MEAN±S.D.	3.2 ± 4.6	6.6 ± 21.2	5.6 ± 6.5	16.8 ± 22.9**

PREIMPLANTATION LOSS = (NUMBER OF CORPORA LUTEA - NUMBER OF IMPLANTATIONS)/NUMBER OF CORPORA LUTEA
POSTIMPLANTATION LOSS = (NUMBER OF IMPLANTATIONS - NUMBER OF VIABLE EMBRYOS)/NUMBER OF IMPLANTATIONS
a. Dosage occurred on day 1 of study through day 7 of gestation.
b. Totaled value per group.
c. Mean value per litter.
* Significantly different from the vehicle control group value ($p \leq 0.05$).
** Significantly different from the vehicle control group value ($p \leq 0.01$).

Embryofetal development

Study title: Embryo-fetal Development in Rats with Intravenous Treatment with PG/EtOH formulation (Study for effects of YM087 on embryo-fetal development in rats by intravenous injection)

Key study findings: There were no deaths at intravenous doses of 0.5, 1.25 and 2.5 mg/kg/d. There were no gross external, visceral or skeletal alterations in fetuses at any dose level. Live fetal weight was reduced at 1.25 mg/kg/d. The NOAEL for maternal toxicity was less than 0.5 mg/kg/d and 2.5 mg/kg/d for fetal development.

Study no.: R087-TX-092 (125-014)
Volume #, and page #: not applicable (electronic document, 196 pages)
Conducting laboratory and location: [redacted]
Date of study initiation: Jan 27, 00
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: 08701, [redacted] purity

Methods

Doses: 0, 0.5 (LD), 1.25 (MD) and 2.5 mg/kg/d (HD)
Species/strain: [redacted]CD ®SD (IGS) BR VAF/Plus female rats
Number/sex/group: 25 animals /dose
Route, formulation, volume, and infusion rate: intravenous, 10 ml/kg, 1 ml/min
Satellite groups used for toxicokinetics: yes
Study design:

Conivaptan was dissolved in PG/EtOH, diluted with 5% dextrose and administered via tail vein to 9 to 10 week old rats from gestation day (GD) 7 to 17. A c-section was performed on GD 21. The number and distribution of corpora lutea and implantation sites, and uterine contents were recorded. The tails, ovaries, uterus, vagina and mammary glands were retained in neutral buffered. Fetal weight, sex, and gross external alterations were recoded. Fetal soft tissue/visceral and skeletal malformations were also evaluated.

Results

Mortality (dams): No deaths
Clinical signs (dams): No change in clinical signs. One female rat in the 2.5 mg/kg/day dosage group delivered before Caesarean-sectioning on DG 21 and was sacrificed. This delivery was not considered related to the test article because deliveries before Caesarean-sectioning on DG 21 have been observed in a few animals at the Testing Facility. All other rats survived until scheduled sacrificed.

Body weight (dams): No change in body weight or BW gains

Food consumption (dams): Feed consumption values were significantly reduced on DGs 7 to 10, 10 to 12 and during the entire dosage period (DG5 7 to 18) in the 0.5 mg/kg/day and higher dosage groups

Toxicokinetics:

Embryo-fetal development in rats with intravenous treatment – results in dams [R087-TX-092]

Daily Dose (mg/kg)		0	0.5	1.25	2.5
Number Pregnant		25	25	23	24 [a]
Dams/Does:					
Food Consumption (g/day):	GD7-10	23.2	21.1**	20.2**	19.0**
	GD10-12	24.0	22.3*	22.2*	21.4**
	GD7-18	24.9	23.6*	23.1**	22.7**
Toxicokinetics:					
C_{max} (ng/mL) [b]:	GD7	NA	156	459	933
AUC_{0-24}: (ng·hr/mL) [b]:	GD7	NA	317	1810	3803

GD = Gestation day. Dunnett's Test: * - P<0.05 ** - p<0.01. NA – Not applicable.
a - One dam was removed due to delivery on GD 21.
b – From Study No. R087-TX-091, Study for Effects of YM087 on Prenatal and Postnatal Development in Rats by Intravenous Injection, Including Maternal Function.

Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.):

- No gross external, visceral or skeletal alterations were observed in fetuses.
- Live fetal weight was significantly reduced at 1.25 mg/kg but this observation was considered to be related to a slightly larger number of pups per litter and was not treatment-related.
- Pregnancy occurred in 23 to 25 rats in each dosage group. No Caesarean sectioning or litter parameters were affected by dosages of the test article as high as 2.5 mg/kg/day.
- No gross external, soft tissue or skeletal fetal alterations (malformations or variations) were caused by dosages of the test article as high as 2.5 mg/kg/day.

Offspring (malformations, variations, etc.):

Embryo-fetal development in rats with intravenous treatment – results in fetuses [R087-TX-092]

Daily Dose (mg/kg)		0	0.5	1.25	2.5
Number Pregnant		25	25	23	24 [a]
Number of Litters Evaluated		25	25	23	23
Number of Live Fetuses		348	371	344	335
Number of Implantations		14.5	15.4	15.2	15.2
Live Fetuses		13.9	14.8	15.0	14.6
Mean Fetal Body Weight (g):	Male	5.76	5.71	5.50**	5.68
	Female	5.52	5.38	5.28**	5.38

Dunnett's Test: ** - p<0.01. a - One dam was removed due to delivery on day 21 of gestation.

Study title: Embryo-Fetal Development in Rabbits with bolus Intravenous Treatment with PG/EtOH formulation (Study for effects of YM087 on embryo-fetal development in rabbits by intravenous injection)

Key study findings: Injection site findings such as abrasions and purple, swollen ear at the injection sites were dose-related (6 and 12 mg/kg/d). There were no treatment related deaths. No effect on BW gain at 6 mg/kg/d, however, the 12 mg/kg/d dose reduced maternal BW gain during GD 6 to 18 by 66.7% relative to control. The food intake at 12 mg/kg/d was reduced transiently on GD 6 to 8. The maternal reproductive NOAEL and developmental NOAEL were >12 mg/kg/d. The maternal NOAEL was 3 mg/kg/d due to incidence of injection site findings at 6 mg/kg/d.

Study no.: R087-TX-094 (125-012)
Volume #, and page #: not applicable (electronic document, 248 pages)
Conducting laboratory and location:
Date of study initiation: Jan 20, 00
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: 08701, [redacted] purity

Methods

Dosage Administration

Dosage Group	Dosage[a] (mg/kg/day)	Concentration (mg/mL)	Volume (mL/kg)	Injection Rate (mL/min)	Number of Rabbits	Assigned Rabbit Numbers
I	0 (Vehicle/Diluent)[b]	0	10	6	20	2486-2505
II	3	0.3	10	6	20+3[c]	2506-2525/ 2566-2568[d]
III	6	0.6	10	6	20+3[c]	2526-2545/ 2569-2571[d]
IV	12	1.2	10	6	20+3[c]	2546-2565/ 2572-2574[d]

a. The test article (assay value of [redacted] was considered to be [redacted] pure for the purpose of dosage calculations.
b. The control group was administered the vehicle diluted in the same proportion as the high dosage solution.
c. Additional rabbits assigned to satellite Groups II, III and IV.
d. Animal numbers for rabbits assigned to satellite Groups II, III and IV.

Doses: 0, 3 (LD), 6 (MD) and 12 mg/kg/d (HD) at volume of 10 ml/kg
Species/strain: New Zealand white female pregnant rabbits [Hr: (NZW) SPF], [redacted]
Number/sex/group: 20 animals /dose + 3/group for TK evaluation
Route, formulation, volume, and infusion rate: intravenous, ear, 10 ml/kg, 1 ml/min
Satellite groups used for toxicokinetics: yes

Study design: Conivaptan was prepared in PG/EtOH, diluted with 5% dextrose and administered daily via marginal ear vein to 6-months old pregnant New Zealand rabbits (n=20/group) from gestation day (GD) 6 to 18. Doses selection was based on a dose ranging study where 25 mg/kg/d lead to early sacrifice due to

severe injection site irritation. Three additional animals/ group were used for TK blood collections on GD6 and 18. Daily BW and food intake were measured during the treatment phase. Blood samples were collected from medial auricular artery at 10 and 30 min, 2, 4 and 24 hrs post dose. A c-section was performed on GD 29 and standard developmental parameters were evaluated: maternal toxicity, abortions, premature deliveries, the number of corpora lutea, number of implantation sites, number of viable and nonviable fetuses, early and late resorptions, fetal body weight, placental weight, proportion of male fetuses, gross lesion, and incidence of fetal morphological findings (external, visceral, and skeletal).

Results

Mortality (dams): No treatment related deaths. One female rabbit at 3 mg/kg/d was moribund on GD 7 due to restraint accident leading to hindlimb limp (possible spinal cord trauma) and was euthanized.

Clinical signs (dams): Significant increase in injection site findings in treated rabbits such as purple discoloration at ≥6 mg/kg/d and abrasions at 6 mg/kg/d. Other notable findings were swollen ear and scab on the ear.

TABLE 1 (PAGE 1): CLINICAL OBSERVATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (MG/KG/DAY)a		0 (VEHICLE/DILUENT)	3	6	12
MAXIMUM POSSIBLE INCIDENCE		480/ 20	458/ 20	480/ 20	480/ 20
MORIBUND SACRIFICED		0	1b	0	0
EAR(S): PURPLE		0/ 0	20/ 3	31/ 6*	84/ 10**
LOCALIZED ALOPECIA:	TOTAL	14/ 3	5/ 2	0/ 0	8/ 4
	LIMBS	10/ 2	5/ 2	0/ 0	3/ 3
	UNDERSIDE	3/ 1	0/ 0	0/ 0	5/ 1
	BACK	4/ 1	0/ 0	0/ 0	0/ 0
EAR(S): PURPLE AND SWOLLEN		0/ 0	3/ 1	16/ 5	5/ 3
SOFT OR LIQUID FECES		0/ 0	4/ 3	1/ 1	3/ 2
LEFT OR RIGHT EAR: SCAB		0/ 0	0/ 0	10/ 3	4/ 1
LEFT OR RIGHT EAR: ABRASION		0/ 0	0/ 0	4/ 3**	0/ 0
SCANT FECES		5/ 1	6/ 4	3/ 2	0/ 0
NO USE OF HINDLIMBS		0/ 0	1/ 1b	0/ 0	0/ 0
RALES		0/ 0	1/ 1	0/ 0	0/ 0

STATISTICAL ANALYSES OF CLINICAL OBSERVATION DATA WERE RESTRICTED TO THE NUMBER OF RABBITS WITH OBSERVATIONS.
MAXIMUM POSSIBLE INCIDENCE = (DAYS x RABBITS)/NUMBER OF RABBITS EXAMINED PER GROUP ON DAYS 6 THROUGH 29 OF PRESUMED GESTATION.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RABBITS WITH OBSERVATION.
a. Dosage occurred on days 6 through 18 of presumed gestation.
b. Rabbit 2523 was moribund sacrificed on day 7 of presumed gestation.
* Significantly different from the vehicle control group value ($p \leq 0.05$).
** Significantly different from the vehicle control group value ($p \leq 0.01$).

Body weight (dams):

No significant change in body weigh, however, the decrease in BW gain on GD 7 and 8 was maintained to the end of the treatment day. The BW gain was reduced by 66.7% in the 12 mg/kg/d group relative to control group. The 3 and 6 mg/kg/d had no notable effect on BW or BW gains.

Food consumption (dams): A transient decrease in feed intake (FI) was noted initially (GD 6 and GD 8) at 12 mg/kg/d that corresponded to decrease in BW gain in the HD group. The final food intake GD6 vs. 18 or 29 were not different. No change in FI in LD or MD.

Table 2.6.6-104: Embryo-fetal development study in rabbits with intravenous treatment [R087-TX-094]

Daily Dose (mg/kg)		0	3	6	12
Number Pregnant		19	18	20	19
No. Died or Sacrificed Moribund:		0	1[a]	0	0
No. Aborted or with Total Resorption of Litter:		0	0	0	0
Clinical Observations:					
Purple ears		0	3	6#	10##
Abrasion of the ears		0	0	3##	0
Purple and swollen ears		0	1	5	3
Scab on the ears		0	0	3	1
Necropsy Observations:		-	-	-	-
Body Weight (kg):	GD6	3.79	3.77	3.78	3.80
	GD7	3.80	3.80	3.78	3.76
	GD18	3.98	3.97	3.96	3.93
Body Weight gain (kg):	GD6–18	+0.18	+0.20	+0.18	+0.12
Food Consumption (g/day):	GD6–7	152.5	160.6	146.2	126.9
	GD7–8	155.4	153.3	140.6	123.4**
	GD6–18	147.7	145.3	136.4	130.6

- No noteworthy finding. GD = Gestation day.
Dunnett's Test or Satterthwaite Analysis: ** - p<0.01 Chi-Square Test: # - P<0.05 ## - p<0.01.
a - One animal was moribund sacrificed on GD7 as the result of a restraint accident.

Toxicokinetics:

- AUC was dose-proportional
- No change in AUC from GD 6 to GD 18

Table 2.6.6-105: Embryo-fetal development study in rabbits with intravenous treatment – toxicokinetics [R087-TX-094]

Daily Dose (mg/kg)		3	6	12
C_{max} (ng/mL):	GD6	1843	4203	8773
	GD18	2820	3940	10423
AUC_{0-24} (ng-hr/mL):	GD6	2614	5885	24298
	GD18	3458	5645	27413

GD = Gestation day.

Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.):

- Pregnancy occurred in 18 to 20 rabbits in each group
- No Caesarian section or litter parameters were affected by the YM087
- Caesarian-delivered fetuses in control, LD, MD and HD were 19, 18, 20 and 18 litters, respectively
- The litter corpora lutea, implantations, litter size, live fetuses, early and late resorptions, fetal body weights, percent resorbed conceptuses did not significantly differ among groups.
- There were no dead fetuses and all placenta appeared normal
- No notable clinical observations in the satellite rabbits were observed. One doe in the MD satellite group (6 mg/kg/d) was not pregnant.

PROTOCOL 125-012: STUDY FOR EFFECTS OF YM087 ON EMBRYO-FETAL DEVELOPMENT IN RABBITS BY INTRAVENOUS INJECTION

TABLE 7 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE/DILUENT)	II 3	III 6	IV 12
RABBITS TESTED	N	20	20	20	20
PREGNANT	N(%)	19(95.0)	18(90.0)	20(100.0)	19(95.0)
RABBITS PREGNANT AND CAESAREAN-SECTIONED ON DAY 29 OF GESTATION	N	19	18	20	19
CORPORA LUTEA	MEAN±S.D.	9.8 ± 1.8	10.5 ± 2.0	9.6 ± 1.4	10.1 ± 2.0
IMPLANTATIONS	MEAN±S.D.	9.4 ± 1.5	9.7 ± 2.3	9.0 ± 1.4	8.5 ± 2.5
LITTER SIZES	MEAN±S.D.	9.1 ± 1.2	9.2 ± 2.6	8.4 ± 1.0	8.3 ± 2.4
LIVE FETUSES	N	173	166	168	157
	MEAN±S.D.	9.1 ± 1.2	9.2 ± 2.6	8.4 ± 1.0	8.3 ± 2.4
DEAD FETUSES	N	0	0	0	0
RESORPTIONS	MEAN±S.D.	0.3 ± 0.8	0.5 ± 1.2	0.6 ± 0.9	0.2 ± 0.6
EARLY RESORPTIONS	N	0	3	1	0
	MEAN±S.D.	0.0 ± 0.0	0.2 ± 0.5	0.0 ± 0.2	0.0 ± 0.0
LATE RESORPTIONS	N	6	6	11	4
	MEAN±S.D.	0.3 ± 0.8	0.3 ± 1.2	0.6 ± 0.9	0.2 ± 0.6
DOES WITH ANY RESORPTIONS	N(%)	3(15.8)	4(22.2)	7(35.0)	2(10.5)
DOES WITH ALL CONCEPTUSES RESORBED	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
DOES WITH VIABLE FETUSES	N(%)	19(100.0)	18(100.0)	20(100.0)	19(100.0)
PLACENTAE APPEARED NORMAL	N(%)	19(100.0)	18(100.0)	20(100.0)	19(100.0)

a. Dosage occurred on days 6 through 18 of gestation.

TABLE 8 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) AND PLACENTAL WEIGHTS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE/DILUENT)	II 3	III 6	IV 12
LITTERS WITH ONE OR MORE LIVE FETUSES	N	19	18	20	19
IMPLANTATIONS	MEAN±S.D.	9.4 ± 1.5	9.7 ± 2.3	9.0 ± 1.4	8.5 ± 2.5
LIVE FETUSES	N	173	166	168	157
	MEAN±S.D.	9.1 ± 1.2	9.2 ± 2.6	8.4 ± 1.0	8.3 ± 2.4
LIVE MALE FETUSES	N	91	83	79	82
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	53.3 ± 24.3	51.1 ± 15.6	47.3 ± 13.6	53.0 ± 14.7
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	42.17 ± 3.96	41.76 ± 4.79	43.90 ± 3.97	43.97 ± 5.52
MALE FETUSES	MEAN±S.D.	42.53 ± 4.59	42.11 ± 5.31	45.20 ± 4.47	44.82 ± 5.38
FEMALE FETUSES	MEAN±S.D.	41.60 ± 4.12 [18]b	41.52 ± 5.04	42.95 ± 4.12	43.10 + 6.21
PLACENTAL WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	5.56 ± 0.78	5.87 ± 0.75	5.69 ± 0.68	5.90 ± 0.85
MALE FETUSES	MEAN±S.D.	5.67 ± 0.80	6.03 ± 0.76	6.01 ± 0.90	6.06 ± 0.84
FEMALE FETUSES	MEAN±S.D.	5.41 ± 0.81 [18]b	5.74 ± 0.89	5.44 ± 0.67	5.69 ± 0.98
% RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	2.7 ± 6.9	5.0 ± 12.4	5.8 ± 9.1	1.9 ± 5.7

[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 6 through 18 of gestation.
b. Doe 2494 had no female fetuses.

Offspring (malformations, variations, etc.):

- There were no dose dependant or significant difference in litter or fetal incidence of gross external, soft tissue or skeletal abnormalities (table 9)
- The developmental NOAEL was > 12 mg/kg/d

Several malformations in 3 control and 2 LD (3 mg/kg/d) and 1 HD (12 mg/kg/d) groups were observed that appear to be coincidental:

- Control Fetus 2493-2 had a meningocele. This fetus had additional soft tissue and skeletal alterations: a small brain, incompletely ossified left frontal bone and both parietal bones contained a hole.
- Control Fetus 2496-7 had a short tail. This fetus had additional skeletal alterations: fused 1st -6th, 12th and 13th, 14th and 15th caudal vertebrae present.
- Control Fetus 2496-10 had a threadlike tail. This fetus had additional skeletal alterations: fused 7th - 9th, 13th and 14th caudal vertebrae and only 14 caudal vertebrae present.
- LD Fetus 2513-1 had abdominal distention. This fetus also had a large heart.
- LD Fetus 2522-12 had a protruding tongue, anencephaly, absent snout, absent eyes and absent facial papilla(e). This fetus also had additional skeletal alterations: absent skull and incompletely ossified 1st sternal centrum and asymmetric 1st to 4th sternal centra.
- HD Fetus 2561-1 had a short tail. The skeletal alterations included incompletely ossified 2nd sternal centrum and only 9 caudal vertebrae present.
- No other fetal gross external malformations occurred

TABLE 9 (PAGE 1): FETAL ALTERATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0 (VEHICLE/DILUENT)	II 3	III 6	IV 12
LITTERS EVALUATED	N	19	18	20	19
FETUSES EVALUATED	N	173	166	168	157
LIVE	N	173	166	168	157
LITTERS WITH FETUSES WITH ANY ALTERATION OBSERVED	N(%)	10(52.6)	11(61.1)	15(75.0)	9(47.4)
FETUSES WITH ANY ALTERATION OBSERVED	N(%)	18(10.4)	16(9.6)	24(14.3)	15(9.6)
% FETUSES WITH ANY ALTERATION/LITTER	MEAN±S.D.	9.7 ± 12.7	10.4 ± 10.6	14.6 ± 12.8	9.6 ± 14.7
LITTERS WITH FETUSES WITH ANY MALFORMATION OBSERVED b	N(%)	2(10.5)	2(11.1)	1(5.0)	2(10.5)
FETUSES WITH ANY MALFORMATION OBSERVED b	N(%)	3(1.7)	2(1.2)	1(0.6)	2(1.3)
% FETUSES WITH ANY MALFORMATION/LITTER b	MEAN±S.D.	1.6 ± 5.0	1.5 ± 4.5	0.6 ± 2.5	1.0 ± 3.1
LITTERS WITH FETUSES WITH ANY VARIATION OBSERVED c	N(%)	8(42.1)	9(50.0)	14(70.0)	7(36.8)
FETUSES WITH ANY VARIATION OBSERVED c	N(%)	15(8.7)	14(8.4)	23(13.7)	13(8.3)
% FETUSES WITH ANY VARIATION/LITTER c	MEAN±S.D.	8.1 ± 12.8	8.9 ± 10.9	14.0 ± 12.7	8.6 ± 14.5

a. Dosage occurred on days 6 through 18 of gestation.
b. Restricted to fetuses with malformations or malformations and variations.
c. Restricted to fetuses with variations only.

TABLE 9 (PAGE 2): FETAL ALTERATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (MG/KG/DAY)a		0 (VEHICLE/DILUENT)	3	6	12
LITTERS EVALUATED	N	19	18	20	19
FETUSES EVALUATED	N	173	166	168	157
LIVE	N	173	166	168	157
GROSS EXTERNAL ALTERATIONS:					
LITTERS WITH FETUSES WITH ANY MALFORMATION OBSERVED b	N(%)	2(10.5)	2(11.1)	0(0.0)	1(5.3)
FETUSES WITH ANY MALFORMATION OBSERVED b	N(%)	3(1.7)	2(1.2)	0(0.0)	1(0.6)
LITTERS WITH FETUSES WITH ANY VARIATION OBSERVED c	N(%)	0(0.0)	1(5.6)	0(0.0)	0(0.0)
FETUSES WITH ANY VARIATION OBSERVED c	N(%)	0(0.0)	1(0.6)	0(0.0)	0(0.0)
SOFT TISSUE ALTERATIONS:					
LITTERS WITH FETUSES WITH ANY MALFORMATION OBSERVED b	N(%)	1(5.3)	1(5.6)	0(0.0)	0(0.0)
FETUSES WITH ANY MALFORMATION OBSERVED b	N(%)	1(0.6)	1(0.6)	0(0.0)	0(0.0)
LITTERS WITH FETUSES WITH ANY VARIATION OBSERVED c	N(%)	1(5.3)	4(22.2)	0(0.0)	1(5.3)
FETUSES WITH ANY VARIATION OBSERVED c	N(%)	4(2.3)	4(2.4)	0(0.0)	1(0.6)
SKELETAL ALTERATIONS:					
LITTERS WITH FETUSES WITH ANY MALFORMATION OBSERVED b	N(%)	0(0.0)	1(5.6)	1(5.0)	1(5.3)
FETUSES WITH ANY MALFORMATION OBSERVED b	N(%)	0(0.0)	1(0.6)	1(0.6)	1(0.6)
LITTERS WITH FETUSES WITH ANY VARIATION OBSERVED c	N(%)	10(52.6)	7(38.9)	14(70.0)	7(36.8)
FETUSES WITH ANY VARIATION OBSERVED c	N(%)	15(8.7)	10(6.0)	23(13.7)	13(8.3)

a. Dosage occurred on days 6 through 18 of gestation.
b. Restricted to fetuses with malformations or malformations and variations.
c. Restricted to fetuses with variations only.

TABLE 10 (PAGE 1): FETAL GROSS EXTERNAL ALTERATIONS - SUMMARY
(See footnotes on the last page of this table.)

DOSAGE GROUP		I	II	III	IV
DOSAGE (MG/KG/DAY)a		0 (VEHICLE/DILUENT)	3	6	12
LITTERS EVALUATED	N	19	18	20	19
FETUSES EVALUATED	N	173	166	168	157
LIVE	N	173	166	168	157
HEAD: MENINGOCELE (M)					
LITTER INCIDENCE	N(%)	1(5.3)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.6)	0(0.0)	0(0.0)	0(0.0)
TAIL: SHORT (M)					
LITTER INCIDENCE	N(%)	1(5.3)	0(0.0)	0(0.0)	1(5.3)
FETAL INCIDENCE	N(%)	1(0.6)	0(0.0)	0(0.0)	1(0.6)
TAIL: THREAD-LIKE (M)					
LITTER INCIDENCE	N(%)	1(5.3)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.6)	0(0.0)	0(0.0)	0(0.0)
TONGUE: PROTRUDED (M)					
LITTER INCIDENCE	N(%)	0(0.0)	1(5.6)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)b	0(0.0)	0(0.0)
HEAD: ANENCEPHALY (M)					
LITTER INCIDENCE	N(%)	0(0.0)	1(5.6)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)b	0(0.0)	0(0.0)
SNOUT: ABSENT (M)					
LITTER INCIDENCE	N(%)	0(0.0)	1(5.6)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)b	0(0.0)	0(0.0)
EYES: ABSENT (M)					
LITTER INCIDENCE	N(%)	0(0.0)	1(5.6)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)b	0(0.0)	0(0.0)
FORELIMBS: FLEXED (V)					
LITTER INCIDENCE	N(%)	0(0.0)	1(5.6)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)	0(0.0)	0(0.0)
BODY: ABDOMINAL DISTENTION (M)					
LITTER INCIDENCE	N(%)	0(0.0)	1(5.6)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)	0(0.0)	0(0.0)
HEAD: FACIAL PAPILLA(E) ABSENT (M)					
LITTER INCIDENCE	N(%)	0(0.0)	1(5.6)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)b	0(0.0)	0(0.0)

M = MALFORMATIONS (RESTRICTED TO FETUSES WITH MALFORMATIONS OR MALFORMATIONS AND VARIATIONS)
V = VARIATIONS (RESTRICTED TO FETUSES WITH VARIATIONS ONLY)
a. Dosage occurred on days 6 through 18 of gestation.
b. Fetus 2522-32 had other gross external alterations.

PRENATAL AND POSTNATAL DEVELOPMENT

Study title: Intravenous Dosage Range-Finding Study for Effects on Pre- and Postnatal Development (Including Maternal Function) of YM087 in Rats (R087-TX-090)

Key study findings: In this dose-ranging study (10/group), YM087 PG/EtOH formulation administered by IV had no notable effect on pregnant rats at doses up to 2.5 mg/kg/d except for small decrease in BW gain during the gestation period with accompanying decrease in food consumption at 2.5 mg/kg/d. Conivaptan had no effect on any pre- and postnatal development at any dose or any effect on BW at 0.5 or 1.25 mg/kg/d. The maternal and littler toxicity NOEL was 0.5 mg/kg/d. Based on this study, the sponsor chose 0.5, 1.25 and 2.5 mg/kg/d for the definitive intravenous formulation of Conivaptan.

Study no.: R087-TX-090 (20030320)
Volume #, and page #: 171 pages
Conducting laboratory and location: [redacted]
Date of study initiation: Oct 6, 1999
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Lo# 08701, [redacted] purity

Methods

Dosage Group	Dosage (mg/kg/day)[a]	Concentration (mg/mL)	Dosage Volume (mL/kg)	Injection Rate (mL/min)	Number of Female Rats	Fo Generation Rat Numbers
I	0 (Vehicle/Diluent)[b]	0	10	1	10	13151 - 13154; 9581[c]; 13156 - 13160
II	0.1	0.01	10	1	10	13161 - 13170
III	0.5	0.05	10	1	10	13171 - 13180
IV	1.25	0.125	10	1	10	13181 - 13190
V	2.5	0.25	10	1	10	13191 - 13200

a. The test article (assay value of [redacted] was considered to be [redacted] pure for the purpose of dosage calculations.
b. The control group was given vehicle diluted in the same proportion as the high dosage solution.
c. Rat 13155 was excluded from study on DG 7 due to difficulty in dosing and replaced with rat 9581.

Doses: 0, 0.1, 0.5, 1.25 and 2.5 mg/kg/d
Species/strain: [redacted] CD ®SD (IGS) BR VAF/Plus
Number/sex/group: 10/group
Route, formulation, volume, and infusion rate:
Satellite groups used for toxicokinetics:
Study design: Pregnant rats were treated with YM087 , [redacted] PG and [redacted] EtOH formulation (diluted with 5% dextrose) via tail vein from gestation day 7 to lactation day (DL) 6 or to GD 24. The early concentration analysis found most solution concentrations about 10% below the target concentrations. The lowest dose solution was 36.7% below the target dose solution. The final dose solution concentration analyses were on target.

Parameters and endpoints evaluated: Injection sites, BW, FI, parturition, duration of gestation, delivered litter size, live litter size and pup viability, pup BW, gross lesion in F0 and F1 generation, implantation site,

Results

F_0 in-life:

- No deaths at any dose.
- Pregnancy frequency was 10/10 for all doses except for 9/10 for HD group.
- Red prevaginal substance was noted in most treated rats on DL1 and 2.
- Transient decrease in BW at 2.5 mg/kg/d during gestation period but significant decrease in BW gain was noted at GD 7 through GD 21. BW and BW gains were not affected during lactation at 2.5 mg/kg/d
- The lower doses had no effect on BW or BW gains.
- Food consumption was reduced at different time intervals during gestation by 2.5 mg/kg/d dose
- No effect on duration of gestation, implantation, live litter size, number of dams with pups dying during lactation

F_0 necropsy: No change in viability index, pup sex ratio, pup body weight or necropsy observations. One pup at 0.1 mg/kg/d dose was dead on DL6 with a dark red area on the spleen noted at necropsy.

F_1 physical development: No effect was observed

Study title: Study for Effects of YM087 on Prenatal and Postnatal Development in Rats by Intravenous Injection, Including Maternal Function

Study # Ro87-TX-091

Key study findings: Pregnant rats were treated with 0.5, 1.25 and 2.5 mg/kg/d of Conivaptan hydrochloride in PG/EtOH intravenous dose from gestation day 7 to lactation day 20 (0.06, 0.16 and 0.4 x clinical dose based on AUC_{0-24} of 3580 ng.h/ml). No treatment related death in dams. Food intake was decreased in early gestation and lactation phase in 1.25 and 2.5 mg/kg. BW and BW gain was not significantly altered by the highest dose (2.5 mg/kg/d) in the study. There were no treatment related changes in clinical signs, gross pathology, maintenance of pregnancy, parturition or lactation. Viability, weaning indices and pup weight per litter were reduced at 2.5 mg/kg. There was however, a delayed development of several reflexes in pups at 2.5 mg/kg (surface righting, acoustic startle, turning on an inclined plane and air righting) which may have correlated with lower BW of F1 pups. Body weights in F_1 pups of dams treated with 2.5 mg/kg/d were lower than controls but recovered during post weaning period. Sexual maturity was delayed at 2.5 mg/kg but this delay was also likely due to lower BW of F_1 rats. No abnormalities were observed in mating or fertility of F_1 rats or findings in Caesarian section.
Overall, the maternal NOAEL was 2.5 mg/kg/d. Developmental delays in F1 at 2.5 mg/kg/d and mating F1 showed increased preimplantation loss $\geq$1.25 mg/kg/d.

Study no.: R087-TX-091 (20031212, Project ID 125-015)
Volume #, and page #: 1-579 pages
Conducting laboratory and location: [redacted]

Date of study initiation: Feb 07, 2000
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Lo# 08701, [redacted] purity
Methods

Doses: 0, 0.5, 1.25 and 2.5 mg/kg/d
Species/strain: [redacted]CD ®SD (IGS) BR VAF/Plus female rats
Number/sex/group: 25/group
Route, formulation, volume, and infusion rate:
Satellite groups used for toxicokinetics:
Study design: Pregnant rats were treated with YM087 in [redacted]PG and [redacted]EtOH formulation via tail vein from gestation day (GD)7 through lactation day (DL) 20. The drug solution was diluted as needed with 5% dextrose. Additional nine rats were assigned to treatment group for TK analysis on GD 7 and LD20. F0 generation rats were housed individually. F1 generation rats were housed to three per cage for 1 wk post weaning and 1 per cage until cohabitation.

Fo Generation

Dosage Group	Dosage[a] (mg/kg/day)	Concentration (mg/mL)	Volume (mL/kg)	Injection Rate (mL/min)	Number of Rats	Assigned Fo Generation Numbers
I	0 (Vehicle/ Diluent)[b]	0	10	1	25	2001-2025
II	0.5	0.05	10	1	25+9[c]	2026-2050, 15522[d,e], 15748[d,e], 15176-15182[d]
III	1.25	0.125	10	1	25+9[c]	2051-2075, 15183-15191[d]
IV	2.5	0.25	10	1	25+9[c]	2076-2100, 15192-15200[d]

a. The test article (assay value of [redacted]) was considered to be [redacted] pure for the purpose of dosage calculation.
b. The control group was administered the vehicle diluted in the same proportion as the high dosage solution.
c. Additional rats assigned to satellite Groups II, III and IV.
d. Numbers for rats assigned to satellite Groups II, III and IV.
e. Rats 15174 and 15175 were administered the vehicle control article, rather than the test article, on DG 7 and were replaced with rats 15522 and 15748, respectively[a].

F1 Generation

Dosage Group	Maternal Dosage (mg/kg/day)	Number of Rats Per Sex	Assigned F1 Generation Numbers	
			Male	Female
I	0 (Vehicle/ Diluent)	25	5701 - 5725	5801 – 5825
II	0.5	25	5726 - 5750	5826 - 5850
III	1.25	23	5751 - 5773	5851 – 5873
IV	2.5	24	5776 - 5799	5876 - 5899

Parameters and endpoints evaluated:

- Standard reprotox parameters (parturition, duration of gestation, delivered litter size, live litter size and pup viability, pup BW, gross lesion in F0 and F1 generation, implantation site plus injection sites, BW, FI were evaluated.
- On LD 21, dams and pup not selected for continued evaluation were sacrificed and necropsies and the number of implantation sites in the dams were recorded. Pups were preserved for possible future skeletal evaluation.
- The F1 generation rats were assessed for sensory functions (surface righting, acoustic startle reflex, included plane, air righting and pupil construction) and physical development (pinna unfolding, eye opening, hair growth and incisor eruption).
- At 90 days of age, F1 generation rats were mated. Pregnant F1 generation rats were sacrificed on GD 21, c-sectioned and the reproductive endpoints were evaluated. The fetal weight and external alteration and the sex of the fetuses were determined.

Results

F_0 in-life:

- There were no drug related deaths.
- One HD F0 female was killed accidentally on PD 8 (caught in the feeder and the cage when closed).
- No notable adverse clinical observation except for red prevaginal substance in most treated rats
- Overall BW and BW gains were not significantly affected by 2.5 mg/kg/d dose, although significant decrease in BW gain during lactation day10 to 14 was noted at all doses corresponding to reduced food intake.
- Food intake was also reduced during early gestation and lactation at 2.5 mg/kg/d dose level
- One MD rat delivered a litter before c-section on GD 21 and sacrificed. She had one live pup, 3 resorptions. The remaining fetuses were normal.
- 23 to 25 rats were pregnant and delivered (see table below)

PROTOCOL 125-015: STUDY FOR EFFECTS OF YM087 ON PRENATAL AND POSTNATAL DEVELOPMENT IN RATS BY INTRAVENOUS INJECTION, INCLUDING MATERNAL FUNCTION

TABLE B8 (PAGE 1): NATURAL DELIVERY OBSERVATIONS - SUMMARY - Fo GENERATION FEMALE RATS

DOSAGE GROUP		I	II	III	IV
DOSAGE (MG/KG/DAY)a		0 (VEHICLE/DILUENT)	0.5	1.25	2.5
RATS ASSIGNED TO NATURAL DELIVERY	N	25	25	23	24
PREGNANT	N	25	25	23	24
DELIVERED LITTERS	N(%)	25(100.0)	25(100.0)	23(100.0)	24(100.0)
DELIVERY INDEX b,c	%	95.1	93.1	93.9d	94.9
	N/N	385/405	376/404	323/344d	371/391
DELIVERY INDEX b,e	MEAN±S.D.	95.0 ± 6.3	93.0 ± 12.5	93.8 ± 5.8d	94.9 ± 7.4
DURATION OF GESTATION f	MEAN±S.D.	22.6 ± 0.5	22.6 ± 0.5	22.8 ± 0.4	22.8 ± 0.4
IMPLANTATION SITES	N	405	404	344d	391
PER DELIVERED LITTER	MEAN±S.D.	16.2 ± 2.0	16.2 ± 2.4	15.6 ± 1.5d	16.3 ± 1.6
DAMS WITH STILLBORN PUPS	N(%)	1(4.0)	4(16.7)	3(13.0)	1(4.2)
DAMS WITH NO LIVEBORN PUPS	N	0	0	0	0
GESTATION INDEX g	%	100.0	100.0	100.0	100.0
	N/N	25/ 25	25/ 25	23/ 23	24/ 24
DAMS WITH ALL PUPS DYING DAYS 1-4 POSTPARTUM	N	0	0	0	0
DAMS WITH ALL PUPS DYING DAYS 5-21 POSTPARTUM	N	0	0	0	0

a. Dosage occurred on day 7 of gestation through day 20 of lactation.
b. Number of live pups/number of implantation sites.
c. Totaled value per group.
d. Excludes values for dam 2062; the number of pups exceeded the number of implantation sites.
e. Mean value per litter.
f. Calculated as the time (in days) elapsed between confirmed mating (arbitrarily defined as 0 hour) and the time (in days) the first pup was delivered.
g. Number of rats with live offspring/number of pregnant rats.

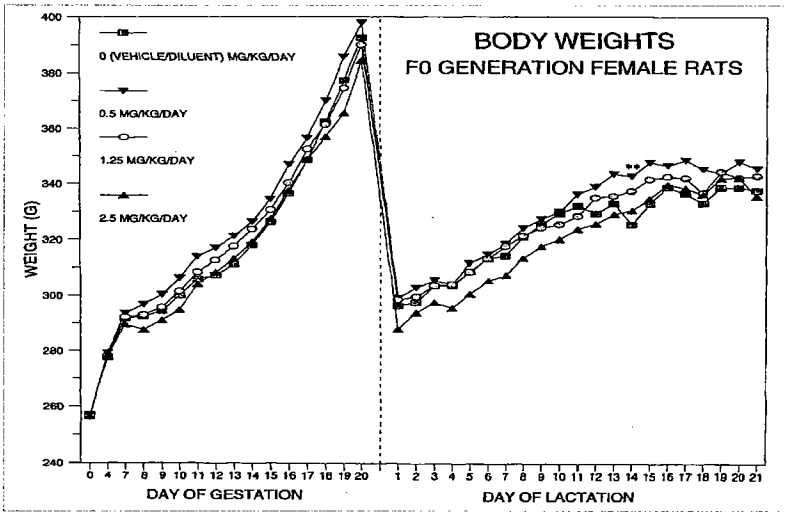
Prenatal and postnatal development including maternal function in rats with intravenous treatment – results in F_0 females [R087-TX-091]

Daily Dose (mg/kg)		0	0.5	1.25	2.5
Number Pregnant		25	25	23	24
F_0 Females:					
Gestation Food Consumption (g/day):					
	GD7-10	22.1	21.9	19.6**	18.0**
	GD18-20	23.4	24.3	22.2	21.1*
	GD0-20	22.6	23.1	22.1	21.4*
Lactation Food Consumption (g/day):					
	LD7-10	58.1	55.9	54.5	51.1**
	LD10-14	64.5	67.4	64.5	59.6*
	LD18-21	83.0	75.4*	79.9	74.8*
	LD1-21	60.8	59.3	59.3	56.2
Mean Duration of Gestation (days):		22.6	22.6	22.8	22.8

GD = Gestation day. LD = Lactation day. NA = Not applicable.
Dunnett's Test: * - P<0.05 ** - p<0.01.

F_0 necropsy:

- No gross lesions at necropsy
- No notable change in delivery indices, duration of gestation, number of implantation sites delivered per litter, dams with stillborn pups , gestation index, pups delivered, pups stillborn, pups surviving (LD 1, 4, 7, 14 and 21) and live pup weight and sex ratio
- No dam had all stillborn pups or lost the entire litter



PK parameters in dams treated with YM087 IV and evaluated on GD 7 and LD 20

Summary Toxicokinetic Parameters of YM087 (free base) in Rats

Dose Level (mg/kg/day)	Group	Day	C_{max} (ng/mL)	T_{max} (hours)	$AUC_{0\text{-}4hr}$ (ng·hr/mL)	$AUC_{0\text{-}24hr}$ (ng·hr/mL)
0.5	2	7	156	0.0833	229	317
1.25	3	7	459	0.0833	730	1810
2.5	4	7	933	0.0833	1686	3803
0.5	2	20	131	0.0833	132	203
1.25	3	20	372	0.0833	412	541
2.5	4	20	693	0.0833	1113	1582

Note: $AUC_{0\text{-}4}$ is equivalent to $AUC_{0\text{-}t}$.

Safety margins in humans:

Reprotoxicity Study	Dose, mg/kg/d	AUC_{0-24}, ng.h/ml	Safety margins (based on AUC animal/human)
Pre-and postnatal rat study with IV Conivaptan in PG/EtOH	0.5 *	203	0.056
	1.25	541	0.15
	2.5	1582	0.44
Human Therapeutic dose, 20 mg IV bolus plus 40 mg IV infusion for 4 days		3580	

* NOAEL dose

F_1 physical development:

- No notable clinical findings in pups that could be attributed to treatment at doses up to 2.5 mg/kg/d were reported
- The number of dead pups (cannibalized) was significantly increased and viability and weaning indices were decreased at 2.5 mg/kg/d.
- The viability and weaning indices per litter were reduced in groups from HD dams.
- Pup BW in the HD group were lower at several time points (DL4, 7, 14 and 21).
- The BW of F1 males were lower than control until sacrifice.

PROTOCOL 125-015: STUDY FOR EFFECTS OF YM087 ON PRENATAL AND POSTNATAL DEVELOPMENT IN RATS BY INTRAVENOUS INJECTION, INCLUDING MATERNAL FUNCTION

TABLE B9 (PAGE 1): LITTER OBSERVATIONS (NATURALLY DELIVERED PUPS) - SUMMARY - F1 GENERATION LITTERS

MATERNAL DOSAGE GROUP		I	II	III	IV
MATERNAL DOSAGE (MG/KG/DAY)a		0 (VEHICLE/DILUENT)	0.5	1.25	2.5
DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS	N	25	25	23	24
PUPS DELIVERED (TOTAL)	N	386	387	325b	373
	MEAN±S.D.	15.4 ± 2.2	15.5 ± 2.2	14.8 ± 1.6b	15.5 ± 1.7
LIVEBORN	MEAN±S.D.	15.4 ± 2.2	15.0 ± 2.9	14.5 ± 1.6b	15.4 ± 1.9
	N(%)	385(99.7)	376(97.2)**	320(98.5)b	371(99.5)
STILLBORN INDEX c	MEAN±S.D.	0.0 ± 0.2	0.3 ± 0.8	0.2 ± 0.5b	0.1 ± 0.4
	N(%)	1(0.2)	8(2.1)	4(1.2)b	2(0.5)
UNKNOWN VITAL STATUS d	N	0	3	1	0
PUPS FOUND DEAD OR PRESUMED CANNIBALIZED					
DAY 1	N/N(%)	0/385(0.0)	1/376(0.3)	1/320(0.3)b	3/371(0.8)
DAYS 2- 4	N/N(%)	4/385(1.0)	15/375(4.0)**	9/337(2.7)	19/368(5.2)**
DAYS 5- 7	N/N(%)	1/381(0.3)	3/360(0.8)	1/328(0.3)	11/349(3.2)**
DAYS 8-14	N/N(%)	1/380(0.3)	2/357(0.6)	0/327(0.0)	2/338(0.6)
DAYS 15-21	N/N(%)	0/379(0.0)	1/355(0.3)	1/327(0.3)	3/336(0.9)
VIABILITY INDEX e,f	%	99.0	95.7**	96.9b	94.1**
	N/N	381/385	360/376	310/320b	349/371
VIABILITY INDEX e,g	MEAN±S.D.	99.0 ± 2.3	95.0 ± 9.2	97.1 ± 5.4b	94.2 ± 12.1
WEANING INDEX f,h	%	99.5	98.3	99.4	95.4**
	N/N	379/381	354/360	326/328	333/349
WEANING INDEX g,h	MEAN±S.D.	99.5 ± 1.6	98.6 ± 3.2	99.5 ± 1.8	94.4 ± 16.5

DAY(S) = DAY(S) POSTPARTUM
a. Dosage occurred on day 7 of gestation through day 20 of lactation.
b. Excludes values for litter 2057; four additional pups were delivered on day 2 of lactation.
c. Number of stillborn pups/number of liveborn pups.
d. Maternal cannibalization or autolysis precluded identification of vital status at birth.
e. Number of live pups on day 4 postpartum/number of liveborn pups on day 1 postpartum.
f. Totaled value per group.
g. Mean value per litter.
h. Number of live pups on day 21 postpartum/number of live pups on day 4 postpartum.
** Significantly different from the vehicle control group value ($p \leq 0.01$).

F_1 behavioral evaluation:

- BW of F1 during post weaning period was lower in the HD group, however it was not significantly different from control during gestation
- Pups in the 2.5 mg/kg/d dose group had delayed reflex development (surface righting, acoustic startle, turning on an inclined plane and air righting).
- No treatment effect on motor activity or passive avoidance at any dose.

Prenatal and postnatal development including maternal function in rats with intravenous treatment – results in F_1 litters [R087-TX-091]

Daily Dose (mg/kg)		0	0.5	1.25	2.5
Number of Litters Evaluated		25	25	23	24
% Viability Index (Totaled value per group) [a]		99.0	95.7^{++}	96.9 [b]	94.1^{++}
% Weaning Index (Totaled value per group) [c]		99.5	98.3	99.4	95.4^{++}
Mean Body weight (g):	LD1	6.3	6.3	6.3	6.1
	LD4	8.7	8.6	8.5	8.0**
	LD7	12.2	12.2	12.1	10.9**
	LD14	22.9	23.7	22.9	20.1**
	LD21	35.7	36.8	35.5	32.1*
Pups Necropsy Observations (scheduled)		-	-	-	-
No Milk in Stomach (unscheduled) [d]		0/(1+2)	2/(5+7)	3/(4+5)	9/(1+23)
Reflex and Physical Development					
Surface Righting [e] (%):	LD6	74.0	73.3	71.5	56.4^{++}
	LD11	100.0	99.5	100.0	96.3^{++}
	LD13	100.0	100.0	100.0	100.0
Inclined Plane [e] (%):	LD10	81.5	80.5	74.6	65.8^{-}
	LD15	100.0	100.0	100.0	100.0
Acoustic Startle [e] (%):	LD14	98.3	87.8^{+}	92.3	79.4^{++}
	LD16	100.0	100.0	100.0	97.0^{++}
	LD17	100.0	100.0	100.0	97.6^{-}
	LD20	100.0	100.0	100.0	100.0
Air Righting [e] (%):	LD17	67.3	59.8	59.6	47.1^{++}
	LD21	99.0	96.3	96.7	94.1

- No noteworthy findings. LD = Lactation day. Dunnett's Test: * - P<0.05 ** - p<0.01.
Kruskal-Wallis Test and Dunn's Test: $^{+}$ - P<0.05 $^{++}$ - p<0.01.

a - (Number of live pups on LD4/numbe of liveborn pups on LD1) x 100.
b - Excludes values for one litter; four additional pups were delivered on day 2 of lactation.
c - (Number of live pups on LD21/number of live pups on LD4) x 100.
d - Number of pups affected/(number of stillborns + number of pups found dead).
e - Mean % of pups meeting the criterion for the developmental landmark tested on each day postpartum.

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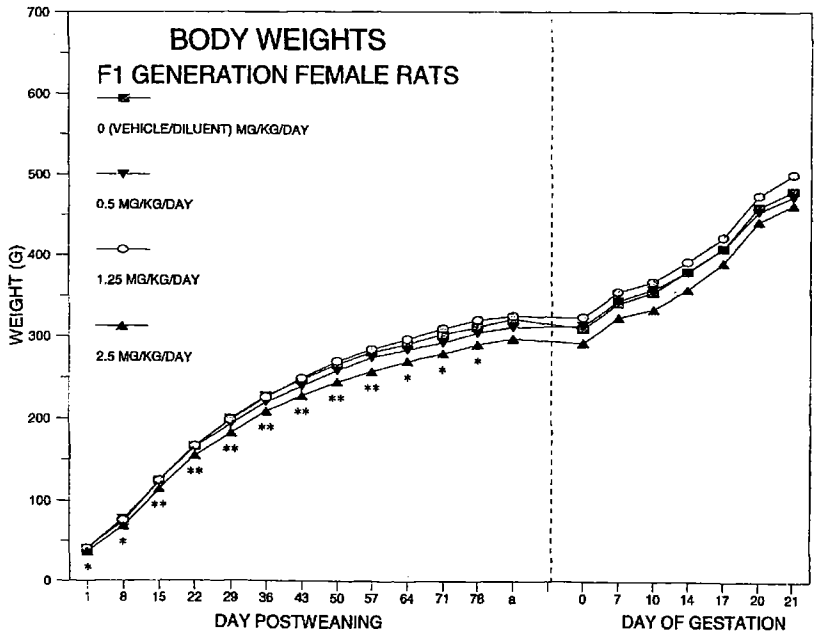
TABLE B11 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - F1 GENERATION PUPS

MATERNAL DOSAGE GROUP		I	II	III	IV
MATERNAL DOSAGE (MG/KG		0 (VEHICLE/DILUENT)	0.5	1.25	2.5
LITTERS EXAMINED	N	25	25	23	24
TOTAL UNSCHEDULED NECROPSIES b,c	N	3	12	9	24
STILLBORN	N	1	5	4	1
FOUND DEAD	N	2	7	5	23
NO MILK IN STOMACH d	N(%)	0(0.0)	2(16.7)	3(33.3)	9(37.5)
SCHEDULED PUP NECROPSIES ON DAYS 21 POSTPARTUM c					
LITTERS EVALUATED	N	25	25	23	24
PUPS EVALUATED	N	329	304	280	285
APPEARED NORMAL					
LITTER INCIDENCE	N(%)	25(100.0)	25(100.0)	23(100.0)	24(100.0)
PUP INCIDENCE	N(%)	329(100.0)	304(100.0)	280(100.0)	285(100.0)

a. Dosage occurred on day 7 of gestation through day 20 of lactation.
b. Restricted to pups in which complete necropsies were performed. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded evaluation.
c. Refer to the individual pup clinical observation table (Table B24) for external observations confirmed at necropsy.
d. Analysis restricted to pups found dead and necropsied.



F_1 reproduction:

- Significant decrease in implantation loss at 1.25 and 2.5 mg/kg/d.
- No other drug-related findings were noted.

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TABLE C17 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY - F1 GENERATION FEMALE RATS

MATERNAL DOSAGE GROUP		I	II	III	IV
MATERNAL DOSAGE (MG/KG/DAY)		0 (VEHICLE/DILUENT)	0.5	1.25	2.5
RATS TESTED	N	25	24a	23	23b
PREGNANT	N(%)	21(84.0)	20(83.3)	18(78.3)	19(82.6)
PREMATURELY DELIVERED	N(%)	0(0.0)	0(0.0)	1(5.6)	0(0.0)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 21 OF GESTATION	N	21	20	17c	19
CORPORA LUTEA	MEAN±S.D.	19.3 ± 4.3	17.4 ± 2.4	19.4 ± 3.2	17.3 ± 3.3
IMPLANTATIONS	MEAN±S.D.	15.5 ± 2.9	14.0 ± 4.6	16.6 ± 2.9	15.0 ± 2.1
LITTER SIZES	MEAN±S.D.	14.8 ± 2.9	13.5 ± 4.8	15.6 ± 2.7	14.3 ± 1.9
LIVE FETUSES	N	312	270	266	272
	MEAN±S.D.	14.8 ± 2.9	13.5 ± 4.8	15.6 ± 2.7	14.3 ± 1.9
DEAD FETUSES	N	0	0	0	0
FETAL MORTALITY d	N/N	0/325	0/281	0/282	0/286
	(%)	(0.0)	(0.0)	(0.0)	(0.0)
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
RESORPTIONS	MEAN±S.D.	0.6 ± 0.7	0.6 ± 0.8	0.9 ± 1.2	0.7 ± 0.8
EARLY RESORPTIONS	N	13	11	16	14
	MEAN±S.D.	0.6 ± 0.7	0.6 ± 0.8	0.9 ± 1.2	0.7 ± 0.8
LATE RESORPTIONS	N	0	0	0	0
DAMS WITH ANY RESORPTIONS	N(%)	10(47.6)	8(40.0)	9(52.9)	10(52.6)
DAMS WITH ALL CONCEPTUSES RESORBED	N(%)	0(0.0)	1(5.0)	0(0.0)	0(0.0)

a. Excludes values for rat 5828, which was missing on day 1 postweaning.
b. Excludes values for rat 5894, which had an accidental death on day 8 postweaning (caught in feeder when cage was closed).
c. Excludes values for dam 5864, which prematurely delivered on day 21 of gestation.
d. Number of dead fetuses/number of implantations.

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TABLE C17 (PAGE 2): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY - F1 GENERATION FEMALE RATS

MATERNAL DOSAGE GROUP		I	II	III	IV
MATERNAL DOSAGE (MG/KG/DAY)		0 (VEHICLE/DILUENT)	0.5	1.25	2.5
RATS TESTED	N	25	24a	23	23b
PREGNANT	N(%)	21(84.0)	20(83.3)	18(78.3)	19(82.6)
PREMATURELY DELIVERED	N(%)	0(0.0)	0(0.0)	1(5.6)	0(0.0)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 21 OF GESTATION	N	21	20	17c	19
DAMS WITH VIABLE FETUSES	N(%)	21(100.0)	19(95.0)	17(100.0)	19(100.0)
PLACENTAE APPEARED NORMAL d	N(%)	21(100.0)	19(100.0)	17(100.0)	19(100.0)
PREIMPLANTATION LOSS e	N/N	80/405	67/348	47/329**	42/328**
	(%)	(19.8)	(19.2)	(14.3)	(12.8)
PREIMPLANTATION LOSS f	MEAN±S.D.	17.4 ± 18.3	18.9 ± 27.1	13.9 ± 11.7	11.2 ± 12.8

PREIMPLANTATION LOSS = (NUMBER OF CORPORA LUTEA - NUMBER OF IMPLANTATIONS)/NUMBER OF CORPORA LUTEA X 100
a. Excludes values for rat 5828, which was missing on day 1 postweaning.
b. Excludes values for rat 5894, which had an accidental death on day 8 postweaning (caught in feeder when cage was closed).
c. Excludes values for dam 5864, which prematurely delivered on day 21 of gestation.
d. Excludes dams with all early resorptions.
e. Totaled value per group.
f. Mean value per litter.
** Significantly different from the vehicle control group value ($p \leq 0.01$).

F_2 findings:

- There were no notable drug-related findings in F2 generation.

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TABLE C18 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY - F2 GENERATION LITTERS

MATERNAL DOSAGE GROUP		I	II	III	IV
MATERNAL DOSAGE (MG/KG/DAY)		0 (VEHICLE/DILUENT)	0.5	1.25	2.5
LITTERS WITH ONE OR MORE LIVE FETUSES	N	21	19	17a	19
IMPLANTATIONS	MEAN±S.D.	15.5 ± 2.9	14.7 ± 3.6	16.6 ± 2.9	15.0 ± 2.1
LIVE FETUSES	N	312	270	266	272
	MEAN±S.D.	14.8 ± 2.9	14.2 ± 3.7	15.6 ± 2.7	14.3 ± 1.9
LIVE MALE FETUSES	N	142	136	129	126
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	46.2 ± 14.9	52.0 ± 19.5	48.2 ± 12.0	47.4 ± 15.3
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	5.20 ± 0.32	5.36 ± 0.33	5.26 ± 0.29	5.25 ± 0.41
MALE FETUSES	MEAN±S.D.	5.32 ± 0.38	5.50 ± 0.34	5.41 ± 0.31	5.41 ± 0.39
FEMALE FETUSES	MEAN±S.D.	5.11 ± 0.33	5.17 ± 0.29 [18]b	5.12 ± 0.28	5.11 ± 0.49
% RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	4.1 ± 4.9	3.7 ± 6.0	5.3 ± 6.6	4.7 ± 5.3

[ ] = NUMBER OF VALUES AVERAGED
a. Excludes values for dam 5864, which prematurely delivered on day 21 of gestation.
b. Litter 5841 had no female fetuses.

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Special Reproductive toxicity studies:

The sponsor had also performed several mechanistic studies in rats to determine the effect of conivaptan on reproductive hormones during different stages of pregnancy. Summary of the reproductive mechanistic studies are shown in the tabulated summary section.
The effect of single or 7 daily multiple oral dose of conivaptan at 100 mg/kg/d was examined in in female rats. The plasma levels of prolactin, luteinizing hormone (LH), follicular stimulating hormone (FSH), progesterone, estradiol-17β and arginine vasopressin (AVP) were measured. Progesterone level at 3 hours after dosing was 204.8 ng/ml (Cmax 296.4 ng/ml) at 6 hr on day 1, nearly 20 times higher than that of the control. After multiple oral doses progesterone level reached a maximum value of 236.6 ng/ml at 12 hours after dosing on Day 7 suggesting that conivaptan was potent inducer of progesterone release in female SD rats. Plasma AVP level also showed similar pattern of the change to progesterone. Plasma AVP level also increased on Day 7 with a peak value nearly 23 time that of control. There were no changes in plasma LH, FSH, prolactin or estradiol-17β.
When lower doses of conivaptan (3 and 10 mg/kg single dose, po) were administered in another study, plasma progesterone level increased by 4 fold higher than control (normal) at 3 hours at 3 mg/kg/d and 12 time higher at 10 mg/kg/d suggesting that conivaptan increased plasma progesterone in a dose-dependent manner. After 3 mg/kg/d, the plasma progesterone levels returned to normal (control levels) within 6 hrs, however in the 10 mg/kg/d dose group, progesterone levels were elevated at 12 hr but retuned to normal at 24 hrs. Both these studies suggest that conivaptan is a potent inducer of progesterone release in rats and thus may interfere with maintenance of pregnancy.

The sponsor had also examined the effect of single oral dose of conivaptan on ovariectomized, adrenoectomized and ovari-adrenoectomized female rats. In intact females, progesterone levels were significantly increased as noted previously (20 fold at 6 hrs post dose) and declined but it was still high at 12 hrs post dose. ACTH levels were also higher than that noted in controls (without treatment) at 3 and 6 hrs. Corticosterone levels were higher than control but not statistically. It is possible that conivaptan had suppressed the increase in corticosterone from adrenal cortex, since ACTH release should have speeded the release of corticosterone from adrenal cortex. Since the progesterone levels were markedly increased in ovariectomized rats but not in adrenoectomized female rats suggest that increase in plasma progesterone induced by conivaptan comes from adrenal glands. In the mass balance and toxicology studies, adrenal glands had high concentration of the administered conivaptan dose and were generally hypertrophied. All together they point out to a significant conivaptan interaction (receptor binding, accumulation) with adrenal gland.

The sponsor also evaluated the effect of conivaptan on Brattleboro and Long-Evans female rats to find whether the conivaptan induced increase in plasma progesterone is via AVP receptors since Brattleboro rats lack ability to synthesize AVP. Conivaptan at 30 mg/kg dose prolonged the diestrus period in both Brattleboro and long-Evans rats. In a similar study, plasma progesterone levels increased with increasing dose in both Brattleboro and Long-Evans rats, however, the increase in progesterone in Long-Evans rats was 4.6 fold higher than Brattleboro rats at 100 mg/kg. Since conivaptan did increase progesterone levels in both rats although some what less in Brattleboro rats lacking AVP, suggests that AVP may play a role in progesterone response but not solely dependent on AVP.

2.6.6.7 Local tolerance

Dermal
The dermal effect of conivaptan was tested in rabbits. A 0.5 g powder conivaptan hydrochloride was directly applied to the clipped clean dorsal skin of 3 female New Zealand White rabbits for 4 hrs. The drug exposed area was evaluated at 1, 24, 48 and 72 hours after patch removal. There was no notable dermal response at the test site of any animal during the 72-hour observation period.

Intramuscular:
The intramuscular irritation potential of the IV formulation at 0.5 mg/ml vs. vehicle was evaluated in rabbits after giving a single 1 ml intramuscular injection in the lateral muscle of the left hind leg. Two concentrations of acetic acid (0.425% and 1.7%) were used as positive controls to elicit both mild and severe pathologic changes. Physiologic saline was injected in the right hind leg of each rabbit to serve as a negative control. Animals were examined daily for clinical signs. Two and 14 days after IM administration, 3 animals in each group were euthanatized and examined for local irritation and microscopic changes at the injection sites.

There were no observed clinical signs after IM injections of YM087. However, at necropsy on Day 2, dark red lesions from 1 to 22 mm were noted at almost all injection sites in animals given saline, vehicle, or YM087. On Day 14, gross pathologic changes similar to those seen on Day 2 were noted in positive controls, but such changes were absent in other groups. Microscopic changes observed at a similar incidence and severity in controls and YM087-treated animals included muscle fiber necrosis/ regeneration, fibroblast proliferation, and inflammatory cell infiltrates. In chronic toxicology studies, IM injection of YM087 has consistently produced local injection site lesions.

Intravascular injections:
The IV formulation of YM087 at 0.5 mg/ml in PG/EtOH , vehicle, or a positive control (5% bromosulfophthalein sodium) were injected into 3 rabbits (0.05 ml) once daily for 8 days (posterior auricular veins). In the opposite ear, each rabbit received an IV injection of 0.05 ml physiologic saline as a negative control. Blood flow at injection sites was interrupted for 3 minutes to maintain the dosing solution at the injection site.
Rabbits treated with positive control had dark red area at the injection site on from Day 2 through 6 with auricular swelling and non-obstructive thrombus was noted on Days 5 and 6. Dosing was discontinued due to obstructive thrombosis on noted Day 7 on positive controls. Histopathological evaluation revealed vascular changes such as obstructive thrombosis, endothelial loss or necrosis, and changes in the perivascular region such as hemorrhage, edema, and inflammation and fibroblast proliferation in all positive controls. In contrast to positive controls, there were no drug-related gross pathologic or histopathological changes at IV injection sites in conivaptan group. Redness around the injection site or the vessel was observed in either one or both ears of all rabbits between Days 2 and 8. There were no histological findings at conivaptan injection sites.

Ocular:
Two studies were performed. In the first study, a single dose of 100 mg of YM087 was instilled in the left eye of 6 rabbits for 10 seconds. Primary ocular irritation was evaluated at 1 and 2

hours, and 1, 2, 3, 4, and 8 days post treatment. All animals in the non-flushed group had minimal conjunctival redness, chemosis and discharge, and iris hyperemia up to 2 hours after drag exposure. There were no effects on the cornea. No changes were observed after Day 1. In the flushed group, there were no ocular abnormalities. In a second study, 100 µL of an IV formulation of 0.5 mg/ml of YM087 in lactate and glycerin or vehicle alone was instilled in the left eye of 6 rabbits. Again, there were no notable abnormalities in any of the drug-treated eyes.

2.6.6.8 Special toxicology studies

Anaphylaxis:
Guinea pigs were sensitized by 3 subcutaneous injections of YM087 in Freund's complete adjuvant at 0.05 or 1 mg at 1-week intervals. A separate group of animals received cephalothin sodium (CET, 10 mg, positive control). Twelve days after final sensitization, animal serum samples were obtained for passive cutaneous anaphylaxis (PCA). Four untreated guinea pigs were injected intradermally with sera from YM087-treated animals. 24 hrs later, 2 of the 4 animals were injected IV with YM087. The 2 other animals received YM087 with guinea pig serum albumin (GPSA). All IV injection solutions included 1% (w/v) Evans blue stain. After 1 hour, the skin around the injection site was examined for chromogenic plaque formation and plaque size. Active systemic anaphylaxis (ASA) was not observed in any of the YM087-sensitized guinea pigs, YM087 did not elicit passive cutaneous anaphylaxis. No antibody to YM087 was detected. CET-treated guinea pigs had a positive ASA response and a positive PSA reaction.

Hemolysis Studies
When the compatibility of an YM087 intravenous formulation of YM087 or vehicle (contained glycerin) with human blood was performed, hemolysis was noted in both the IV formulation of YM087 (0.5 mg/ml) and vehicle solution. However, no hemolysis was present in the lactate or physiologic saline solutions. Since hemolysis was present in the glycerin and water solutions as well, glycerin was identified as the cause of hemolysis in the vehicle solution. In the second test, when glycerin was removed from the IV formulation, no hemolysis was observed in the IV formulation of YM087 at 0.05 mg/ml, suggesting that YM087 was compatible with human blood at 0.05 mg/ml and was not the cause of hemolysis. Both glycerin and PG/EtOH (1 mg/ml) formulations caused hemolysis when mixed with human blood at 10:1 but not at 1:10.

Colony Forming Unit (CFU) Assay using rat bone marrow cells (E087-TX-098):
The effect of conivaptan hydrochloride (lot #BC0874Z, [redacted] purity) on the differential proliferation/viability of hemopoietic precursor cells obtained from femur bone of female Fisher rats [redacted] were examined. The concentrations of conivaptan used in [redacted] studies were 1, 2.5, 5, 10, 25, 50 and 100 µg/ml). Doxorubicin served as positive control (25 ng/ml).
In these assays, all colonies showed a dose-dependent decrease in percentage viability. At drug

[redacted]

[redacted]

These results suggest that YM087 has a differential proliferation inhibition or lethal effect as a direct effect on rat hemopoietic precursor cells. The dose-response curves suggest that neutrophil and macrophage colonies have a similar concentration-dependent decrease in response. Decrease in response in erythrocyte colonies occurred at a higher drug exposure levels than neutrophil and macrophage colonies. Differential proliferation inhibition effect of conivaptan was stronger on leukocytic series of cells than on erythrocytic series of cells.

Table 11. LD_{50} of YM087 in rat [redacted] assay

	[redacted] assay (μg/mL)	[redacted] assay, Neutrophil (μg/mL)	[redacted] assay, Macrophage (μg/mL)
First assay	[redacted]	[redacted]	[redacted]
Second assay			
Third assay			
Fourth assay			
Fifth assay			
Mean	30.7	12.9	11.3

–: Not done

Colony Forming Unit (CFU) Assay using dog bone marrow cells (E987-TX-098):
The effect of conivaptan (lot #BC0874Z, [redacted] purity) on the differential proliferation/viability of hemopoietic precursor cells obtained from iliac bone of female beagle dogs [redacted] were examined. Similar to the rat study, the concentrations of conivaptan used in CFU-erythroid (CFU-E) and CFU-granulocyte/macrophage (CFU-GM) studies were 1, 2.5, 5, 10, 25, 50 and 100 μg/ml). Doxorubicin served as positive control (25 ng/ml).

In these assays, all colonies showed a dose-dependent decrease in percentage viability. Precipitation was noticed when the drug solution was added to the CFU-E medium at concentration ≥ 25 mg/ml and in CFU-MG medium at ≥ 5μg/ml. At drug concentrations of 10 μg/ml, the percent viability of erythroblast colonies was 77% of the solvent control. At 50 μg/ml, few erythroblast colonies were formed (0.6%). In the neutrophil colonies, percent viability decreased at 5 μg/ml (66.6% of control). At 25 μg/ml (2.8% of control) there were nearly no cell viability. In the macrophage colonies, the percent viability was 76.1% at 10 μg/ml, with no colonies present at 50 μg/ml.. The percent viability with positive control for erythrocyte, neutrophil and macrophage colonies were 64.5%, 69.1% and 63%, respectively. LD50 was estimated to be 10 to 20 μg/ml for erythroblast, neutrophil and macrophage colonies. The concentration was similar to Cmax in animal oral gavage myelotoxicity observed in the 13 and 52 wk dog study.
The results indicate that the numbers of erythroblast colonies, neutrophil colonies, and macrophage colonies showed a concentration-dependent decrease at exposure concentrations of 5μg/ml or more. LD50 of conivaptan which causes the colony count to decrease to 50% of the solvent control value, was estimated to be 10-20 μg/ml for the three kinds of colonies. This CFU assay using dog bone marrow suggest that conivaptan has a differential proliferation inhibition or lethal effect as a direct effect on dog hemopoietic precursor cells.

2.6.6.9 Discussion and Conclusions

Marked aquaresis mediated via the V_2 receptor was commonly observed in toxicology studies with conivaptan in mice, rats and dogs. Decreased body weight in repeat dose studies can be attributed to the increased water consumption, decreased food consumption and increased urine output in these animals. Kidney, bone marrow and liver were the main target organs of toxicity in addition to injection site inflammation with intravenous administration. Distribution studies indicate that these organs along with adrenal gland have significant exposures to conivaptan.

Kidney toxicity including renal tubular degeneration/regeneration, fibrosis and edema which may also be contributed to the diuretic effects of conivaptan. The kidney changes are considered secondary to aquaresis since these findings are reported with diuretics of different classes as reported in literature according to the sponsor. These renal tubular degeneration was observed in rats given 30 mg/kg for 1 week IV (4X therapeutic exposure) and 100 mg/kg for 26 weeks orally (13X therapeutic exposure) and this addition to fibrosis and renal edema were observed in dogs given 20 mg/kg (>100X clinical exposure) by IV infusion for 4 weeks. This would suggest some possibility of renal tubular degeneration in a clinical setting. However the patient population is likely to have underlying renal pathology.

Bone marrow changes occurred in dogs at exposures ≥ 164 μg h/ml with oral or ≥ 173 μg h/ml intravenous administration (2-, 13- ,52- oral and 4-week bolus/infusion IV studies) at exposures >40X therapeutic systemic exposure. However following 1 week of IV treatment bone marrow toxicity was not observed even though conivaptan systemic exposure exceeded 526 μg h/ml suggesting that high sustained exposures were needed to elicit this lesion for more than one week. The bone marrow changes (focal/multifocal necrosis/degeneration, decreased erythrobastic islands, myeloid hyperplasia, hypocellularity, fibrosis) were reversible in dogs following a 6 week recovery after a 13 week oral study. Together this suggests limited potential for bone marrow effects in the clinical setting. The sponsor has suggested that these particular bone marrow findings are associated with vasoconstriction within the microcirculation mediated by inhibition of V_2 receptor vasodilation. However canine microvascular vasoconstriction in bone marrow has not been demonstrated.

Histopathological changes in the liver (elevated enzymes, bile duct hyperplasia, sinusoidal dilatation, hepatocyte hypertrophy, inflammation, jaundice) and elevated liver enzymes were observed in dogs following high exposure to conivaptan (≥173 μg h/ml or 40 X clinical exposure). 2-Week oral dog studies in males at 100 and 300 mg/kg showed jaundice, increased ALT< AST and ALT along with cholestasis/dilation of bile canaliculi, bile duct hyperplasia, sinusoidal dilatation and mononuclear cell and macrophage infiltration around the central vein. Slight increases in liver enzymes, hepatocellular hypertrophy and hepatocyte necrosis were observed in one week continuous infusion rat studies at exposures 60 μg h/ml (15X clinical exposure) this is the lowest exposure for these findings. Lower exposures of 24 μg h/ml resulted in slight elevations in ALT and AST only (6X clinical exposure). The NOAEL for hepatotoxicity are at >5X therapeutic exposure. These findings are clinically monitorable and are unlikely based on the limited clinical duration of use and minimal safety margins.

Note in the table below provided by the sponsor the clinical exposure is based on a 40 mg/day dose achieving an AUC=1378 ng h/ml which differs from the AUC=3580 ng h/ml used for

calculations in this review. The later AUC values is based on clinical studies in healthy volunteers given a 20 mg bolus IV dose on day 1 followed by IV infusion at 40 mg/day for 3 days since PK is unavailable from SIADH patients.

Table 2.4-1: Ratios of Systemic Exposures (AUC_{0-24}) in Laboratory Animals to Those in Humans

Animal Species	Dosing Route	Sampling time	Daily dose levels (mg/kg)		Exposure ratio (AUC_{0-24})† Male	Female
Repeat-Dose Toxicity						
Rat	po	13 weeks	1	NOAEL in males	<1	-
			3	NOAEL in females	-	<1
			3	LOAEL in males	<1	-
			10	LOAEL in females	-	<1
			100	HD	3.58	4.94
		26 weeks	1	NOAEL	<1	<1
			3	LOAEL	<1	<1
			100	HD	2.25	2.61
			100	HD in the additional study	3.29	-
	iv bolus	4 weeks	1.25	NOAEL	<1	<1
			2.5	HD and LOAEL	<1	<1
	iv infusion	4 weeks	10	NOAEL	<1	<1
			30	LOAEL	<1	1.95
			100	HD	<1	<1
Dog	po	13 weeks	10	NOAEL	2.98	2.68
			30	HD and LOAEL	8.27	9.65
		52 weeks	10	NOAEL	5.45	8.10
			20	HD and LOAEL	7.05	6.37
	iv bolus	4-weeks	2	NOAEL	<1	<1
			5	LOAEL	3.78	2.87
			10	HD	15.32	7.26
	iv infusion	4 weeks	10	NOAEL	9.97	8.72
			20	HD and LOAEL	38.14	21.38
Pregnant Animals						
Rat	po	GD17	1	NOAEL for dams	-	<1
			100	No teratogenicity	-	2.84
	iv	GD7	2.5	No teratogenicity	-	<1
Rabbit	po	GD18	6	No teratogenicity	-	<1
	iv	GD18	3	NOAEL for dams	-	<1
			12	No teratogenicity	-	1.99

† Exposure ratio relative to the human exposure (13.78 μg·hr/mL) at the RHD (40 mg/day) [R087-CL-027]. Data at the final determination in each animal study were used.
- No data exists. NOAEL: No observed adverse effect level.
LOAEL: Lowest observed adverse effect level. HD: Highest dose. GD: Gestation day.

Tissue distribution studies in rats show retention of conivaptan in testes. In the 4-week continuous IV infusion study in dogs, 2/3 males with deteriorating health given 20 mg/kg had mild-slight multi-focal degeneration of seminiferous tubules. Exposures in these dogs were >30X therapeutic exposure the NOAEL for the study provides a 3X safety margin relative to clinical exposures. This finding was not observed in a 1 week continuous IV infusion study in dogs at higher exposures. No changes in male fertility were observed in rat reprotoxicity studies at doses up to 2.5 mg/kg/day. The sponsor attributes this to poor health in these dogs. The rat distribution studies suggest testicular exposure to conivaptan are greater than plasma

exposure. Regardless the finding only occurs with relatively high, prolonged (>1 week) exposures.
Reprotoxicity studies demonstrate reversible prolongation of diestrus, decreased fertility and increased pre-/post-implantation loss which are attributed to the effects of conivaptan on steroidogenesis in the HPA axis (predominately adrenal). Conivaptan was not teratogenic in rats and rabbits when given to pregnant animals during organogenesis. Some delayed development and maternal toxicity were observed. Exposure for at least one week adversely affected parturition and maternal care leading to deteriorated growth/development of neonates. The sponsor attributes the delayed parturition and inhibition of lactation to antagonism of the oxytocin receptor. Conivaptan has a Ki ~ 44 nM for the oxytocin receptor. Oxytocin is also synthesized via a macromolecular precursor that is encoded by a gene located very near the AVP gene. Radiolabeled distribution studies in pregnant, lactating or suckling rats demonstrate placental and milk transfer of conivaptan to fetuses/neonates.

In pregnant rats given oral gavage conivaptan during organogenesis maternal toxicity, decreased fetal body weight and delayed ossification of sternebrae and vertebrae occurred at doses of 10 and 100 mg/kg. Similar early developmental studies in rabbits during organogenesis at 6 mg/kg by oral gavage or 12 mg/kg by IV were without fetal adverse effects. In oral pre and postnatal studies in rats maternal behavior and care were adversely affected resulting in increased neonatal mortality in dams given ≥0.3 mg/kg. Delayed parturition was observed at ≥10 mg/kg. In bolus IV postnatal rat studies adverse effects were not observed in maternal care but decreased neonatal viability, weaning indices, delayed growth/physical development and sexual maturation of offspring were observed at 2.5 mg/kg.

Reproductive studies have been performed by IV and oral routes in rats and rabbits. Fertility studies in male rats demonstrate no effect of conivaptan on fertility or reproductive performance. In female fertility studies rats had prolonged diestrus, decreased fertility and increased pre-/post-implantation loss at oral doses of ≥10 mg/kg/day and 2.5 mg/kg IV. Maternal toxicity (decreased body weight, clinical signs, mortality) was evident in pregnant rats dosed with 100 mg/kg oral conivaptan when given during organogenesis. Decreased body weight and delayed ossification of sternebrae and vertebrae were observed in fetuses from this group. The evidence of maternal toxicity (decreased food and body weight gain) occurs in the rabbit following oral gavage dosing at even the lowest dose 0.2 mg/kg/day during organogenesis. Conivaptan disrupts postnatal maternal behavior and care (e.g. pups scattered in cage, lack of nursing reflex) which results in neonatal mortality at ≥10 mg/kg/day. The sponsor reports underdevelopment of mammary gland lactation which may relate to oxytocin receptor interactions by conivaptan (K_i ~ 44 nM). An absence of milk in the stomach and decreased pup body temperature were observed at ≥10 mg/kg/day. The oral NOAEL for postnatal developmental effects appears to be 1 mg/kg/day. No effects on maternal gestation, delivery or nursing were noted in bolus IV rat studies up to 2.5 mg/kg but decreased pup viability, weaning indices, delayed growth/physical development including sexual maturation and delayed reflex development was observed at 2.5 mg/kg/day during pre- and postnatal administration to dams. Distribution studies in pregnant rats reveals placental (2-3X higher than maternal plasma levels) and milk transfer (maximal at 1 h post dose IV and reaches 2-3X higher than plasma levels) of conivaptan. Tissue levels in the fetuses <10% of maternal plasma concentrations but clearance was much slower (even after 24h post IV dose fetal levels were 39% of the Cmax) and accumulation in the fetus is possible.

Conivaptan was not mutagenic or carcinogenic in a series of studies designed to address this potential.

Special Pharmacology Studies:
Toxicology studies had found significant injection site lesions after intravenous administration of conivaptan IV formulation in PG/EtOH to rats and dogs, several special toxicology studies. To examine the effect of IV formulation, conivaptan at 0.5 mg/ml along with vehicle and a positive control were injected to rabbit ear vein. Except for redness around the injection site or the vessel in all rabbits between Days 2 and 8, there were no drug-related gross pathologic or histopathologic changes.

In the dermal irritation study, YM087 at 0.5 g did not induce dermal irritation when applied to intact rabbit skin. YM087 was nonirritating in rabbits given an intramuscular injection of 1 ml of a 0.5 mg/ml solution. At 100 mg YM087 induces ocular irritation in rabbits; flushing eyes immediately with physiological saline eliminated irritation. YM087 does not induce vascular irritation in rabbits given intravenous injections of 0.05 ml of a 0.5 mg/ml solution for 8 days. YM087 is compatible with human blood at 0.05 mg/ml and does not induce anaphylaxis in guinea pigs.

As noted earlier, the glycerin vehicle originally selected for IV formulation was replaced with PG/EtOH. Studies found both glycerin and PG/EtOH (1 mg/ml) formulations caused hemolysis when mixed with human blood at 10:1 but no at 1:10. Glycerin was identified as the cause of hemolysis in the vehicle solution in the early hemolysis assay. When glycerin was removed from the IV formulation, no hemolysis occurred with IV formulation of YM087 at 0.05 mg/ml, suggesting that YM087 was compatible with human blood at 0.05 mg/ml and was not the cause of hemolysis.

The sponsor had also examined the role of conivaptan on colony forming unit (CFU) cells isolated from rat and dogs bone marrow. In the rat bone marrow assay, conivaptan has a differential proliferation inhibition or lethal effect as a direct effect on rat hemopoietic precursor cells. The dose-response curves suggested that neutrophil and macrophage colonies had a similar concentration-dependent decrease in response. Decrease in response in erythrocyte colonies occurred at a higher drug exposure levels than neutrophil and macrophage colonies. Differential proliferation inhibition effect of conivaptan was stronger on leukocytic series of cells than on erythrocytic series of cells.
In dog CFU-assay, the numbers of erythroblast colonies, neutrophil colonies, and macrophage colonies showed a concentration-dependent decrease at exposure concentrations of 5μg/ml or more. LD_{50} of conivaptan which causes the colony count to decrease to 50% of the solvent control value, was estimated to be 10-20 μg/ml for the three kinds of colonies. This CFU assay using dog bone marrow suggest that conivaptan has a differential proliferation inhibition or lethal effect as a direct effect on dog hemopoietic precursor cells

2.6.6.10 Tables and Figures
Tables and figures were presented in each study.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Repeat Dose Oral and Intravenous Toxicology Studies:

2.6.7.7A Repeat-Dose Toxicity **Report Title:** 13-Week Oral Gavage Toxicity Study with YM087 in F-344 Rats with a 5-Week and a 10-Week Recovery **Test Article:** Conivaptan hydrochloride

Species/Strain: F344 Rat
Initial Age: 6 Weeks
Date of First Dose: 8 Apr 1994
Duration of Dosing: 13 Weeks
Duration of Postdose: 5 Weeks and 10 Weeks
Method of Administration: Gavage
Vehicle/Formulation: 0.5% Methylcellulose solution
Study No. R087-TX-005
GLP Compliance: Yes

Special Features: None
No Observed Adverse Effect Level: <3 mg/kg (male), 3mg/kg (female)

Daily Dose (mg/kg) / Number of Animals		0 (Control) M: 22	0 (Control) F: 22	3 M: 10	3 F: 10	10 M: 10	10 F: 10	30 M: 22	30 F: 22	100 M: 22	100 F: 22
Toxicokinetics:											
C_{max} (ng/mL):	Week 1 [a]	NA	NA	77.2	47.3	388	499	1853	2060	3577	4553
	Week 14	NA	NA	85.4	84.0	684	928	1593	2620	3667	5523
AUC_{0-24} (ng·hr/mL):	Week 1 [a]	NA	NA	268	372	2343	4988	12710	23320	43889	53579
	Week 14	NA	NA	545	549	4158	6131	18379	17762	49377	68110
Noteworthy Findings											
Died or Sacrificed Moribund		0	1 [b]	0	0	0	0	1 [b]	0	0	1 [b]
Clinical Observations		-	-	-	-	-	-	-	-	-	-
Body Weight (g):	Week 1	125.8	99.8	124.3	101.1	120.8	100.5	127.1	102.0	126.3	101.2
	Week 4	211.7	135.5	200.3	137.7	195.6*	136.5	207.0	139.4	200.8	136.9
	Week 9	264.5	160.7	246.8*	160.8	242.1*	162.1	249.4	167.3	243.8*	162.2
	Week 14	285.2	174.7	274.8	171.2	262.7*	175.4	271.0	178.8	265.2*	172.0
Cumulative Body Weight Gain (g):											
	Week 1	30.3	13.7	28.6	15.1	28.6	14.6	29.0	14.6	27.5	13.8
	Week 4	102.0	43.6	91.1*	42.3	86.9*	41.5	92.0*	43.3	88.5*	42.3
	Week 9	145.0	63.1	130.7*	60.8	127.5*	62.8	128.0*	67.4	124.7*	63.8
	Week 13	159.4	74.8	150.5	70.1	141.8	74.9	143.8	76.7	139.0*	70.8

- No noteworthy findings. NA = Not applicable.
Dunnett's Test: * - P<0.05
a - Data from Study No. R087-TX-112.
b - Accidental death.

Daily Dose (mg/kg) / Number of Animals	0 (Control) M: 22	0 (Control) F: 22	3 M: 10	3 F: 10	10 M: 10	10 F: 10	30 M: 22	30 F: 22	100 M: 22	100 F: 22
Food Consumption (g/animal/day):										
Week 1	15.1	11.9	15.0	12.3	14.9	12.1	15.2	12.2	15.1	11.7
Week 4	18.6	13.3	18.0	13.7	18.0	13.2	17.7	13.9	17.9	13.3
Week 9	19.3	13.8	18.8	13.8	17.5*	13.8	18.5	14.2	18.7	13.8
Week 14	16.7	12.6	17.7	13.0	16.2	12.7	16.8	13.0	16.8	12.2
Water Consumption (mL/animal/day):										
Week 4	21.0	22.2	86.6*	54.6*	159.3*	104.6*	176.3*	115.5*	165.4*	110.9*
Week 8	19.6	19.9	82.4*	63.2*	161.3*	122.7*	188.1*	133.5*	179.6*	125.5*
Week 12	18.9	16.7	95.4*	66.5*	147.8*	126.4*	176.4*	129.3*	172.5*	122.6*
Auditory evaluation: Negative response	0	0	0	0	0	0	0	0	0	1
Ophthalmoscopy	-	-	-	-	-	-	-	-	-	-
Hematology: Week 12										
Number Examined	10	10	10	10	10	10	10	10	10	10
RBC (10^6/µL)	8.75	7.92	8.77	7.83	8.66	7.84	8.52	7.93	8.68	7.84
Hemoglobin (g/dL)	15.0	14.6	15.2	14.5	15.3	14.6	15.1	14.7	15.0	14.4
PCV (%)	42.6	41.2	43.4	40.7	43.3	41.0	42.4	41.2	42.8	40.8
Platelet (10^3/µL)	670	659	683	603	650	558*	710	543*	804*	661
Reticulocyte (%)	0.0	1.0	0.1	1.1	0.2	0.8	0.0	1.0	0.1	1.2
Reticulocyte (10^3/µL)	4	82	12	84	15	60	0	79	7	92
WBC (10^3/µL)	4.6	3.2	4.5	3.5	5.0	3.4	4.6	3.6	4.9	3.8
Hematology: Week 14										
Number Examined	10	10	10	10	10	10	10	10	10	10
PT (sec)	16.4	16.2	17.0	16.5	17.1	17.0	17.6	16.5	17.0	16.4
APTT (sec)	17.9	17.2	20.0	16.5	19.6	18.0	19.4	16.4	19.6	15.8
Blood Chemistry: Week 12										
Number Examined	10	10	10	10	10	10	10	10	10	10
Glucose (mg/dL)	128	110	128	108	119	102	118	112	117	105
BUN (mg/dL)	15	16	19*	20	18*	18	18*	17	15	14
Creatinine (mg/dL)	0.7	0.7	0.6	0.7	0.6	0.6*	0.7	0.6	0.6	0.6
Total protein (g/dL)	6.7	6.4	6.4*	6.1*	6.5	5.8*	6.8	6.3	7.2*	6.8*

- No noteworthy findings.
Dunnett's Test: * - P<0.05
a - Number of animals

2.6.7.7.A Repeat-Dose Toxicity — Study No. R087-TX-005 (Continued)

Daily Dose (mg/kg)	0 (Control)		3		10		30		100	
Number of animals	M: 22	F: 22	M: 10	F: 10	M: 10	F: 10	M: 22	F: 22	M: 22	F: 22
Blood Chemistry: Week 12 (Continued)										
Albumin (g/dL)	4.5	4.5	4.4	4.3*	4.5	4.2*	4.7*	4.5	5.0*	4.9*
Globulin (g/dL)	2.1	1.9	2.0	1.8	2.0	1.7*	2.0	1.8	2.1	1.9
Total bilirubin (mg/dL)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Cholesterol (mg/dL)	54	89	52	82	54	67*	58	76*	60	92
AST (IU/L)	104	106	94	104	108	107	118	93	96	91
ALT (IU/L)	57	53	49*	45	58	42*	58	36*	53	43
ALP (IU/L)	101	78	100	76	100	81	90*	69	85*	66*
Calcium (mg/dL)	10.4	10.4	10.3	10.1	10.4	9.8*	10.3	10.3	10.6	10.5
Inorganic phosphorous (mg/dL)	7.6	6.4	7.6	6.5	8.1	7.5*	8.2	7.5*	8.0	7.4*
Sodium (mmol/L)	146	144	144*	141*	144*	141*	144	143	146	143
Potassium (mmol/L)	3.5	3.4	3.7	3.5	3.6	3.6	3.8	3.7	3.7	3.7
Chloride (mmol/L)	107	108	104*	106*	104*	105*	105	107	106	108
Protein electrophoresis										
Albumin (g/dL)	4.5	4.3	4.3	4.2	4.3	3.9*	4.7	4.4	4.8	4.6*
α-1 Globulin (g/dL)	0.2	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.2
α-2 Globulin (g/dL)	0.4	0.3	0.3	0.4	0.4	0.3	0.3	0.3	0.4	0.3
β Globulin (g/dL)	1.4	1.4	1.4	1.3	1.4	1.3	1.4	1.4	1.5	1.6*
γ Globulin (g/dL)	0.2	0.1	0.2	0.2	0.2	0.1	0.1	0.1	0.2	0.1
Triglyceride (mg/dL): Week 14	25	25	27	24	31	24	24	25	24	23
Urinalysis										
Number Examined	10	10	10	10	10	10	10	10	10	10
Volume (mL):										
Week 4 [a]	10.2	10.9	5.8	10.6	26.8*	6.4	32.8*	37.0*	50.3*	45.2*
Week 9 [a]	5.0	8.6	10.4	12.3	49.0*	35.1*	57.6*	35.5*	85.3*	36.2*
Week 12 [b]	4.0	1.8	15.3*	6.4*	30.7*	14.4*	58.6*	23.4*	94.3*	36.5*
8 hr Volume (mL):										
Week 12 [c]	1.4	0.4	64.1*	37.6*	86.9*	65.6*	89.8*	63.5*	84.7*	43.0*

- No noteworthy findings.
Dunnett's Test: * - P<0.05
a - 16-hour overnight collection.
b - 8-hour collection after dosing.
c - 16-hour collection following 8-hour collection.

Daily Dose (mg/kg)	0 (Control)		3		10		30		100	
Number of animals	M: 22	F: 22	M: 10	F: 10	M: 10	F: 10	M: 22	F: 22	M: 22	F: 22
Urinalysis (Continued)										
Osmolality (mOsm/kg):										
Week 4 [a]	509	361	452	235*	132*	402	149*	121*	104*	122*
Week 9 [a]	1510	1665	373*	276*	133*	122*	118*	138*	84*	122*
Week 12 [b]	1767	2288	329*	430*	209*	213*	116*	194*	90*	147*
pH:										
Week 4 [a]	7.3	7.1	6.8*	7.2	7.2	7.4	7.1	7.2	7.2	7.2
Week 9 [a]	7.1	7.2	7.6	7.5	7.4	7.2	7.6	7.4	7.5	7.4
Week 12 [b]	7.4	7.2	8.0*	8.1*	8.0	8.2*	7.5	8.0*	7.3	7.9*
Creatinine (mg/dL):										
Week 4 [a]	39.6	19.0	38.7	13.8	9.4	24.2	11.7	6.0	7.2	6.1
Week 9 [a]	122.4	87.5	34.9	18.6	10.0	7.1	9.1	8.9	6.4	8.3
Week 12 [b]	130.4	115.0	29.3	26.8	15.7	13.4	8.9	11.5	6.6	8.6
Sodium (mmol/L):										
Week 4 [a]	9	8	0	0	0	0	0	0	0	2
Week 9 [a]	64	85	4	0	0	0	0	0	0	0
Week 12 [b]	71	124	2	9	2	2	0	4	0	0
Potassium (mmol/L):										
Week 4 [a]	87	50	51	26	18	49	19	16	15	12
Week 9 [a]	240	270	36	28	17	14	15	16	9	12
Week 12 [b]	290	324	45	49	31	24	18	21	12	17
Chloride (mmol/L):										
Week 4 [a]	26	16	16	2	2	14	2	2	0	3
Week 9 [a]	95	119	2	0	0	0	0	0	0	0
Week 12 [b]	108	168	13	26	6	4	0	3	0	2

Dunnett's Test: * - P<0.05
a - 16-hour overnight collection.
b - 8-hour collection after dosing.

2.6.7.7A Repeat-Dose Toxicity Study No. R087-TX-005 (Continued)

Daily Dose (mg/kg)		0 (Control)		3		10		30		100	
Number of animals		M: 22	F: 22	M: 10	F: 10	M: 10	F: 10	M: 22	F: 22	M: 22	F: 22
Organ Weights (g)											
Adrenal:	Absolute (g)	0.0423	0.0480	0.0419	0.0480	0.0509*	0.0596*	0.0586*	0.0624*	0.0684*	0.0714*
	Relative (%)	0.0157	0.0300	0.0163	0.0305	0.0208*	0.0373*	0.0237*	0.0382*	0.0283*	0.0461*
Brain:	Absolute (g)	1.8474	1.7287	1.8327	1.7096	1.7990	1.7319	1.8450	1.7293	1.8117	1.6901
	Relative (%)	0.6820	1.0784	0.7143	1.0876	0.7389*	1.0841	0.7414*	1.0572	0.7493*	1.0913
Heart:	Absolute (g)	0.9082	0.6083	0.8343*	0.5682*	0.7992*	0.5603*	0.8488	0.5994	0.8313*	0.6105
	Relative (%)	0.3356	0.3791	0.3247	0.3609	0.3269	0.3505*	0.3394	0.3663	0.3436	0.3937
Kidney:	Absolute (g)	1.8609	1.2198	1.8228	1.1902	1.7015*	1.1908	1.8203	1.2102	1.8213	1.2254
	Relative (%)	0.6867	0.7605	0.7093	0.7567	0.6969	0.7449	0.7285*	0.7395	0.7523*	0.7897
Liver:	Absolute (g)	7.0547	4.3946	6.9829	4.4317	6.4705	4.3490	7.1060	4.8159*	8.0870*	5.7244*
	Relative (%)	2.6011	2.7398	2.7147*	2.8120	2.6476	2.7214	2.8356*	2.9414*	3.3440*	3.6963*
Lung:	Absolute (g)	1.0832	0.8134	1.0408	0.8123	1.0285	0.8578	1.0637	0.8274	1.0536	0.8703
	Relative (%)	0.3994	0.5072	0.4050	0.5165	0.4216	0.5384	0.4261	0.5055	0.4361*	0.5647
Ovary:	Absolute (g)	NA	0.0926	NA	0.1056	NA	0.0887	NA	0.0962	NA	0.0868
	Relative (%)	NA	0.0578	NA	0.0664	NA	0.0552	NA	0.0588	NA	0.0557
Pituitary:	Absolute (g)	0.0097	0.0133	0.0098	0.0127	0.0095	0.0117*	0.0097	0.0112*	0.0098	0.0110*
	Relative (%)	0.0036	0.0083	0.0038	0.0081	0.0039	0.0073*	0.0039	0.0069*	0.0041*	0.0071*
Prostate:	Absolute (g)	0.6530	NA	0.5139	NA	0.4168*	NA	0.5072	NA	0.4453*	NA
	Relative (%)	0.2412	NA	0.1998	NA	0.1711	NA	0.2017	NA	0.1825	NA
Spleen:	Absolute (g)	0.6117	0.4352	0.5750	0.4469	0.5854	0.4159	0.5509	0.4400	0.5616	0.4260
	Relative (%)	0.2256	0.2711	0.2236	0.2836	0.2395	0.2596	0.2203	0.2689	0.2320	0.2732
Submaxillary	Absolute (g)	0.5384	0.3705	0.5217	0.3629	0.5001	0.3640	0.5111	0.3678	0.5118	0.3787
salivary gland:	Relative (%)	0.1984	0.2311	0.2031	0.2306	0.2051	0.2285	0.2053	0.2246	0.2115	0.2437*
Testis:	Absolute (g)	2.9663	NA	2.9228	NA	2.8188*	NA	2.8803	NA	2.8379*	NA
	Relative (%)	1.0956	NA	1.1387	NA	1.1563	NA	1.1569	NA	1.1739	NA
Thymus:	Absolute (g)	0.2308	0.1942	0.2053	0.1885	0.1904*	0.1658	0.1975*	0.1898	0.1927*	0.1608*
	Relative (%)	0.0850	0.1211	0.0800	0.1195	0.0778	0.1037	0.0786	0.1159	0.0799	0.1030
Thyroid:	Absolute (g)	0.0138	0.0125	0.0131	0.0104	0.0160	0.0106	0.0143	0.0115	0.0164	0.0120
	Relative (%)	0.0051	0.0078	0.0051	0.0066	0.0065	0.0066	0.0058	0.0070	0.0068*	0.0077
Uterus:	Absolute (g)	NA	0.7306	NA	0.5973	NA	0.4160*	NA	0.4046*	NA	0.3519*
	Relative (%)	NA	0.4596	NA	0.3813	NA	0.2593*	NA	0.2472*	NA	0.2248*

NA = Not applicable.
Dunnett's Test: * - P<0.05

Daily Dose (mg/kg)		0 (Control)		3		10		30		100	
Number of Animals		M: 22	F: 22	M: 10	F: 10	M: 10	F: 10	M: 22	F: 22	M: 22	F: 22
Gross Pathology		-	-	-	-	-	-	-	-	-	-
Histopathology[a]											
Stage of estrus											
Proestrus		NA	0	NA	1	NA	5	NA	4	NA	7
Estrus		NA	6	NA	7	NA	0	NA	1	NA	1
Metestrus		NA	2	NA	0	NA	1	NA	0	NA	1
Diestrus		NA	2	NA	2	NA	4	NA	5	NA	1
Postdose Evaluation (Week 20 and 25)											
Number Evaluated		12	12	0	0	0	0	12	12	12	11
Noteworthy findings											
Died or Sacrificed Moribund		0	0	NA	NA	NA	NA	0	0	0	0
Body weight (g):	Week 20	322.9	181.8	NA	NA	NA	NA	289.1*	183.4	293.0*	180.9
	Week 25	322.4	180.9	NA	NA	NA	NA	300.5	173.4	298.8	177.9
Cumulative Body Weight gain (g):	Week 19	197.6	82.7	NA	NA	NA	NA	162.8*	81.8	167.0*	79.9
	Week 24	196.0	79.7	NA	NA	NA	NA	178.5	73.8	173.5	76.6
Food consumption (g/animal/day):	Week 19	16.9	12.2	NA	NA	NA	NA	16.3	12.4	16.9	11.8
	Week 24	16.5	12.2	NA	NA	NA	NA	16.4	11.5	16.1	12.0
Water consumption (mL/animal/day):	Week 16	20.1	16.7	NA	NA	NA	NA	18.3	18.8	22.9*	18.4
	Week 18	18.4	16.2	NA	NA	NA	NA	17.8	15.2	19.4	15.8
Clinical Observations		-	-	-	-	-	-	-	-	-	-

- No noteworthy findings. NA = Not applicable.
Dunnett's Test: * - P<0.05
a - Number of animals.

2.6.7.7A Repeat-Dose Toxicity Study No. R087-TX-005 (Continued)

Daily Dose (mg/kg)			0 (Control)		3		10		30		100	
Number of animals			M: 22	F: 22	M: 10	F: 10	M: 10	F: 10	M: 22	F: 22	M: 22	F: 22
Postdose Evaluation												
Blood Chemistry: Week 18												
Number Examined			6	6	0	0	0	0	6	6	6	5
Total protein (g/dL)			7.1	6.9	NA	NA	NA	NA	6.8	6.5*	7.1	6.6*
Albumin (g/dL)			4.6	4.4	NA	NA	NA	NA	4.4	4.2*	4.6	4.4
ALP (IU/L)			99	74	NA	NA	NA	NA	94	74	93	66*
Blood Chemistry: Week 23												
Number Examined			6	6	0	0	0	0	6	6	6	6
ALP (IU/L)			83	65	NA	NA	NA	NA	85	66	81	58
Urinalysis: Week 18												
No. Examined			6	6	0	0	0	0	6	6	6	6
8 hr Volume (mL)			0.6	0.3	NA	NA	NA	NA	0.4	0.5	0.9	0.5
Volume (mL) [a]			6.6	3.9	NA	NA	NA	NA	5.8	4.5	8.6	6.2
Osmolality (mOsm/kg)			1294	1960	NA	NA	NA	NA	1646	1368	1023	1500
pH			6.9	6.8	NA	NA	NA	NA	7.2	6.8	7.3*	6.8
Creatinine (mg/dL)			112.2	109.0	NA	NA	NA	NA	119.3	84.6	85.7	56.3
Sodium (mmol/L)			60	106	NA	NA	NA	NA	77	59	39	30
Potassium (mmol/L)			204	307	NA	NA	NA	NA	269	162	146	115
Chloride (mmol/L)			76	92	NA	NA	NA	NA	110	62	46	20
Urinalysis: Week 23												
Number Examined			6	6	0	0	0	0	6	6	6	6
Volume (mL)			9.4	7.8	NA	NA	NA	NA	9.8	3.4	9.5	7.0
Organ Weights (g)												
Adrenal:	Week 20	Absolute (g)	0.0409	0.0463	NA	NA	NA	NA	0.0343*	0.0519	0.0401	0.0511
		Relative (%)	0.0134	0.0274	NA	NA	NA	NA	0.0127	0.0303	0.0147	0.0306
Kidney:	Week 20	Absolute (g)	2.0565	1.2628	NA	NA	NA	NA	1.9557	1.3100	2.0910	1.2983
		Relative (%)	0.6751	0.7488	NA	NA	NA	NA	0.7230	0.7645	0.7649*	0.7725
Kidney:	Week 25	Absolute (g)	2.0728	1.2863	NA	NA	NA	NA	1.9872	1.2708	1.9589	1.3160
		Relative (%)	0.6752	0.7489	NA	NA	NA	NA	0.6935	0.7688	0.6887	0.7779

NA = Not applicable.
Dunnett's Test: * - P<0.05
a - 16-hour overnight collection following 8-hour collection

Daily Dose (mg/kg)			0 (Control)		3		10		30		100	
Number of Animals			M: 12	F: 12	M: 0	F: 0	M: 0	F: 0	M: 12	F: 12	M: 12	F: 11
Postdose Evaluation												
Number Examined			12	12	0	0	0	0	12	12	12	12
Organ Weights (g)												
Liver:	Week 20	Absolute (g)	7.9980	4.4784	NA	NA	NA	NA	7.1412	4.5666	7.7451	4.5762
		Relative (%)	2.6205	2.6572	NA	NA	NA	NA	2.6389	2.6653	2.8314	2.7239
Lung:	Week 20	Absolute (g)	1.1501	0.8630	NA	NA	NA	NA	1.0746	0.9073	1.1676	0.8393
		Relative (%)	0.3789	0.5126	NA	NA	NA	NA	0.3977	0.5296	0.4270	0.4996
Pituitary:	Week 20	Absolute (g)	0.0093	0.0127	NA	NA	NA	NA	0.0093	0.0121	0.0097	0.0121
		Relative (%)	0.0030	0.0076	NA	NA	NA	NA	0.0035	0.0071	0.0035	0.0072
Prostate:	Week 20	Absolute (g)	0.5567	NA	NA	NA	NA	NA	0.6273	NA	0.5912	NA
		Relative (%)	0.1832	NA	NA	NA	NA	NA	0.2323	NA	0.2164	NA
Submaxillary salivary gland:	Week20	Absolute (g)	0.6077	0.3862	NA	NA	NA	NA	0.5552*	0.4018	0.5722	0.3659
		Relative (%)	0.2000	0.2293	NA	NA	NA	NA	0.2055	0.2352	0.2093	0.2182
Testis:	Week 20	Absolute (g)	3.0322	NA	NA	NA	NA	NA	2.9840	NA	2.9794	NA
		Relative (%)	0.9982	NA	NA	NA	NA	NA	1.1051*	NA	1.0908*	NA
Testis:	Week 25	Absolute (g)	3.1496	NA	NA	NA	NA	NA	3.1187	NA	3.0318	NA
		Relative (%)	1.0275	NA	NA	NA	NA	NA	1.0886	NA	1.0668	NA
Thymus:	Week 20	Absolute (g)	0.1985	0.1658	NA	NA	NA	NA	0.1529	0.1585	0.1618	0.1521
		Relative (%)	0.0657	0.0989	NA	NA	NA	NA	0.0566	0.0925	0.0593	0.0901
Uterus:	Week 20	Absolute (g)	NA	0.8846	NA	NA	NA	NA	NA	0.7101	NA	0.6038
		Relative (%)	NA	0.5216	NA	NA	NA	NA	NA	0.4139	NA	0.3576
Uterus:	Week 25	Absolute (g)	NA	0.8208	NA	NA	NA	NA	NA	0.7350	NA	0.6666
		Relative (%)	NA	0.4770	NA	NA	NA	NA	NA	0.4409	NA	0.3938
Gross Pathology			-	-	NA	NA	NA	NA	-	-	-	-
Histopathology			-	-	NA	NA	NA	NA	-	-	-	-

- No noteworthy findings. NA = Not applicable. NE = Not examined.
Dunnett's Test: * - P<0.05

2.6.7.7C Repeat-Dose Toxicity **Report Title:** 26-Week Oral Gavage Toxicity Study with YM087 in Rats **Test Article:** Conivaptan hydrochloride

Species/Strain: F344 Rats
Initial Age: 6 Weeks
Date of First Dose: 15 Sep 1995
Duration of Dosing: 26 Weeks
Duration of Postdose: None
Method of Administration: Gavage
Vehicle/Formulation: 0.5% Methylcellulose solution
Study No. R087-TX-045
GLP Compliance: Yes
Special Features: None
No Observed Adverse Effect Level: 1 mg/kg

Daily Dose (mg/kg)	0 (Control)		1		3		10		100	
Number of animals	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15
Toxicokinetics: Week 27										
C_{max} (ng/mL)	NA	NA	19.0	22.2	98.3	156	505	763	4387	4127
AUC_{0-24} (ng·hr/mL)	NA	NA	86.0	117	643	1006	4612	7271	31015	35952
Noteworthy findings										
Died	0	0	0	0	0	0	1	0	0	0
Sacrificed Moribund	0	0	0	0	0	0	2	4	4	2
Clinical Observations[a]										
Thin	0	0	0	0	0	3	3	7	10	3
Hunched posture	0	0	0	0	0	0	3	3	7	2
No feces	0	0	0	0	0	0	0	1	0	1
Few feces	1	0	0	0	0	0	2	2	2	1
Labored respiration	0	0	0	0	0	0	1	2	0	1
Audible respiration	0	0	0	0	0	2	4	7	7	5
Rough hair coat	0	0	0	0	0	3	3	6	5	4
Nasal discharge (total)	0	0	0	0	0	0	2	3	4	1
Clear	0	0	0	0	0	0	2	2	2	1
Cloudy	0	0	0	0	0	0	0	1	1	0
Red	0	0	0	0	0	0	0	0	1	0
Incoordination	0	0	0	0	0	0	1	2	1	1
Hypoactivity	0	0	0	0	0	0	2	4	3	2
Cold to touch	0	0	0	0	0	0	2	4	3	2

NA = Not applicable.
a - Number of animals.

Daily Dose (mg/kg)	0 (Control)		1		3		10		100	
Number of animals	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15
Body Weights (g):										
Week 1	122.5	92.0	116.3	94.5	116.5	90.6	118.8	95.0	121.0	92.4
Week 6	238.0	149.7	231.5	153.2	228.7	148.2	227.7	153.4	233.1	161.3*
Week 13	304.6	175.2	294.1	179.0	284.8*	169.6	279.0*	177.9	284.8*	189.7*
Week 20	336.8	191.2	320.9	194.1	310.7*	180.5*	289.3*	189.8	287.0*	192.0
Week 27	354.3	196.1	337.0	196.9	327.8*	180.9*	299.0*	181.2*	239.5*	178.8*
Body Weights Gain (g):										
Week 1-2	32.6	17.8	31.6	18.4	31.5	17.0	29.6*	16.6	28.6*	16.8
Week 6-7	12.1	6.0	12.4	5.8	12.4	6.3	10.7	7.0	12.5	7.0
Week 12-13	8.0	2.3	7.3	0.9	4.3*	0.5	4.9	1.2	1.2*	1.2
Week 20-21	3.5	0.1	2.6	0.7	3.7	1.6	1.7	-0.7	-5.6*	-0.9
Week 26-27	1.3	-0.2	-0.3	-0.6	-0.4	-1.6	-0.6	-0.9	-15.9*	-6.8*
Week 1-27	231.8	104.1	220.7	102.4	211.4*	90.3*	179.2*	86.4*	117.8*	86.3*
Food Consumption (g/animal/day):										
Week 1	15.2	11.8	14.5	11.8	14.5	11.7	14.6	11.7	14.5	11.3
Week 6	16.0	11.7	15.5	11.7	16.3	12.0	15.8	12.8*	16.3	12.9*
Week 13	20.2	13.7	20.2	14.0	20.3	13.8	19.1	13.2	18.7	13.7
Week 19	17.0	12.7	16.3	12.4	16.9	12.2	15.2*	12.0	15.0*	12.2
Week 26	19.5	13.5	18.9	13.6	18.9	13.6	17.9	12.8	14.4*	12.5
Water Consumption (mL/animal/day):										
Week 13	21.1	19.5	46.5*	32.3*	93.9*	57.8*	161.1*	97.9*	165.6*	115.5*
Week 24	19.7	20.7	45.9*	37.2*	114.6*	73.0*	170.0*	116.4*	201.4*	132.4*
Hematology: Week 26										
Number examined	15	15	15	15	15	15	12	13	12	14
RBC (10^6/µL)	8.85	7.97	8.81	7.91	8.64	7.83	8.67	7.96	8.48	8.10
Hemoglobin (g/dl)	15.6	15.3	15.6	15.2	15.7	15.3	15.8	15.5	15.2	15.5
PCV (%)	42.4	41.6	42.8	41.3	42.7	41.2	43.3	42.2	42.2	42.7
Platelet (10^3/µL)	648	629	624	631	623	635	632	610	764*	704*
Reticulocyte (%)	0.9	1.2	1.1	1.2	1.2	1.1	1.0	0.9	1.2	1.2

- No noteworthy findings. NA= Not applicable.
Dunnett's Test: * - P<0.05

2.6.7.7C Repeat-Dose Toxicity Study No. R087-TX-045 (Continued)

Daily Dose (mg/kg)	0 (Control)		1		3		10		100	
Number of animals	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15
Hematology: Week 26 (Continued)										
Reticulocyte (10^3/µL)	83	97	96	91	105	87	82	73	104	98
PT (sec)	15.9	15.5	15.8	15.5	16.0	15.5	16.8*	16.7*	17.3*	16.8*
APTT (sec)	18.9	15.7	19.2	16.1	19.5	15.6	18.6	16.2	18.3	15.7
WBC (10^3/µL)	6.7	4.2	6.7	4.6	7.0	5.2*	7.6	6.4*	6.8	5.7*
Blood Chemistry: Week 26										
Number examined	15	15	15	15	15	15	12	13	12	14
Glucose (mg/dL)	106	106	104	105	108	101	94*	95	96	94
BUN (mg/dL)	14	16	16*	18*	18*	21*	16*	19*	17*	13
Creatinine (mg/dL)	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Total protein (g/dL)	7.5	7.3	7.4	7.5	7.2	6.9*	7.4	6.8*	8.0*	7.8*
Albumin (g/dL)	4.9	4.9	4.9	5.0	4.7	4.6*	4.8	4.5*	5.1	5.2*
Globulin (g/dL)	2.6	2.4	2.5	2.5	2.5	2.3	2.6	2.3	2.9	2.6
A/G Ratio	1.9	2.1	1.9	2.0	1.9	2.0	1.9	2.0	1.8	2.1
Total bilirubin (mg/dL)	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0
Cholesterol (mg/dL)	70	116	72	122	68	92*	65	69*	105*	107
Triglyceride (mg/dL)	81	38	74	37	89	32	53*	33	40*	42
AST (IU/L)	98	95	91	90	99	110	88	120	91	82
ALT (IU/L)	73	75	68	74	69	83	65	87	87	59
ALP (IU/L)	94	68	95	66	94	88	101	150*	109	81
Calcium (mg/dL)	11.4	11.1	11.4	11.3	11.3	10.9	11.4	10.9*	11.6	11.4
Inorganic phosphorus (mg/dL)	7.6	6.1	7.9	6.5	7.9	7.0	8.2	7.6*	8.0	8.0*
Sodium (mmol/L)	148	147	149	145	148	145	149	147	154*	151
Potassium (mmol/L)	4.6	4.5	4.8	4.5	4.7	4.4	4.7	4.4	4.4	4.3
Chloride (mmol/L)	105	106	104	104*	104	103*	104	103*	108*	107
Protein electrophoresis										
Albumin (g/dL)	4.9	4.8	4.9	4.8	4.7	4.4*	4.8	4.2*	5.0	5.0
α-1 Globulin (g/dL)	0.2	0.2	0.2	0.1	0.1	0.1	0.2	0.1	0.1	0.1
α-2 Globulin (g/dL)	0.5	0.4	0.6	0.5	0.5	0.4	0.4	0.4	0.5	0.4
β Globulin (g/dL)	1.8	1.8	1.6	1.8	1.7	1.7	1.7	1.8	2.3*	2.0
γ Globulin (g/dL)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

Dunnett's Test: * - P<0.05

Daily Dose (mg/kg)	0 (Control)		1		3		10		100	
Number of animals	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15
Urinalysis										
Number examined:										
Week 13	15	15	15	15	15	15	15	15	14	15
Week 24	15	15	15	15	15	15	13	13	13	15
8 hr - Volume (mL):										
Week 13	2.4	2.0	25.7*	17.8*	60.8*	41.7*	93.4*	48.4*	83.1*	52.0*
Week 24	1.3	1.6	22.8*	23.5*	76.8*	50.3*	101.4*	54.5*	90.6*	59.7*
16 hr - Volume (mL):										
Week 13	8.0	3.8	2.4*	1.8*	8.6	7.4*	43.3*	34.1*	81.1*	34.7*
Week 24	5.4	3.5	1.7*	2.2	13.9*	11.7*	64.0*	38.6*	88.9*	50.6*
24 hr - Volume (mL):										
Week 13	10.3	5.7	28.0*	19.5*	69.4*	49.1*	136.7*	82.5*	164.2*	86.7*
Week 24	6.7	5.1	24.5*	25.9*	90.7*	62.0*	160.5*	93.0*	179.5*	110.2*
Osmolality (mOsm/kg):										
Week 13	1068	1390	1549*	1348	558*	416*	156*	176*	101*	196*
Week 24	1516	1412	1573	1141	378*	293*	100*	166*	88*	127*
pH:										
Week 13	7.5	6.7	6.8*	6.4	7.7	7.0	7.5	6.8	7.5	7.3*
Week 24	7.2	6.5	6.7*	6.5	7.4	6.7	7.3	6.5	7.2	6.9*
8 hr - Sodium (mmol/L):										
Week 13	120	120	26*	35*	12*	15*	8*	10*	8*	10*
Week 24	175	107	39*	24*	10*	12*	8*	10*	8*	8*
8 hr - Potassium (mmol/L):										
Week13	236	245	44*	45*	24*	24*	17*	23*	18*	24*
Week24	405	228	66*	38*	21*	24*	17*	23*	19*	22*
8 hr - Chloride (mmol/L):										
Week13	a	100	30	39	13	17	7	14	7	12
Week24	156	118	43	27	11	14	7	12	7	8
8 hr - Sodium Excretion (mmol):										
Week 13	0.27	0.20	0.64*	0.56*	0.66*	0.59*	0.70*	0.47*	0.62*	0.49*
Week 24	0.20	0.16	0.72*	0.54*	0.76*	0.59*	0.68*	0.52*	0.70*	0.42*

Dunnett's Test: * - P<0.05

a - The number of animals with reportable values is 1 or less, therefore no data was reported for the mean urine concentration and excretion.

(Continued)

2.6.7.7C Repeat-Dose Toxicity Study No. R087-TX-045 (Continued)

Daily Dose (mg/kg)	0 (Control)		1		3		10		100	
Number of animals	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15
Urinalysis (Continued)										
8 hr - Potassium Excretion (mmol):										
Week13	0.53	0.40	1.10*	0.77*	1.36*	0.97*	1.57*	0.99*	1.44*	1.16*
Week24	0.47	0.34	1.24*	0.85*	1.57*	1.15*	1.55*	1.22*	1.68*	1.14*
8 hr - Chloride Excretion (mmol):										
Week13	a	0.33	0.73	0.64	0.74	0.66	0.67	0.60	0.51	0.58
Week24	0.43	0.29	0.80	0.60	0.83	0.68	0.69	0.63	0.62	0.43
16 hr - Sodium (mmol/L):										
Week 13	49	35	a	a	8*	7	4*	4	4*	4
Week 24	62	40	a	7*	5*	5*	4*	4*	3*	4*
16 hr - Potassium (mmol/L):										
Week13	149	95	a	a	50*	34	19*	18	11*	19
Week24	196	136	a	107	33*	27*	10*	23*	7*	11*
16 hr - Chloride (mmol/L):										
Week13	42	32	a	a	5*	b	b	b	b	b
Week24	60	a	a	a	14	a	a	a	a	a
16 hr - Sodium Excretion (mmol):										
Week 13	0.37	0.24	a	a	0.07*	0.05	0.15*	0.13	0.30	0.14
Week 24	0.34	0.18	a	0.02*	0.07*	0.05*	0.25*	0.12*	0.34	0.18
16 hr - Potassium Excretion (mmol):										
Week13	1.18	0.66	a	a	0.50*	0.27	0.70*	0.52	0.83*	0.44
Week24	1.09	0.62	a	0.34*	0.47*	0.27*	0.60*	0.45*	0.66*	0.48*
16 hr - Chloride Excretion (mmol):										
Week13	0.43	0.24	a	a	0.05*	b	b	b	b	b
Week24	0.40	a	a	a	0.14	a	a	a	a	a
Ophthalmology	-	-	-	-	-	-	-	-	-	-

Dunnett's Test: * - P<0.05

a - The number of animals with reportable values was 1 or less, therefore no data was reported for the mean urine concentration and excretion.

b - More than half of the animals did not have a measurable concentration value, therefore no data was reported for the mean urine concentration and excretion.

Daily Dose (mg/kg)		0 (Control)		1		3		10		100	
Number of animals		M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15
Organ Weights											
Number Examined		15	15	15	15	15	15	12	11	11	13
Terminal Body Weights		332.0	183.1	315.1	182.9	302.8*	166.0*	273.2*	168.6*	217.4*	168.1*
Adrenal:	**Absolute (g)**	0.0435	0.0514	0.0420	0.0519	0.0444	0.0548	0.0534*	0.0685*	0.0839*	0.0895*
	Relative (%)	0.0132	0.0281	0.0134	0.0284	0.0147*	0.0333*	0.0198*	0.0413*	0.0401*	0.0534*
Brain:	**Absolute (g)**	1.9300	1.7537	1.8937	1.7590	1.8582*	1.7466	1.8668	1.7137	1.8020*	1.7445
	Relative (%)	0.5832	0.9603	0.6025	0.9630	0.6149*	1.0593*	0.6891*	1.0253	0.8477*	1.0437*
Heart:	**Absolute (g)**	1.0338	0.6674	0.9814	0.6914	0.9304*	0.6375	0.8570*	0.6463	0.7836*	0.6687
	Relative (%)	0.3115	0.3645	0.3116	0.3784	0.3075	0.3861	0.3145	0.3859	0.3627*	0.3989*
Kidney:	**Absolute (g)**	2.1608	1.3265	2.0649	1.3628	2.0460	1.3261	1.9309*	1.3219	1.8126*	1.4057*
	Relative (%)	0.6509	0.7250	0.6554	0.7462	0.6754*	0.8025*	0.7081*	0.7880*	0.8424*	0.8401*
Liver:	**Absolute (g)**	8.5389	4.8012	8.1267	5.0494	7.9259	4.6310	7.0318*	4.7219	8.1369	6.6700*
	Relative (%)	2.5736	2.6221	2.5747	2.7636*	2.6148	2.7908*	2.5744	2.8140*	3.7730*	3.9746*
Lung:	**Absolute (g)**	1.2632	0.9505	1.2081	0.9492	1.2088	0.9586	1.1822	0.9799	1.2008	1.0430*
	Relative (%)	0.3814	0.5200	0.3834	0.5187	0.3991	0.5821*	0.4351*	0.5897*	0.5677*	0.6246*
Ovary:	**Absolute (g)**	NA	0.1012	NA	0.0928	NA	0.0914	NA	0.0915	NA	0.0718*
	Relative (%)	NA	0.0552	NA	0.0508	NA	0.0550	NA	0.0537	NA	0.0426*
Pituitary:	**Absolute (g)**	0.0088	0.0115	0.0089	0.0116	0.0085	0.0105	0.0083	0.0107	0.0088	0.0089*
	Relative (%)	0.0027	0.0063	0.0028	0.0063	0.0028	0.0063	0.0030	0.0063	0.0041*	0.0053
Prostate:	**Absolute (g)**	0.7183	NA	0.6051	NA	0.5747*	NA	0.5417*	NA	0.3135*	NA
	Relative (%)	0.2153	NA	0.1920	NA	0.1890	NA	0.1956	NA	0.1374*	NA
Seminal Vesicle:	**Absolute (g)**	1.3208	NA	1.2738	NA	1.1247	NA	1.1276	NA	0.3782*	NA
	Relative (%)	0.3999	NA	0.4014	NA	0.3712	NA	0.4101	NA	0.1660*	NA
Spleen:	**Absolute (g)**	0.7570	0.5736	0.6929*	0.5874	0.6897*	0.5366	0.6341*	0.5033	0.4046*	0.4843*
	Relative (%)	0.2282	0.3137	0.2200	0.3222	0.2279	0.3217	0.2317	0.2950	0.1814*	0.2874*
Submaxillary salivary gland:	**Absolute (g)**	0.6182	0.4049	0.5813	0.3997	0.5530*	0.3958	0.5627*	0.4397	0.5745	0.4687*
	Relative (%)	0.1865	0.2213	0.1847	0.2191	0.1826	0.2407	0.2064*	0.2651*	0.2694*	0.2810*
Testis:	**Absolute (g)**	3.0735	NA	3.0475	NA	3.0891	NA	2.9348	NA	2.3119*	NA
	Relative (%)	0.9278	NA	0.9687	NA	1.0221*	NA	1.0812*	NA	1.0594*	NA

NA = Not applicable.

Dunnett's Test: * - P<0.05

(Continued)

2.6.7.7C Repeat-Dose Toxicity Study No. R087-TX-045 (Continued)

Daily Dose (mg/kg)		0 (Control)		1		3		10		100	
Number of animals		M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15
Organ Weights (Continued)											
Thymus:	Absolute (g)	0.1235	0.1299	0.1146	0.1221	0.1082	0.1047*	0.0826*	0.0871*	0.0500*	0.0815*
	Relative (%)	0.0372	0.0710	0.0362	0.0668	0.0357	0.0624	0.0300*	0.0506*	0.0225*	0.0479*
Thyroid	Absolute (g)	0.0171	0.0153	0.0178	0.0137	0.0169	0.0138	0.0167	0.0138	0.0194	0.0157
/Parathyroid:	Relative (%)	0.0052	0.0084	0.0057	0.0075	0.0056	0.0083	0.0061	0.0081	0.0091*	0.0093
Uterus:	Absolute (g)	NA	0.8385	NA	0.9404	NA	0.7937	NA	0.4350*	NA	0.2917*
	Relative (%)	NA	0.4575	NA	0.5153	NA	0.4631	NA	0.2526*	NA	0.1719*
Gross Pathology											
Terminal sacrifice:	Number examined	15	15	15	15	15	15	12	11	11	13
General: Thin		0	0	0	0	0	2	0	3	8	4
Esophagus: Large		0	1	0	0	3	7	10	9	11	12
Kidney: Diffusely dark		0	0	0	0	0	0	0	0	2	0
Liver: Diffusely dark		0	0	0	0	0	0	0	0	1	0
Thymus: Small		0	0	0	0	0	0	0	1	4	0
Adrenal: Large		0	0	0	0	0	0	0	0	1	0
Glandular Stomach: Dark areas		0	0	0	0	0	1	1	0	5	1
/Erosion/Ulceration		0	0	0	0	0	0	1	0	1	0
Prostate: Small		0	NA	0	NA	0	NA	0	NA	5	NA
Seminal vesicle: Small		0	NA	0	NA	0	NA	0	NA	5	NA
Uterus: Lumen filled with fluid		NA	6	NA	6	NA	5	NA	0	NA	0
Ovary: Cyst		NA	2	NA	1	NA	0	NA	0	NA	0
Unscheduled sacrifice:	Number examined	0	0	0	0	0	0	3	4	4	2
General: Thin		NA	NA	NA	NA	NA	NA	2	4	4	2
Lung: Mottled		NA	NA	NA	NA	NA	NA	1	2	2	1
/Dark foci		NA	NA	NA	NA	NA	NA	0	0	1	0
Esophagus: Large		NA	NA	NA	NA	NA	NA	1	4	2	1
Kidney: Diffusely dark		NA	NA	NA	NA	NA	NA	1	0	1	1
Liver: Diffusely dark		NA	NA	NA	NA	NA	NA	1	0	1	1
Spleen: Small		NA	NA	NA	NA	NA	NA	2	2	3	2
Glandular Stomach: Dark areas		NA	NA	NA	NA	NA	NA	1	0	1	0
Seminal vesicle: Small		NA	NA	NA	NA	NA	NA	2	NA	1	NA

NA = Not applicable.
Dunnett's Test: * - P<0.05

Daily Dose (mg/kg)		0 (Control)		1		3		10		100	
Number of animals		M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15
Histopathology: Terminal sacrifice											
Esophagus:	Number examined	15	15	15	15	15	15	12	11	11	13
Luminal dilatation		0	2	0	0	4	11	11	10	11	13
Left Lung:	Number examined	15	15	15	15	15	15	12	11	11	13
Granulomatous/ pyogranulomatous inflammation		0	0	0	0	0	3	3	5	8	8
Foreign material		0	0	0	0	0	1	0	1	3	3
Right Lung:	Number examined	15	15	15	15	15	15	12	11	11	13
Granulomatous/ pyogranulomatous inflammation		0	1	0	0	0	1	1	4	6	3
Foreign material		0	0	0	0	0	0	0	1	3	0
Kidney:	Number examined	15	15	15	15	15	15	12	11	11	13
Proteinaceous cast		1	0	0	0	0	0	0	0	9	2
Tubular epithelial regeneration		8	1	9	1	4	0	4	2	11	9
+		8	1	9	1	4	0	4	2	3	5
++ or +++		0	0	0	0	0	0	0	0	8	4
Spleen:	Number examined	15	15	15	15	15	15	12	11	11	13
Extramedullary hematopoiesis		14	14	15	15	15	15	12	11	3	11
+		1	0	0	0	0	1	2	4	1	4
++ or +++		13	14	15	15	15	14	10	7	2	7
Thymus:	Number examined	15	15	15	0	15	0	12	0	9	13
Lymphocytic depletion		0	0	1		0		0		5	0
Adrenal:	Number examined	15	15	15	15	15	15	12	11	11	13
Cortical vacuolation		15	2	15	0	15	0	12	0	8	0
+		0	1	3	0	2	0	2	0	2	0
++ or +++		15	1	12	0	13	0	10	0	6	0
Cortical hypertrophy/hyperplasia		0	1	0	2	0	1	3	11	11	13
Stomach:	Number examined	15	15	0	0	0	0	0	0	11	13
Glandular erosion		0	0							4	0

- Minimal. ++ Slight. ---+ Moderate.
NA = Not applicable.

(Continued)

2.6.7.7C Repeat-Dose Toxicity Study No. R087-TX-045 (Continued)

Daily Dose (mg/kg)	0 (Control)		1		3		10		100	
Number of animals	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15
Histopathology: Terminal sacrifice (Continued)										
Prostate: Number examined	15	NA	15	NA	15	NA	12	NA	11	NA
Atrophy	1		1		1		1		7	
Seminal Vesicle: Number examined	15	NA	15	NA	15	NA	12	NA	11	NA
Atrophy	1		1		1		1		9	
Epididymis: Number examined	15	NA	15	NA	15	NA	12	NA	11	NA
Immature sperm form	0		0		0		0		8	
Uterus: Number examined	NA	15	NA	0	NA	0	NA	0	NA	13
Dilatation		6								0
Estrus cycle: Number examined	NA	15	NA	15	NA	15	NA	11	NA	13
Proestrus		6		2		2		3		1
Estrus		3		7		5		0		1
Metestrus		5		0		4		5		1
Diestrus		1		6		4		3		10
Unscheduled Sacrifice										
Esophagus: Number examined	0	0	0	0	0	0	3	4	4	2
Luminal dilatation							3	4	3	2
Femur/Tibia: Number examined	0	0	0	0	0	0	3	4	4	2
Hypocellularity in marrow							0	1	2	1
Lung/Bronchus: Number examined	0	0	0	0	0	0	3	4	4	2
Granulomatous/ pyogranulomatous inflammation							3	4	3	2
Foreign material							0	0	1	2
Kidney: Number examined	0	0	0	0	0	0	3	4	4	2
Proteinaceous cast							0	0	2	1
Tubular epithelial regeneration							0	1	2	2
+							0	1	2	1
++ or +++							0	0	0	1

+ Minimal. ++ Slight. +++ Moderate.
NA = Not applicable.

Daily Dose (mg/kg)	0 (Control)		1		3		10		100	
Number of animals	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15	M: 15	F: 15
Histopathology: Unscheduled Sacrifice (Continued)										
Spleen: Number examined	0	0	0	0	0	0	3	4	4	2
Lymphocytic depletion							3	4	3	2
Extramedullary hematopoiesis							0	0	0	0
Thymus: Number examined	0	0	0	0	0	0	2	4	4	2
Lymphocytic depletion							2	4	3	2
Mesenteric LN: Number examined	0	0	0	0	0	0	3	4	4	2
Lymphocytic depletion							1	4	0	2
Adrenal: Number examined	0	0	0	0	0	0	3	4	4	2
Cortical vacuolation							2	0	3	0
+							1	0	1	0
++ or +++							1	0	2	0
Cortical hypertrophy/hyperplasia							3	3	2	2
Stomach: Number examined	0	0	0	0	0	0	3	4	4	2
Glandular erosion							1	0	0	0
Prostate: Number examined	0	NA	0	NA	0	NA	3	NA	4	NA
Atrophy							2		1	
Seminal vesicle: Number examined	0	NA	0	NA	0	NA	3	NA	4	NA
Atrophy							2		2	
Epididymis: Number examined	0	NA	0	NA	0	NA	3	NA	4	NA
Immature sperm form							2		2	
Uterus: Number examined	NA	0	NA	0	NA	0	NA	4	NA	2
Dilatation								0		0

+ Minimal. ++ Slight. +++ Moderate.
NA = Not applicable.

2.6.7.7] Repeat-Dose Toxicity **Report Title:** 52-Week Oral Capsule Toxicity Study with YM087 in Dogs **Test Article:** Conivaptan hydrochloride

Species/Strain: Beagle Dogs **Duration of Dosing:** 52 Weeks **Study No.** R087-TX-048
Initial Age: 8-9 Months **Duration of Postdose:** None
Date of First Dose: 26 Sep 1995 **Method of Administration:** Oral (Capsule) **GLP Compliance:** Yes
Vehicle/Formulation: 50% Lactose dilution

Special Features: None
No Observed Adverse Effect Level: 10 mg/kg

Daily Dose (mg/kg)		0 (Control)		1		3		10		20	
Number of animals		M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Toxicokinetics:											
C_{max} (ng/mL):	Day 1	NA	NA	318	380	610	1146	2128	2715	3324	2567
	Week 26	NA	NA	356	333	917	769	3728	5865	6895	4950
	Week 52	NA	NA	292	339	659	979	4590	6193	5744	5285
AUC_{0-24} (ng·hr/mL):	Day 1	NA	NA	2959	3077	5720	12146	28815	41362	53842	38834
	Week 26	NA	NA	3661	3056	9172	8347	54174	95080	114862	88385
	Week 52	NA	NA	2878	3276	7051	13485	75092	111683	97202	87844
Noteworthy findings											
Died		0	0	0	0	0	0	0	0	0	0
Sacrificed Moribund		0	0	0	0	0	0	0	0	0	0
Clinical Observations[a]											
Pale mucous membrane (of oral mucosa)		0	0	1	0	0	0	0	0	2	0
Excessive salivation		0	0	0	0	0	0	0	0	1	0
Hot to touch entire body		0	0	0	0	0	0	0	0	1	0
Hypoactivity		0	0	0	0	0	0	0	0	2	0
Body Weights (kg):											
Pretreatment (Week -1)		10.4	8.8	10.5	8.7	10.5	8.9	10.2	8.8	10.5	8.5
Week 7		10.6	9.7	11.3	9.4	10.5	9.6	10.7	9.1	10.5	9.1
Week 14		11.6	9.1	11.7	9.6	11.1	9.9	10.9	9.2	11.1	9.1
Week 27		11.5	9.6	11.8	9.8	11.1	9.6	11.2	9.5	11.0	9.3
Week 40		12.2	10.0	12.2	10.3	11.8	10.2	11.5	10.0	11.0	9.6
Week 53		13.0	11.0	12.6	11.2	12.6	10.5	12.0	10.6	11.9	9.7

NA = Not applicable
a - Number of animals affected.

Daily Dose (mg/kg)	0 (Control)		1		3		10		20	
Number of animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Body Weights Gain (kg):										
Week 1-2	0.1	0.2	0.3	0.1	0.0	0.0	0.0	0.0	-0.1	-0.2
Week 6-7	-0.2	0.1	0.1	0.1	-0.3	0.2	-0.1	0.1	-0.3	0.0
Week 13-14	0.2	-0.1	0.4	0.3	0.1	0.1	0.0	0.0	-0.2	0.1
Week 26-27	-0.1	-0.3	-0.2	-0.1	-0.2	-0.2	0.0	-0.1	-0.3	0.0
Week 39-40	0.1	0.1	0.0	-0.1	-0.1	-0.2	-0.1	-0.2	-0.1	-0.2
Week 52-53	0.3	0.0	-0.2*	0.0	-0.1	0.1	-0.1	-0.1	-0.2*	0.0
Week 1-53	2.5	2.0	1.9	2.3	2.0	1.6	1.7	1.8	1.3	0.8
Food Consumption (g/animal/week):										
Pretreatment (Week -1)	291	262	253	265	317	262	260	219	268	240
Week 1	255	254	254	218	270	231	206	191	215	209
Week 6	306	277	273	275	326	315	280	251	285	274
Week 13	303	206	243	256	355	264	285	228	301	224
Week 26	304	252	243	248	345	255	290	249	307	228
Week 39	288	161	240	234	305	221	266	204	235	214
Week 52	345	259	280	273	391	264	294	251	323	221
Water Consumption (g/animal/day):										
Pretreatment (Week -1)	725.0	608.3	704.2	645.8	950.0	716.7	725.0	445.8	866.7	679.2
Week 1	492.5	612.5	2203.8*	2262.5*	3636.3*	3478.8*	3070.0*	2621.3*	3413.8*	2941.3*
Week 13	758.8	611.3	848.8	962.5	1623.8*	1395.0	1136.3	1032.5	2028.8*	1123.8
Week 26	680.0	711.3	848.8	1227.5	1720.0*	1325.0	1190.0*	1140.0	1875.0*	1648.8
Week 39	835.0	327.5	935.0	1091.3*	1570.0	1105.0*	1108.8	733.8	1323.8	1121.3*
Week 50	926.3	656.3	872.5	1305.0	1545.0	1292.5	1195.0	1136.3	2000.0*	1313.8
Rectal Body Temperature (°C):										
Pretreatment (Week -2)	39.2	38.9	38.9	39.1	38.8	39.1	39.1	39.0	38.9	39.2
Week 26	38.7	38.8	38.8	39.1	38.8	38.9	38.7	38.8	38.6	38.7
Week 50	39.6	39.6	39.5	39.5	39.2	39.8	39.2	39.2	39.3	39.1
Respiration Rate (Breaths/half-minute):										
Pretreatment (Week -2)	13	15	13	11	14	14	14	13	12	11
Week 26	14	21	16	20	15	15	18	19	16	15
Week 50	20	16	18	20	19	17	24	33	23	17

Dunnett's Test: * - P<0.05

(Continued)

2.6.7.7I Repeat-Dose Toxicity — Study No. R087-TX-048 (Continued)

Daily Dose (mg/kg)	0 (Control)		1		3		10		20	
Number of animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Heart Rate (Beats/half-minute):										
Pretreatment (Week -2)	49	53	40	51	39	51	52	42	48	54
Week 26	31	39	31	38	32	31	33	33	30	42
Week 50	59	61	55	50	62	55	56	53	64	57
Electrocardiography										
Heart rate (Beats/minute):										
Pretreatment (Week -2)	100	75	115	100	85	75	150	125	85	125
Week 26	75	115	95	135	95	75	120	90	95	125
Week 50	105	135	105	120	110	75	100	110	70	110
PR Interval (s):										
Pretreatment (Week -2)	0.10	0.08	0.11	0.09	0.08	0.11	0.09	0.10	0.010	0.10
Week 26	0.11	0.10	0.09	0.10	0.10	0.09	0.09	0.11	0.08	0.09
Week 50	0.10	0.09	0.09	0.11	0.08	0.10	0.09	0.11	0.09	0.09
QRS Interval (s):										
Pretreatment (Week -2)	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.03	0.04
Week 26	0.04	0.04	0.04	0.04	0.05	0.04	0.04	0.05	0.04	0.04
Week 50	0.04	0.04	0.05	0.04	0.04	0.05	0.05	0.04	0.04	0.03
QT Interval (s):										
Pretreatment (Week -2)	0.18	0.20	0.20	0.18	0.22	0.20	0.18	0.18	0.20	0.18
Week 26	0.19	0.18	0.19	0.17	0.20	0.18	0.20	0.19	0.20	0.19
Week 50	0.20	0.16	0.20	0.18*	0.20	0.19*	0.19	0.20*	0.21	0.20*

Dunnett's Test: * - P<0.05

Daily Dose (mg/kg)	0 (Control)		1		3		10		20	
Number of animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Blood Pressure										
Systolic (mm Hg):										
Pretreatment (Week -2)	153	145	130	159	142	158	154	146	165	165
Week 26	126	149	142	148	136	142	157	147	148	147
Week 50	176	160	176	175	174	159	152	162	143	163
Diastolic (mm Hg):										
Pretreatment (Week -2)	83	82	81	86	83	89	90	87	96	96
Week 26	77	96	85	85	88	77	100	86	93	79
Week 50	104	95	116	102	96	91	92	87	84	91
Mean arterial (mm Hg):										
Pretreatment (Week -2)	121	109	107	126	119	128	135	124	131	131
Week 26	106	127	114	118	123	109	139*	113	126	113
Week 50	130	122	134	134	130	129	117	120	111	135
Ophthalmology	-	-	-	-	-	-	-	-	-	-
Hematology										
RBC (10^6/µl.):										
Pretreatment (Week -1)	7.05	6.72	6.65	6.55	6.72	6.48	6.85	7.00	6.35	6.62
Week 13	7.00	6.75	6.65	6.95	6.90	6.50	6.90	7.10	6.25	6.65
Week 26	6.70	6.92	6.65	6.95	7.15	6.85	6.82	7.02	6.28	6.42
Week 39	7.00	6.88	6.98	6.98	7.08	6.58	7.08	7.20	5.52*	6.88
Week 50	7.30	6.98	6.88	7.35	7.20	6.95	7.20	7.38	6.45	6.58
Hemoglobin (g/dl):										
Pretreatment (Week -1)	16.2	16.2	15.9	15.8	16.0	16.2	16.2	16.2	15.4	16.1
Week 13	16.2	16.3	16.1	17.1	16.6	16.3	16.6	16.7	15.1	16.1
Week 26	15.6	16.9	16.5	17.1	17.2	17.3	16.3	16.6	15.2	15.8
Week 39	16.4	17.0	17.2	17.3	17.2	16.6	17.2	17.3	13.2	17.0
Week 50	17.0	17.1	17.1	18.2	17.5	17.6	17.6	17.7	15.6	16.2

- No noteworthy findings.
Dunnett's Test: * - P<0.05

(Continued)

2.6.7.7I Repeat-Dose Toxicity Study No. R087-TX-048 (Continued)

Daily Dose (mg/kg)	0 (Control)		1		3		10		20	
Number of animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Hematology (Continued)										
PCV (%):										
Pretreatment (Week -1)	45.8	45.7	45.2	45.1	45.5	45.0	46.0	45.6	43.1	45.6
Week 13	45.4	45.1	45.1	47.4	46.1	44.8	46.2	46.7	42.2	45.3
Week 26	43.9	47.1	45.8	47.5	48.0	47.8	45.8	46.2	42.0	44.0
Week 39	45.7	46.6	47.9	47.5	47.4	45.8	47.7	47.5	36.8	47.2
Week 50	47.5	47.8	47.7	50.5	48.2	48.4	49.0	48.9	43.1	45.1
Platelet (10^3/µL):										
Pretreatment (Week -1)	248	308	238	278	242	288	288	248	305	278
Week 13	225	262	208	275	222	288	270	260	330*	268
Week 26	215	278	212	280	220	258	262	252	225	268
Week 39	242	330	220	302	225	325	285	270	175	262
Week 50	242	285	222	282	232	288	288	258	195	282
Reticulocyte (%):										
Pretreatment (Week -1)	0.5	0.5	0.4	0.3	0.5	0.3	0.5	0.6	0.4	0.2
Week 13	1.0	0.4	0.3	0.8	1.0	0.7	0.7	0.5	1.0	0.4
Week 26	0.2	0.2	0.2	0.4	0.3	0.2	0.4	0.4	0.4	0.2
Week 39	0.2	0.2	0.2	0.6	0.3	0.2	0.4	0.4	0.3	0.2
Week 50	0.6	0.3	0.3	0.5	0.3	0.3	0.4	0.7	0.3	0.4
Reticulocyte (10^3/µL):										
Pretreatment (Week -1)	35	36	24	21	34	21	34	41	24	12
Week 13	74	26	21	54	68	45	48	36	62	29
Week 26	11	10	12	26	23	14	30	30	22	11
Week 39	14	15	12	42	24	12	28	31	14	14
Week 50	42	22	18	39	24	19	27	48	19	24
PT (sec):										
Pretreatment (Week -1)	7.7	8.0	7.9	7.8	7.8	7.8	7.9	7.6	7.7	7.8
Week 13	7.6	7.8	7.8	7.5	7.4	7.4	7.7	7.3	7.5	7.7
Week 26	7.7	7.8	7.9	7.7	7.6	7.6	7.9	7.4	7.6	7.8
Week 39	7.7	7.8	7.8	7.7	7.7	7.6	7.8	7.3	7.7	7.7
Week 50	6.6	6.7	6.8	6.7	6.6	6.5	6.8	6.5	6.7	6.8

Dunnett's Test: * - P<0.05

Daily Dose (mg/kg)	0 (Control)		1		3		10		20	
Number of animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Hematology (Continued)										
APTT (sec):										
Pretreatment (Week -1)	12.3	15.9	13.6	14.5	14.8	13.3	11.6	14.7	12.6	13.2
Week 13	12.9	17.6	12.4	17.2	16.0	17.9	12.3	18.0	13.3	18.8
Week 26	12.8	15.4	13.3	15.0	14.8	15.2	12.6	16.4	12.5	17.0
Week 39	11.5	13.0	11.0	13.5	12.5	13.3	11.0	13.4	11.2	13.8
Week 50	10.2	10.8	10.2	10.8	11.2	10.7	10.4	11.2	9.7	11.4
WBC (10^3/µL):										
Pretreatment (Week -1)	9.7	12.0	11.3	14.9	11.6	10.1	9.2	12.5	9.4	12.6
Week 13	9.5	8.8	8.6	11.5	10.6	8.7	10.2	11.8	10.4	11.2
Week 26	8.9	10.6	8.8	10.4	12.9*	9.2	10.3	12.5	8.5	12.0
Week 39	9.1	10.6	8.2	9.5	11.5	9.7	11.4	11.0	11.9	10.1
Week 50	9.1	8.1	9.2	9.8	11.7	9.7	11.4	10.2	9.0	9.8
Blood Chemistry										
Glucose (mg/dL):										
Pretreatment (Week -1)	110	113	106	104	110	107	110	108	117	110
Week 13	100	104	100	101	96	103	102	96	103	102
Week 26	95	96	96	98	94	93	93	97	102	100
Week 39	101	100	96	106	96	97	93	100	101	100
Week 50	105	106	102	104	96	104	94	104	106	103
BUN (mg/dL):										
Pretreatment (Week -1)	14	12	12	13	11	13	12	13	12	15
Week 13	17	15	14	16	16	17	15	15	17	14
Week 26	16	14	16	16	16	15	14	14	15	14
Week 39	17	16	14*	16	16	15	12*	14	11*	14
Week 50	15	14	14	16	14	14	14	14	14	14
Creatinine (mg/dL):										
Pretreatment (Week -1)	0.9	1.0	1.0	0.9	0.8	1.0	0.9	0.9	0.9	1.0
Week 13	1.0	1.0	1.1	1.0	0.9	1.0	1.0	1.0	1.0	1.0
Week 26	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Week 39	1.0	1.1	1.1	1.1	1.0	1.1	1.0	1.0	0.9	1.0
Week 50	1.0	0.9	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

Dunnett's Test: * - P<0.05

(Continued)

2.6.7.7I Repeat-Dose Toxicity . Study No. R087-TX-048 (Continued)

Daily Dose (mg/kg)	0 (Control)		1		3		10		20	
Number of animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Blood Chemistry (Continued)										
Total protein (g/dL):										
Pretreatment (Week -1)	6.4	6.1	6.1	6.1	6.1	6.0	6.2	5.9	6.2	6.3
Week 13	6.6	6.4	6.2	6.5	6.6	6.5	6.4	6.4	6.7	6.4
Week 26	6.8	6.5	6.3	6.4	6.6	6.4	6.4	6.2	6.7	6.2
Week 39	6.7	6.7	6.2	6.4	6.5	6.4	6.6	6.2	7.0	6.5
Week 50	6.8	6.6	6.2	6.4	6.6	6.4	6.6	6.4	7.0	6.5
Albumin (g/dL):										
Pretreatment (Week -1)	4.2	4.2	4.2	4.2	4.2	4.1	4.3	4.0	4.1	4.4
Week 13	4.1	4.0	4.0	4.2	4.0	4.0	4.0	4.0	3.8	3.9
Week 26	4.2	4.2	4.1	4.2	4.2	4.2	4.0	3.9	4.0	4.0
Week 39	3.9	4.1	3.9	4.1	3.9	3.8	3.9	3.7*	3.5	3.9
Week 50	4.0	4.0	3.8	4.0	3.9	4.0	3.8	3.8	3.5	3.8
Globulin (g/dL):										
Pretreatment (Week -1)	2.1	1.9	1.9	1.9	1.9	2.0	1.9	1.9	2.0	2.0
Week 13	2.6	2.4	2.2	2.3	2.6	2.5	2.4	2.4	2.8	2.5
Week 26	2.6	2.3	2.2	2.2	2.3	2.3	2.4	2.3	2.8	2.2
Week 39	2.8	2.6	2.3	2.3	2.6	2.6	2.7	2.5	3.5*	2.6
Week 50	2.8	2.6	2.4	2.4	2.7	2.5	2.8	2.7	3.5*	2.7
A/G Ratio:										
Pretreatment (Week -1)	2.0	2.2	2.2	2.2	2.2	2.1	2.3	2.2	2.0	2.2
Week 13	1.6	1.7	1.8	1.8	1.6	1.6	1.7	1.7	1.4	1.6
Week 26	1.6	1.8	1.9	2.0	1.8	1.8	1.7	1.8	1.4	1.8
Week 39	1.4	1.6	1.7	1.8	1.5	1.5	1.5	1.5	1.0*	1.5
Week 50	1.4	1.6	1.6	1.7	1.4	1.6	1.4	1.4	1.0*	1.4
Total bilirubin (mg/dL):										
Pretreatment (Week -1)	0.2	0.1	0.1	0.0	0.2	0.2	0.2	0.2	0.1	0.2
Week 13	0.2	0.2	0.1	0.2	0.2	0.2	0.2	0.2	0.1	0.2
Week 26	0.2	0.2	0.1	0.1	0.2	0.1	0.2	0.2	0.2	0.2
Week 39	0.1	0.1	0.1	0.1	0.2	0.2	0.1	0.2	0.2	0.2
Week 50	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

Dunnett's Test: * - P<0.05

Number of animals	0 (Control) M: 4	F: 4	1 M: 4	F: 4	3 M: 4	F: 4	10 M: 4	F: 4	20 M: 4	F: 4
Blood Chemistry (Continued)										
Cholesterol (mg/dL):										
Pretreatment (Week -1)	161	174	156	164	168	174	152	143	160	176
Week 13	152	173	126	193	151	232	136	167	167	180
Week 26	158	158	128	163	154	170	129	161	166	186
Week 39	142	192	118	173	140	207	122	155	172	168
Week 50	156	168	123	158	144	196	124	179	171	230
Triglyceride (mg/dL):										
Pretreatment (Week -1)	42	41	47	42	38	42	42	44	43	45
Week 13	50	46	42	54	55	60	41	51	45	46
Week 26	35	41	35	44	42	38	34	44	41	47
Week 39	31	37	20	44	32	35	28	41	37	40
Week 50	34	40	20	44	34	40	34	37	32	41
AST (IU/L):										
Pretreatment (Week -1)	31	28	28	47	28	34	26	47	29	32
Week 13	29	26	29	29	29	29	28	32	28	29
Week 26	29	28	26	33	32	35	30	33	50	29
Week 39	32	22	27	36	32	30	30	34	43	30
Week 50	37	28	33	41	36	34	35	34	48	30
ALT (IU/L):										
Pretreatment (Week -1)	31	27	34	29	28	34	28	33	30	30
Week 13	36	30	41	30	29	31	32	34	32	28
Week 26	32	32	39	31	30	39	34	31	36	29
Week 39	38	32	43	36	29	36	36	35	35	32
Week 50	46	34	38	37	32	38	36	38	42	31
ALP (IU/L):										
Pretreatment (Week -1)	91	71	86	127	74	89	116	88	92	79
Week 13	76	64	55	94	79	83	85	108	92	78
Week 26	81	64	46	82	65	78	73	70	91	70
Week 39	63	50	43	69	58	77	66	64	101	71
Week 50	61	67	36	66	57	69	66	62	74	64

(Continued)

2.6.7.7I Repeat-Dose Toxicity Study No. R087-TX-048 (Continued)

Daily Dose (mg/kg)	0 (Control)		1		3		10		20	
Number of animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Blood Chemistry (Continued)										
Calcium (mg/dL):										
Pretreatment (Week -1)	10.8	10.8	10.9	11.1	10.6	10.9	10.9	10.6	10.8	10.8
Week 13	10.8	10.6	10.6	11.0	10.6	10.8	10.8	10.6	10.8	10.8
Week 26	10.1	10.6	10.4	10.2	10.1	10.4	10.2	10.1	10.1	10.2
Week 39	10.2	10.7	10.4	10.2	10.1	10.5	10.5	10.2	10.3	10.4
Week 50	10.3	10.5	10.2	10.1	10.2	10.4	10.2	10.2	10.3	10.3
Inorganic phosphorus (mg/dL):										
Pretreatment (Week -1)	6.0	5.2	6.5	5.8	5.5	5.4	5.7	5.3	6.1	5.6
Week 13	5.0	3.9	4.8	4.2	4.6	4.4	4.4	4.0	5.0	3.6
Week 26	4.7	4.5	5.0	4.0	4.5	4.0	4.6	4.1	4.5	3.9
Week 39	4.3	4.8	4.6	3.5	4.3	3.8*	4.3	3.9*	4.0	3.7
Week 50	3.9	4.1	4.0	3.3	4.0	3.2	3.7	3.8	3.7	3.3
Sodium (mmol/L):										
Pretreatment (Week -1)	151	152	151	151	151	151	152	152	152	154
Week 13	151	151	150	150	150	150	152	151	150	150
Week 26	150	152	150	150	150	150	150	150	151	149
Week 39	150	151	150	148	148	150	149	148	149	148
Week 50	148	149	148	147	146	148	148	148	149	148
Potassium (mmol/L):										
Pretreatment (Week -1)	4.2	4.0	4.0	4.1	4.0	3.9	4.1	3.8	4.0	3.9
Week 13	4.1	4.0	4.1	4.2	4.2	3.9	4.0	3.9	4.4	4.0
Week 26	4.0	4.1	4.2	4.1	4.0	3.9	4.0	3.8	4.2	4.0
Week 39	4.0	4.0	3.9	3.9	3.8	3.7	3.8	3.8	4.4	3.8
Week 50	4.1	4.1	3.8	3.9	3.8	3.8	3.9	3.8	4.2	4.2
Chloride (mmol/L):										
Pretreatment (Week -1)	116	120	117	118	118	118	116	119	119	120
Week 13	122	121	122	120	119	118	122	120	118	118
Week 26	114	114	114	113	113	112	113	113	113	112
Week 39	111	114	112	108*	109	111	110	110*	110	110*
Week 50	114	114	114	112	112	114	113	114	114	112

Dunnett's Test: * - P<0.05

Daily Dose (mg/kg)	0 (Control)		1		3		10		20	
Number of animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Blood Chemistry (Continued)										
Albumin (g/dL):										
Pretreatment (Week -1)	3.6	3.6	3.6	3.7	3.5	3.6	3.6	3.5	3.5	3.7
Week 13	3.2	3.2	3.2	3.3	3.2	3.2	3.2	3.0	3.0	3.4
Week 26	3.4	3.4	3.4	3.4	3.4	3.4	3.4	3.0*	3.0	3.2
Week 39	3.4	3.5	3.5	3.7	3.4	3.2	3.3	3.2	2.8	3.4
Week 50	3.2	3.4	3.2	3.6	3.2	3.3	3.3	3.1	2.9	3.2
α-1 Globulin (g/dL):										
Pretreatment (Week -1)	0.2	0.1	0.2	0.2	0.2	0.1	0.2	0.1	0.1	0.1
Week 13	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Week 26	0.2	0.2	0.2	0.2	0.1	0.2	0.1	0.2	0.2	0.2
Week 39	0.2	0.2	0.2	0.2	0.1	0.2	0.2	0.2	0.1	0.2
Week 50	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
α-2 Globulin (g/dL):										
Pretreatment (Week -1)	0.7	0.7	0.6	0.7	0.7	0.7	0.7	0.6	0.8	0.7
Week 13	0.8	0.8	0.8	0.9	0.9	1.0	0.8	0.9	0.9	0.8
Week 26	0.8	0.8	0.8	0.8	0.9	0.8	0.7	0.8	0.9	0.8
Week 39	0.8	0.8	0.6	0.7	0.8	0.8	0.8	0.7	0.9	0.7
Week 50	0.8	0.8	0.8	0.7	0.9	0.8	0.7	0.8	0.8	0.8
β Globulin (g/dL):										
Pretreatment (Week -1)	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.9	0.8
Week 13	1.1	1.0	0.9	1.0	1.1	1.0	1.1	1.0	1.1	1.0
Week 26	1.2	1.0	1.0	0.9	1.1	1.0	1.1	1.0	1.3	0.9
Week 39	1.0	0.9	0.8	0.8	0.9	0.9	1.0	0.8	1.1	0.8
Week 50	1.2	1.0	1.0	0.8	1.1	0.9	1.0	1.0	1.2	1.0
γ Globulin (g/dL):										
Pretreatment (Week -1)	1.0	0.9	0.9	0.8	0.9	0.9	0.9	0.9	0.9	0.9
Week 13	1.2	1.2	1.0	1.1	1.3	1.2	1.2	1.3	1.5	1.2
Week 26	1.2	1.0	1.1	1.1	1.0	1.2	1.1	1.2	1.4	1.1
Week 39	1.4	1.3	1.2	1.1	1.2	1.3	1.4	1.4	2.0*	1.4
Week 50	1.3	1.1	1.2	1.0	1.3	1.2	1.4	1.4	1.8*	1.2

Dunnett's Test: * - P<0.05

(Continued)

2.6.7.7I Repeat-Dose Toxicity Study No. R087-TX-048 (Continued)

Daily Dose (mg/kg)	0 (Control)		1		3		10		20	
Number of animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Urinalysis										
8 hr - Volume (mL):										
Pretreatment (Week -1)	85.0	59.5	74.0	35.0	55.0	52.0	44.5	43.0	42.0	48.5
Week 1	48.0	84.0	993.8*	1287.5*	1148.8*	1150.0*	871.2*	792.5*	1012.5*	1347.0*
Week 14	69.0	47.5	66.0	548.8*	436.5*	376.2*	203.5	282.5	473.8*	274.5
Week 26	58.0	49.5	53.8	299.0	335.0	293.2	138.2	169.5	200.0	171.5
Week 39	36.5	47.2	41.5	283.8*	167.0	208.8	142.0	172.0	187.0	141.2
Week 50	84.2	66.0	113.2	312.0	418.0	205.5	177.8	245.8	336.0	220.0
16 hr - Volume (mL):										
Pretreatment (Week -1)	124.5	151.8	83.5	91.0	73.0	91.8	76.5	90.5	139.8	109.8
Week 1	67.0	89.5	690.0	729.0	1264.5*	1756.0*	1318.2*	1330.5*	1556.0*	1559.0*
Week 14	145.2	119.8	97.5	202.2	425.5	330.0	297.0	355.8	780.2*	309.0
Week 26	63.8	167.2	70.2	184.5	404.5*	209.2	268.2	354.2	571.5*	206.0
Week 39	95.0	106.8	102.2	260.2	526.2*	358.5	236.5	273.8	465.0*	436.5
Week 50	81.5	98.2	135.0	321.0	612.2*	222.2	227.2	348.2	555.8*	337.8
24 hr - Volume (mL):										
Pretreatment (Week -1)	209.5	211.2	157.5	126.0	128.0	143.8	121.0	133.5	181.8	158.2
Week 1	115.0	173.5	1683.8*	2016.5*	2413.2*	2906.0*	2189.5*	2123.0*	2568.5*	2906.0*
Week 14	214.2	167.2	163.5	751.0*	862.0*	706.2*	500.5	638.2	1254.0*	583.5
Week 26	121.8	216.8	124.0	483.5	739.5*	502.5	406.5	523.8	771.5	377.5
Week 39	131.5	154.0	143.8	544.0	693.2*	567.2	378.5	445.8	652.0*	577.8
Week 50	165.8	164.2	248.2	633.0	1030.2*	427.8	405.0	594.0	891.8*	557.8
Osmolality (mOsm/kg):										
Pretreatment (Week -1)	1677	1519	1750	1654	1954	1902	1833	2066	1578	1806
Week 1	2036	1820	218*	219*	180*	138*	232*	147*	116*	170*
Week 14	2341	1578	1109*	721*	690*	821*	919*	608*	529*	664*
Week 26	2590	1666	1570*	831*	832*	745*	1018*	618*	715*	868*
Week 39	2364	1533	1358*	525	565*	744	1022*	734	606*	566
Week 50	2188	2016	1342	696*	574*	949*	1018*	847*	820*	780*

Dunnett's Test: * - P<0.05

Daily Dose (mg/kg)	0 (Control)		1		3		10		20	
Number of animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Urinalysis (Continued)										
pH:										
Pretreatment (Week -1)	7.4	7.5	7.6	7.4	7.4	7.5	7.6	7.5	7.5	7.0
Week 1	7.1	7.1	7.5	6.5	6.9	6.5	6.8	6.2	6.8	6.8
Week 14	7.2	7.4	7.6	7.1	7.4	8.1	8.0	7.4	7.5	7.2
Week 26	6.8	7.1	7.0	7.0	7.5	7.2	7.2	7.5	7.2	7.1
Week 39	7.0	7.4	7.6	7.4	7.5	7.4	7.6	7.6	7.4	7.5
Week 50	7.0	7.2	7.8	7.5	7.5	7.4	7.5	7.0	7.4	7.2
8 hr - Sodium (mmol/L):										
Pretreatment (Week -1)	137	120	214	154	213	152	203	234	118	107
Week 1	259	156	20*	18*	18*	8*	21*	37*	14*	17*
Week 14	244	155	155*	34	46*	58	104*	55	40*	54
Week 26	258	200	140*	63	57*	95	106*	60	51*	58
Week 39	227	63	127*	55	39*	87	72*	78	66*	51
Week 50	190	228	126	59*	41*	97	78	77	54*	41*
8 hr - Potassium (mmol/L):										
Pretreatment (Week -1)	119	120	141	147	218	148	165	140	191	96
Week 1	222	143	14*	13*	12*	9*	14*	10*	14*	14*
Week 14	186	98	78*	32*	35*	34*	64*	38*	32*	32*
Week 26	151	102	71	78	38*	54	58	52	32*	38
Week 39	162	68	111*	36	28*	47	34*	58	34*	41
Week 50	184	166	65	65	28*	34*	75	62	48*	34*
8 hr - Chloride (mmol/L):										
Pretreatment (Week -1)	76	72	133	128	117	100	113	135	110	87
Week 1	211	149	16*	16*	16*	9*	16*	28*	12*	18*
Week 14	126	84	74	31	36*	31	64	31	28*	28
Week 26	194	136	119	81	34*	75	46*	83	46*	44
Week 39	179	41	150	67	26*	42	31*	83	66*	53
Week 50	188	199	143	83*	34*	56*	75*	78*	52*	57*

Dunnett's Test: * - P<0.05

(Continued)

2.6.7.7I Repeat-Dose Toxicity Study No. R087-TX-048 (Continued)

Daily Dose (mg/kg)	0 (Control)		1		3		10		20	
Number of animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Urinalysis (Continued)										
8 hr - Sodium Excretion (mmol):										
Pretreatment (Week -1)	11.77	7.48	12.95	10.91	11.69	7.82	8.77	12.55	8.54	6.38
Week 1	11.17	13.26	18.17	22.57	19.88	9.83	18.25	24.13	14.18	20.78
Week 14	16.86	6.64	10.27	18.60	14.45	16.93	16.20	14.36	14.32	14.44
Week 26	11.42	8.93	6.47	16.70	11.95	13.32	8.93	8.05	8.24	9.23
Week 39	7.64	3.24	4.58	15.35*	5.86	12.26*	8.38	11.04	8.57	6.79
Week 50	10.67	15.03	11.95	15.26	13.38	10.78	9.73	15.12	14.66	9.11
8 hr - Potassium Excretion (mmol):										
Pretreatment (Week -1)	9.72	6.81	7.09	8.36	11.63	7.99	7.69	7.88	16.30	6.16
Week 1	10.23	9.35	12.42	16.72	13.41	10.33	11.85	7.73	14.22	20.59
Week 14	12.78	4.18	5.22	15.72*	12.16	11.16	9.42	10.78*	12.62	8.67
Week 26	7.05	4.63	3.30	12.48	10.07	10.96	4.15	7.36	5.24	7.03
Week 39	5.30	2.91	4.84	9.85	4.92	7.24	4.45	9.44	4.21	5.96
Week 50	12.35	11.00	7.84	14.45	11.04	6.12	8.99	11.88	13.99	6.55
8 hr - Chloride Excretion (mmol):										
Pretreatment (Week -1)	7.78	4.30	8.10	10.39	6.52	6.10	5.68	7.35	10.44	5.11
Week 1	9.28	12.06	14.19	27.15	17.51	11.12	15.28	17.82	12.17	24.11
Week 14	8.72	3.46	5.24	15.10	11.45	10.61	9.70	8.81	11.26	8.10
Week 26	8.51	7.08	5.90	16.02	13.67	16.64	3.15	12.38	9.40	7.80
Week 39	7.20	2.02	6.56	18.02*	5.52	10.69	4.93	13.16*	7.56	7.61
Week 50	15.69	13.24	14.97	18.55	13.52	8.22	10.30	19.34	16.56	10.58
16 hr - Creatinine (mg/dL):										
Pretreatment (Week -1)	159.5	146.9	310.3	179.2	194.6	187.5	235.9	216.0	191.8	188.6
Week 1	247.7	177.0	26.8*	19.7*	14.9*	10.3*	22.2*	17.2*	12.9*	11.4*
Week 14	227.6	213.2	188.0	69.0*	62.7*	70.0*	104.0*	57.2*	50.0*	66.8*
Week 26	303.3	137.6	274.3	85.6	75.3*	60.3	127.9	59.6	64.6*	76.2
Week 39	236.9	221.8	214.0	46.2*	52.0*	65.2*	116.5	62.8*	63.9*	53.6*
Week 50	275.8	180.4	190.5	49.6	50.6*	85.0	109.9	121.8	70.6*	110.3

Dunnett's Test: * - P<0.05

Daily Dose (mg/kg)	0 (Control)		1		3		10		20	
Number of animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Urinalysis (Continued)										
16 hr - Sodium (mmol/L):										
Pretreatment (Week -1)	151	130	151	122	199	158	227	166	146	116
Week 1	148	114	17*	16*	12*	8*	9*	12	7*	7*
Week 14	115	88	98	40	38*	36	59*	30	28*	32
Week 26	160	100	124	49	63	53	62	46	36*	42
Week 39	169	134	126	52	47*	68	68*	66	48*	38
Week 50	139	134	98	62	42	81	52	69	58	34*
16 hr - Potassium (mmol/L):										
Pretreatment (Week -1)	196	167	156	166	194	196	190	230	158	205
Week 1	204	188	22*	22*	18*	12*	28*	12*	13*	11*
Week 14	258	160	84*	75*	71*	91	95*	63*	52*	69*
Week 26	250	191	117*	87*	86*	76*	92*	60*	76*	97*
Week 39	236	159	108	46	50*	67	90*	62	46*	57
Week 50	243	225	112*	63*	54*	96	114*	60*	73*	69*
16 hr - Chloride (mmol/L):										
Pretreatment (Week -1)	171	134	122	113	200	164	190	164	136	147
Week 1	168	166	21*	20	16*	10*	22*	15	12*	6*
Week 14	210	111	91*	61	60*	64	70*	55	36*	54
Week 26	233	163	108*	86	78*	80*	92*	61*	62*	87
Week 39	229	110	132*	52	56*	78	87*	92	52*	56
Week 50	151	182	100	72*	56*	105	81	74*	70*	41*
16 hr - Creatinine Excretion (mg):										
Pretreatment (Week -1)	207.13	196.50	164.64	150.94	140.17	167.88	171.78	174.33	257.27	181.14
Week 1	166.05	153.22	151.57	139.74	177.10	175.12	183.45	165.90	194.71	196.80
Week 14	333.13	206.22	163.02*	136.47	224.37	185.49	210.06*	178.32	247.03	199.15
Week 26	163.44	177.85	164.95	134.75	217.53	123.08	193.41	174.48	207.76	149.42
Week 39	188.34	172.09	192.98	122.97	207.62	158.70	232.35	158.66	233.32	160.72
Week 50	168.60	173.00	232.02	166.58	233.22	153.32	208.76	183.96	214.01	171.00

Dunnett's Test: * - P<0.05

(Continued)

2.6.7.7I Repeat-Dose Toxicity Study No. R087-TX-048 (Continued)

Daily Dose (mg/kg)		0 (Control)		1		3		10		20	
Number of animals		M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Urinalysis (Continued)											
16 hr - Sodium Excretion (mmol):											
Pretreatment (Week -1)		18.93	17.39	11.70	9.76	14.34	12.69	16.32	12.22	18.50	11.91
Week 1		8.81	11.33	10.95	11.26	12.74	12.69	10.17	13.28	9.36	13.54
Week 14		16.46	11.05	8.76	7.70	12.92	9.92	12.41	10.38	15.86	9.79
Week 26		7.90	13.17	8.36	9.62	18.80	10.30	10.74	14.43	17.46	9.38
Week 39		13.70	9.51	12.50	12.36	19.05	14.63	14.31	14.03	16.94	11.36
Week 50		9.02	13.35	13.42	19.77	21.48	13.18	10.42	14.80	18.01	11.50
16 hr - Potassium Excretion (mmol):											
Pretreatment (Week -1)		25.09	22.15	11.77	14.24	14.05	17.62	14.99	20.05	21.44	22.45
Week 1		13.45	15.82	14.36	15.96	20.52	20.54	16.65	15.32	18.32	17.49
Week 14		38.21	18.19	7.73*	15.00	25.28	23.54	19.52*	19.31	27.56	20.14
Week 26		14.41	23.90	7.57	14.65	29.66	14.73	17.42	18.52	30.26	19.70
Week 39		20.86	11.84	9.71	12.37	24.71	14.98	16.90	14.52	16.53	16.48
Week 50		18.99	21.75	15.89	20.76	29.66	17.63	20.64	17..40	26.18	15.23
16 hr - Chloride Excretion (mmol):											
Pretreatment (Week -1)		21.27	17.61	10.95	10.20	14.51	14.12	13.66	13.28	18.35	16.91
Week 1		12.10	14.14	13.81	14.46	17.47	17.30	17.64	17.92	16.90	9.79
Week 14		30.72	13.21	8.73*	11.85	21.59	16.38	14.78*	16.82	20.98	15.80
Week 26		13.26	22.39	7.26	15.85	28.84	15.00	17.97	20.64	24.84	17.96
Week 39		21.14	9.52	12.64	12.36	26.12	19.56	17.03	19.92	17.66	15.59
Week 50		13.86	17.62	14.27	22.12	30.69	17.74	14.69	17.94	22.86	11.90
Organ Weights											
Terminal Body Weights		12465.0	10583.8	12308.8	10671.3	11997.5	10004.3	11637.5	10353.8	11483.8	9188.8
Adrenal:	Absolute (g)	1.3035	1.2183	1.4143	1.4188	1.4520	1.3830	1.4415	1.4178	1.4013	1.4055
	Relative (%)	0.0107	0.0120	0.0115	0.0133	0.0122	0.0140	0.0124	0.0142	0.0122	0.0155
Brain:	Absolute (g)	78.625	73.314	80.442	71.334	79.780	75.123	83.076	80.187	86.542	75.041
	Relative (%)	0.6511	0.7072	0.6567	0.6738	0.6700	0.7596	0.7180	0.7858	0.7537	0.8293
Heart:	Absolute (g)	100.753	80.458	90.660	76.396	101.444	79.513	96.288	76.581	103.057	78.667
	Relative (%)	0.8350	0.7759	0.7384	0.7150	0.8522	0.8070	0.8327	0.7473	0.8963	0.8590

Dunnett's Test: * - P<0.05

Daily Dose (mg/kg)		0 (Control)		1		3		10		20	
Number of animals		M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4
Organ Weights (Continued)											
Kidney:	Absolute (g)	54.1810	40.2785	54.0878	38.9003	59.7815	36.9300	59.4128	41.0575	52.6440	38.2408
	Relative (%)	0.4499	0.3897	0.4402	0.3652	0.4969	0.3760	0.5157	0.3970	0.4577	0.4160
Liver:	Absolute (g)	278.168	240.932	258.885	251.312	301.615	224.224	312.107	288.711	311.273	260.132
	Relative (%)	2.2803	2.2903	2.1030	2.3703	2.5279	2.2316	2.6806	2.7828	2.7210	2.7987*
Lung:	Absolute (g)	80.058	67.916	78.469	71.102	89.337	71.518	79.846	69.484	87.130	69.323
	Relative (%)	0.6552	0.6516	0.6402	0.6612	0.7506	0.7213	0.6889	0.6742	0.7555	0.7577
Ovary:	Absolute (g)	NA	0.9553	NA	1.3283	NA	0.8680	NA	1.4413	NA	1.0548
	Relative (%)	NA	0.0091	NA	0.0126	NA	0.0087	NA	0.0139	NA	0.0117
Pancreas	Absolute (g)	25.4110	20.1800	25.3763	19.6845	23.8775	20.0423	22.1655	21.9178	21.5373	21.2865
	Relative (%)	0.2092	0.1913	0.2071	0.1849	0.1995	0.2035	0.1910	0.2160	0.1879	0.2336
Pituitary:	Absolute (g)	0.068	0.068	0.062	0.069	0.063	0.062	0.058	0.063	0.064	0.057
	Relative (%)	0.0006	0.0006	0.0005	0.0007	0.0005	0.0006	0.0005	0.0006	0.0006	0.0006
Prostate:	Absolute (g)	9.1470	NA	11.0163	NA	12.2163	NA	11.4395	NA	8.7618	NA
	Relative (%)	0.0752	NA	0.0866	NA	0.1007	NA	0.0983	NA	0.0768	NA
Spleen:	Absolute (g)	41.837	37.716	60.862	46.385	43.003	37.703	50.884	46.739	37.257	48.579
	Relative (%)	0.3434	0.3662	0.4895	0.4370	0.3558	0.3780	0.4346	0.4624	0.3252	0.5059
Submaxillary	Absolute (g)	10.0045	8.2570	11.4178	9.2098	11.3650	9.3128	11.6190	8.8433	11.2710	8.1635
salivary gland:	Relative (%)	0.0837	0.0800	0.0925	0.0869	0.0953	0.0946	0.1001	0.0862	0.0985	0.0901
Testis:	Absolute (g)	12.2590	NA	13.6390	NA	20.9025	NA	13.1808	NA	14.3080	NA
	Relative (%)	0.0991	NA	0.1106	NA	0.1874	NA	0.1139	NA	0.1245	NA
Thymus:	Absolute (g)	3.8043	5.0438	5.5173	5.7265	4.0045	4.2987	6.8733	4.9683	7.5305	4.6547
	Relative (%)	0.0294	0.0452	0.0460	0.0532	0.0320	0.0413	0.0575	0.0488	0.0655	0.0526
Thyroid	Absolute (g)	0.8663	0.7238	0.9125	0.7925	0.9942	0.7898	0.8958	0.8523	0.8293	0.8090
/Parathyroid:	Relative (%)	0.0072	0.0069	0.0074	0.0074	0.0084	0.0080	0.0077	0.0082	0.0072	0.0088
Uterus/Cervix:	Absolute (g)	NA	7.7000	NA	10.6840	NA	3.7630	NA	13.4933	NA	6.9675
	Relative (%)	NA	0.0685	NA	0.1007	NA	0.0375	NA	0.1251	NA	0.0793
Gross Pathology		-	-	-	-	-	-	-	-	-	-

NA = Not applicable.
Dunnett's Test: * - P<0.05

(Continued)

Daily Dose (mg/kg)	0 (Control)		1		3		10		20	
Number of animals	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F: 4	M: 4	F:
Histopathology										
Femur/Marrow: Number examined	4	4	4	4	4	4	4	4	4	4
Hyperplasia, Hematopoietic	0	0	0	0	0	0	0	0	1	0
Necrosis, Bone marrow	0	0	0	0	0	0	0	0	1	0
Sternum/Marrow: Number examined	4	4	4	4	4	4	4	4	4	4
Necrosis, Bone marrow	0	0	0	0	0	0	0	0	1	0
Epididymis: Number examined	4	NA	4	NA	4	NA	4	NA	4	NA
Inflammation, Vascular	0		0		0		0		2	
Estrus Cycle: Number examined	NA	4	NA	4	NA	4	NA	4	NA	4
Anestrus		2		0		3		0		2
Proestrus		0		1		0		0		1
Estrus		1		0		0		0		0
Metestrus-Diestrus		1		3		1		4		1

- No noteworthy findings. NA = Not applicable.
Dunnett's Test: * - P<0.05

2.6.7.7E Repeated-Dose Toxicity **Report Title:** 4-Week Intravenous Toxicity and Toxicokinetic Study with YM087 (CI-1025) in Rats. **Test Article:** Conivaptan hydrochloride

Species/Strain: F344 Rats **Duration of Dosing:** 4 Weeks **Study No.** R087-TX-067
Initial Age: 12-13 Weeks **Duration of Postdose:** -
Date of First Dose: 11 Feb 1999 **Method of Administration:** Intravenous, bolus at 10 mL/kg **GLP Compliance:** Yes
Vehicle/Formulation: Vehicle, [redacted] propylene glycol, [redacted] ethanol, and
Special Features: None lactic acid sufficient to adjust pH to 5.3 ± 0.2. Diluent: 5% dextrose solution
No Observed Adverse Effect Level: 1.25 mg/kg

Daily Dose (mg/kg)		0 (Control)		0.5		1.25		2.5	
Number of Animals		M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Toxicokinetics: Day 26									
C_{max} (ng/mL)		NA	NA	232	181	545	593	1190	1015
$AUC_{0\text{-}24}$ (ng·hr/mL)		NA	NA	373	482	1249	1339	4143	3192
Noteworthy Findings									
Died or Sacrificed Moribund		0	0	0	0	0	0	0	0
Clinical Observations		-	-	-	-	-	-	-	-
Body Weights (g):	Week 1	260	163	259	161	260	163	261	162
	Week 2	269	168	267	167	264	166	266	169
	Week 3	283	172	279	173	272	171	275	174
	Week 4	288	171	285	176	281	173	282	177
	Week 5	294	174	290	177	284	176	283	179
Food Consumption (g/week):	Week 1	127	93	125	86	115	81	112 *	85
	Week 2	134	98	135	95	126	99	125	103
	Week 3	127	94	129	93	119	91	128	95
	Week 4	136	97	138	100	132	101	135	108 *
Water Consumption (mL/day):	Week 1	40	37	111 *	106 *	170 *	136 *	248 *	205 *
	Week 2	41	46	114 *	90 *	150 *	115 *	223 *	157 *
	Week 3	44	56	122 *	107 *	169 *	130 *	253 *	162 *
	Week 4	40	43	128 *	108 *	192 *	149 *	251 *	173 *
Ophthalmoscopy		-	-	-	-	-	-	-	-

- No noteworthy findings. NA = Not applicable.
Dunnett's Test: * - P<0.05

Daily Dose (mg/kg)	0 (Control)		0.5		1.25		2.5	
Number of animals	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Hematology: Week 5								
Number examined	10	10	10	10	10	10	10	10
RBC (10^6/µL)	8.31	7.07	8.10	6.86	8.09	6.80*	7.90*	7.07
Hemoglobin (g/dL)	14.6	13.6	14.3	13.3	14.5	13.3	14.1*	13.7
PCV (%)	44.1	40.4	42.8*	39.6	43.6	39.3	42.8*	40.6
Platelet (10^3/µL)	930	1003	901	984	872	1003	872	965
MPV (fL)	5.5	5.5	5.6	5.6	5.5	5.5	5.5	5.5
RDW (%)	18.9	15.3	19.2	15.2	19.7	15.5	19.5	15.6
PT (sec)	12.4	11.7	12.4	12.0	12.2	12.0	12.0	12.0
APTT (sec)	17.0	13.8	17.3	13.7	16.9	13.7	16.8	13.8
WBC (10^3/µL)	5.8	4.2	5.6	4.6	5.9	4.8	5.8	5.0
Blood Chemistry: Week 5								
Number examined	10	10	10	10	10	10	10	10
Glucose (mg/dL)	122	114	126	108	121	112	121	111
BUN (mg/dL)	16	18	19*	19	20*	20*	21*	20*
Creatinine (mg/dL)	0.8	0.8	0.8	0.7	0.7	0.7	0.8	0.8
Total protein (g/dL)	7.4	7.2	7.0*	6.7*	7.0*	6.7*	6.9*	6.7*
Albumin (g/dL)	4.9	4.8	4.7*	4.5*	4.8	4.6*	4.6*	4.6*
Globulin (g/dL)	2.5	2.4	2.3*	2.2*	2.2*	2.1*	2.2*	2.1*
A/G Ratio	2.0	2.0	2.0	2.0	2.2*	2.1*	2.1	2.2*
Total bilirubin (mg/dL)	0.2	0.2	0.1	0.2	0.1	0.2	0.1	0.2
Cholesterol (mg/dL)	65	80	59	76	58	68*	57*	70*
Triglyceride (mg/dL)	113	34	95	38	65*	34	58*	34
AST (IU/L)	87	90	86	84	85	78*	86	82
ALT (IU/L)	51	42	52	40	48	34*	52	36*
ALP (IU/L)	117	93	114	93	113	93	105	91
Calcium (mg/dL)	10.9	10.7	10.8	10.6	10.7	10.5	10.7	10.4*
Inorganic phosphorus (mg/dL)	8.5	6.9	8.1	7.4	8.2	7.3	8.4	7.5
Sodium (mmol/L)	143	143	142*	141*	141*	140*	141*	140*
Potassium (mmol/L)	5.1	5.2	5.3	5.1	5.2	5.1	5.2	5.0
Chloride (mmol/L)	101	103	99	102*	100	102	100	101*

- No noteworthy findings.
Dunnett's Test: * - P<0.05

(Continued)

2.6.7.7.E Repeat-Dose Toxicity Study No. R087-TX-067 (Continued)

Daily Dose (mg/kg)	0 (Control)		0.5		1.25		2.5	
Number of animals	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Hematology: Week 5								
Number examined	10	10	10	10	10	10	10	10
RBC (10^6/µL)	8.31	7.07	8.10	6.86	8.09	6.80*	7.90*	7.07
Hemoglobin (g/dL)	14.6	13.6	14.3	13.3	14.5	13.3	14.1*	13.7
PCV (%)	44.1	40.4	42.8*	39.6	43.6	39.3	42.8*	40.6
Platelet (10^3/µL)	930	1003	901	984	872	1003	872	965
MPV (fL)	5.5	5.5	5.6	5.6	5.5	5.5	5.5	5.5
RDW (%)	18.9	15.3	19.2	15.2	19.7	15.5	19.5	15.6
PT (sec)	12.4	11.7	12.4	12.0	12.2	12.0	12.0	12.0
APTT (sec)	17.0	13.8	17.3	13.7	16.9	13.7	16.8	13.8
WBC (10^3/µL)	5.8	4.2	5.6	4.6	5.9	4.8	5.8	5.0
Blood Chemistry: Week 5								
Number examined	10	10	10	10	10	10	10	10
Glucose (mg/dL)	122	114	126	108	121	112	121	111
BUN (mg/dL)	16	18	19*	19	20*	20*	21*	20*
Creatinine (mg/dL)	0.8	0.8	0.8	0.7	0.7	0.7	0.8	0.8
Total protein (g/dL)	7.4	7.2	7.0*	6.7*	7.0*	6.7*	6.9*	6.7*
Albumin (g/dL)	4.9	4.8	4.7*	4.5*	4.8	4.6*	4.6*	4.6*
Globulin (g/dL)	2.5	2.4	2.3*	2.2*	2.2*	2.1*	2.2*	2.1*
A/G Ratio	2.0	2.0	2.0	2.0	2.2*	2.1*	2.1	2.2*
Total bilirubin (mg/dL)	0.2	0.2	0.1	0.2	0.1	0.2	0.1	0.2
Cholesterol (mg/dL)	65	80	59	76	58	68*	57*	70*
Triglyceride (mg/dL)	113	34	95	38	65*	34	58*	34
AST (IU/L)	87	90	86	84	85	78*	86	82
ALT (IU/L)	51	42	52	40	48	34*	52	36*
ALP (IU/L)	117	93	114	93	113	93	105	91
Calcium (mg/dL)	10.9	10.7	10.8	10.6	10.7	10.5	10.7	10.4*
Inorganic phosphorus (mg/dL)	8.5	6.9	8.1	7.4	8.2	7.3	8.4	7.5
Sodium (mmol/L)	143	143	142*	141*	141*	140*	141*	140*
Potassium (mmol/L)	5.1	5.2	5.3	5.1	5.2	5.1	5.2	5.0
Chloride (mmol/L)	101	103	99	102*	100	102	100	101*

- No noteworthy findings.
Dunnett's Test: * - P<0.05

Daily Dose (mg/kg)		0 (Control)		0.5		1.25		2.5	
Number of animals		M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Urinalysis: Week 5									
Number examined		10	10	10	10	10	10	10	10
Volume: 8 hr (mL)		2.4	1.2	35.8*	25.4*	58.9*	39.6*	76.2*	50.9*
16 hr (mL)		6.0	6.8	1.5*	1.8*	4.1	1.3*	6.8	5.5
24 hr (mL)		8.4	8.0	37.3*	27.2*	62.9*	41.0*	83.0*	56.3*
Specific gravity		1.035	1.030	1.040	1.036	1.024*	1.024	1.014*	1.017*
pH		7.3	7.2	6.8	6.6*	6.8*	7.2	7.2	7.0
Organ Weights									
Adrenal:	Absolute (g)	0.0569	0.0615	0.0564	0.0584	0.0667*	0.0701	0.0683*	0.0654
	Relative (%)	0.0213	0.0394	0.0214	0.0369	0.0262*	0.0452	0.0268*	0.0411
Brain:	Absolute (g)	1.9696	1.8687	1.9729	1.8518	1.9774	1.8278	1.9562	1.8442
	Relative (%)	0.7380	1.1991	0.7499	1.1686	0.7789	1.1800	0.7660	1.1587
Epididymides:	Absolute (g)	1.0217	NA	0.9404	NA	0.9773	NA	0.9557	NA
	Relative (%)	0.3830	NA	0.3574	NA	0.3829	NA	0.3741	NA
Heart:	Absolute (g)	0.8600	0.6435	0.8240	0.6098	0.8677	0.5948	0.8143	0.6006
	Relative (%)	0.3219	0.4122	0.3131	0.3842	0.3403	0.3834	0.3188	0.3768
Kidney:	Absolute (g)	1.7986	1.1831	1.7583	1.1674	1.7505	1.1816	1.7348	1.1950
	Relative (%)	0.6726	0.7582	0.6679	0.7366	0.6880	0.7625	0.6786	0.7502
Liver:	Absolute (g)	7.5463	4.4340	7.4288	4.4158	6.9581	4.3689	7.0537	4.5229
	Relative (%)	2.8217	2.8430	2.8227	2.7861	2.7290	2.8182	2.7538	2.8396
Lung:	Absolute (g)	1.1031	0.8471	1.1217	0.8535	1.0796	0.8493	1.0866	0.8854
	Relative (%)	0.4132	0.5436	0.4263	0.5382	0.4249	0.5481	0.4252	0.5561
Ovary:	Absolute (g)	NA	0.1007	NA	0.0961	NA	0.1007	NA	0.0930
	Relative (%)	NA	0.0645	NA	0.0607	NA	0.0647	NA	0.0583
Pituitary:	Absolute (g)	0.0099	0.0148	0.0081	0.0123	0.0136	0.0129	0.0078	0.0127
	Relative (%)	0.0037	0.0095	0.0031	0.0078	0.0053	0.0083	0.0030	0.0080
Prostate:	Absolute (g)	0.6796	NA	0.6086	NA	0.7113	NA	0.6454	NA
	Relative (%)	0.2535	NA	0.2314	NA	0.2776	NA	0.2523	NA
Spleen:	Absolute (g)	0.6133	0.4366	0.6019	0.4552	0.6065	0.4479	0.5880	0.4419
	Relative (%)	0.2295	0.2800	0.2285	0.2870	0.2386	0.2889	0.2301	0.2773

Dunnett's Test: * - P<0.05

(Continued)

2.6.7.7.E Repeat-Dose Toxicity Study No. R087-TX-067 (Continued)

Daily Dose (mg/kg)		0 (Control)		0.5		1.25		2.5	
Number of animals		M: 10	F: 10	M: 10	F: 10	M: 10	M: 10	F: 10	M: 10
Organ Weights (Continued)									
Salivary Gland,	Absolute (g)	0.4533	0.3362	0.4644	0.3294	0.4527	0.3109	0.4500	0.3130
Submaxillary:	Relative (%)	0.1700	0.2156	0.1763	0.2079	0.1778	0.2008	0.1761	0.1966
Seminal Vesicles:	Absolute (g)	0.9250	NA	0.8519	NA	0.7655	NA	0.8021	NA
	Relative (%)	0.3468	NA	0.3231	NA	0.2970	NA	0.3138	NA
Testis:	Absolute (g)	2.9472	NA	2.8502	NA	2.8680	NA	2.9594	NA
	Relative (%)	1.1039	NA	1.0830	NA	1.1256	NA	1.1584*	NA
Thymus:	Absolute (g)	0.2179	0.2092	0.1886	0.1992	0.1804*	0.2070	0.1711*	0.2026
	Relative (%)	0.0812	0.1340	0.0716	0.1255	0.0710	0.1331	0.0667	0.1270
Thyroid/Parathyroid:	Absolute (g)	0.0191	0.0162	0.0173	0.0157	0.0220	0.0158	0.0152	0.0164
	Relative (%)	0.0071	0.0104	0.0066	0.0099	0.0086	0.0102	0.0059	0.0103
Uterus:	Absolute (g)	NA	0.4989	NA	0.4519	NA	0.4720	NA	0.4249
	Relative (%)	NA	0.3194	NA	0.2849	NA	0.3046	NA	0.2671
Gross Pathology		-	-	-	-	-	-	-	-
Histopathology									
Injection site: Number examined		10	10	10	10	10	10	10	10
Exudate, epidermal surface		1	1	0	1	1	4	0	1
Hemorrhage		6	4	6	7	6	5	7	6
Inflammation, chronic, perivascular		2	0	1	2	1	2	0	0
Inflammation, chronic-active, perivascular		8	10	6	7	7	6	10	9
Inflammation, chronic, subcutaneous		1	0	0	0	0	0	0	0
Necrosis, vascular/perivascular		4	4	1	5	3	6	7	5
Proliferation, vascular intima		2	2	0	1	3	1	6	5
Thrombus		1	3	1	2	2	2	6	1
Ulceration, epidermal		1	0	1	0	0	0	0	0
Vasculitis		6	6	9	5	7	6	8	8
Adrenal, Cortex: Number examined		10	10	10	0	10	0	10	10
Hypertrophy, cortical cell, inner cortex		1	0	1	0	1	0	7	0

- No noteworthy findings. NA = Not applicable.
Dunnett's Test (Aspin Welch Test, if variance was unequal): * - P<0.05 ** - p<0.01

2.6.7.7G Repeated-Dose Toxicity | Report Title: 4-Week Continuous Intravenous Infusion Toxicity | Test Article: Conivaptan

2.6.7.7G Repeat-Dose Toxicity | Study No. R087-TX-069 (Continued)

Daily Dose (mg/kg)		0 (Control)		10		30		100	
Number of animals		M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Blood Chemistry (Continued)		9	10	8	7	4	6	0	0
Globulin (g/dL)		2.8	2.5	2.4	2.4	2.7	2.4	NA	NA
A/G Ratio		1.6	1.9	1.9	2.0	1.7	1.8	NA	NA
Total bilirubin (mg/dL)		0.1	0.2	0.2	0.2	0.2	0.2	NA	NA
Cholesterol (mg/dL)		68	65	72	66	62	57	NA	NA
Triglyceride (mg/dL)		71	36	38*	28	38	32	NA	NA
AST (IU/L)		97	100	104	112	110	131*	NA	NA
ALT (IU/L)		45	39	53	48*	50	44	NA	NA
ALP (IU/L)		181	143	125	122	125	123	NA	NA
Calcium (mg/dL)		10.7	10.8	10.4	10.4*	10.6	10.2*	NA	NA
Inorganic phosphorus (mg/dL)		6.7	6.6	7.3	7.1	7.4	7.0	NA	NA
Sodium (mmol/L)		151	153	152	151	154	152	NA	NA
Potassium (mmol/L)		4.9	4.7	4.8	4.8	5.0	4.6	NA	NA
Chloride (mmol/L)		108	112	111	111	112*	110	NA	NA
Urinalysis: Week 5									
Number examined		9	10	8	7	4	6	0	0
Volume:	16 hr (mL)	13.7	11.0	42.8*	32.3*	39.2*	28.0*	NA	NA
	8 hr (mL)	1.9	1.4	25.0*	15.5*	27.4*	14.1*	NA	NA
	24 hr (mL)	15.6	12.4	67.8*	47.8*	66.6*	42.1*	NA	NA
Specific gravity		1.021	1.020	1.007*	1.007*	1.008*	1.010*	NA	NA
pH		7.4	7.3	7.3	7.3	7.4	7.2	NA	NA
Organ Weights	Number examined	9	10	8	7	4	6	0	0
Adrenal:	Absolute (g)	0.0546	0.0514	0.0543	0.0554	0.0548	0.0585*	NA	NA
	Relative (%)	0.0225	0.0332	0.0242	0.0372	0.0237	0.0403*	NA	NA
Brain:	Absolute (g)	1.9742	1.8393	1.9013	1.7770	1.8691	1.7843	NA	NA
	Relative (%)	0.8084	1.1863	0.8484	1.1945	0.8056	1.2256	NA	NA
Epididymides:	Absolute (g)	0.8609	NA	0.7500	NA	0.7641	NA	NA	NA
	Relative (%)	0.3524	NA	0.3327	NA	0.3271	NA	NA	NA

NA = Not applicable.
Dunnett's Test: * - P<0.05

Daily Dose (mg/kg)		0 (Control)		10		30		100	
Number of Animals		M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Organ Weights (Continued)									
Heart:	Absolute (g)	0.8128	0.5898	0.8309	0.6172	0.8179	0.5773	NA	NA
	Relative (%)	0.3326	0.3802	0.3703*	0.4141	0.3518	0.3941	NA	NA
Kidney:	Absolute (g)	1.6664	1.1097	1.5593	1.1134	1.6319	1.0895	NA	NA
	Relative (%)	0.6809	0.7162	0.6949	0.7486	0.7029	0.7486	NA	NA
Liver:	Absolute (g)	7.1882	4.3037	5.8142*	4.2713	6.5705	4.1194	NA	NA
	Relative (%)	2.9328	2.7730	2.5882*	2.8686	2.8282	2.8205	NA	NA
Lung:	Absolute (g)	1.2269	0.8337	1.0008	0.8778	1.0979	0.8754	NA	NA
	Relative (%)	0.5039	0.5363	0.4468	0.5899	0.4714	0.6014	NA	NA
Ovary:	Absolute (g)	NA	0.0855	NA	0.0770	NA	0.0700	NA	NA
	Relative (%)	NA	0.0548	NA	0.0517	NA	0.0478	NA	NA
Pituitary:	Absolute (g)	0.0089	0.0121	0.0084	0.0114	0.0077	0.0125	NA	NA
	Relative (%)	0.0036	0.0077	0.0038	0.0077	0.0034	0.0087	NA	NA
Prostate:	Absolute (g)	0.4895	NA	0.3450	NA	0.3842	NA	NA	NA
	Relative (%)	0.1983	NA	0.1521	NA	0.1636	NA	NA	NA
Spleen:	Absolute (g)	0.7278	0.4227	0.5266	0.4134	0.5300	0.3593	NA	NA
	Relative (%)	0.3011	0.2733	0.2340	0.2775	0.2282	0.2429	NA	NA
Salivary gland:	Absolute (g)	0.4420	0.3393	0.4156	0.3291	0.4160	0.3204	NA	NA
	Relative (%)	0.1811	0.2190	0.1850	0.2210	0.1791	0.2194	NA	NA
Seminal vesicle:	Absolute (g)	0.5775	NA	0.4048	NA	0.5822	NA	NA	NA
	Relative (%)	0.2319	NA	0.1767	NA	0.2470	NA	NA	NA
Testis:	Absolute (g)	2.7160	NA	2.4443	NA	2.5486	NA	NA	NA
	Relative (%)	1.1115	NA	1.0854	NA	1.0940	NA	NA	NA
Thymus:	Absolute (g)	0.2314	0.2183	0.2102	0.2019	0.1943	0.2381	NA	NA
	Relative (%)	0.0953	0.1404	0.0935	0.1357	0.0838	0.1619	NA	NA
Thyroid/Parathyroid:	Absolute (g)	0.0229	0.0174	0.0149*	0.0132	0.0172	0.0134	NA	NA
	Relative (%)	0.0094	0.0111	0.0067	0.0088	0.0074	0.0092	NA	NA
Uterus:	Absolute (g)	NA	0.3375	NA	0.3074	NA	0.2598	NA	NA
	Relative (%)	NA	0.2149	NA	0.2061	NA	0.1783	NA	NA

NA = Not applicable.
Dunnett's Test: * - P<0.05

(Continued) l)

2.6.7.7G Repeated-Dose Toxicity Study Number: R087-TX-069 (Continued)

Daily Dose (mg/kg)	0 (Control)		10		30		100	
Number of Animals	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Gross Pathology								
Liver:								
Raised focus/area	0	0	0	0	0	0	1	0
Diffusely light	0	0	0	0	0	0	1	0
Large	0	0	0	0	0	0	1	0
Lung:								
Light focus/area	0	0	0	0	0	0	1	1
Heart:								
Mottled	0	0	0	0	0	1	0	1
Spleen:								
Small	0	0	0	0	0	0	1	0
Thymus:								
Diffusely red	3	3	0	2	1	2	2	5
Light focus/area	0	0	0	0	0	1	1	1
Lacrimal grand:								
Red focus/area	0	0	0	0	0	0	1	0
Catheter exit/entrance/tip:								
Red focus/area	0	0	0	2	2	0	1	2
Thickened	3	1	5	2	8	9	9	10
Skin:								
Crusted area	0	0	0	0	0	0	1	0
Seminal vesicles:								
Gelatinous	0	0	0	0	0	0	1	0
Lymph nodes, mediastinal:								
Large	1	0	1	0	4	2	1	1
Mottled	0	0	0	0	0	0	0	2
Pericardial sac:								
Contains fluid	0	0	0	0	0	0	0	2
Adhesion	0	0	0	0	0	0	0	1

Daily Dose (mg/kg)	0 (Control)		10		30		100	
Number of Animals	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Histopathology								
Liver: Number examined	10	10	10	10	10	10	10	10
Vacuolation, hepatocellular	0	0	0	0	0	0	1	0
Eye: Number examined	10	10	2	3	6	4	10	10
Inflammation, acute, corneal	0	0	0	0	0	0	0	1
Mineralization, corneal	0	0	1	1	3	0	1	2
Ulceration, corneal	0	0	0	1	0	0	0	1
Lung: Number examined	10	10	2	3	6	4	10	10
Edema, pleural	0	0	0	0	0	0	0	1
Emboli	0	0	0	0	0	0	1	0
Fibrosis, pleural/subpleural	0	0	0	0	0	0	1	2
Hemorrhage	0	0	0	0	0	0	1	1
Infiltrate, eosinophils	0	0	0	0	2	1	0	1
Inflammation	2	0	0	1	1	3	5	6
Thrombus	1	0	0	0	0	1	0	1
Trachea: Number examined	10	10	2	3	6	4	10	10
Edema/Fibrosis	0	0	0	0	0	0	0	1
Esophagus: Number examined	10	10	2	3	6	3	10	10
Edema/Fibrosis / Inflammation	0	0	0	0	0	0	1	1
Heart: Number examined	10	10	2	3	6	5	10	10
Inflammation	0	0	0	0	0	0	0	2
Thymus: Number examined	10	10	5	4	7	7	9	10
Depletion, lymphocytic	0	0	1	0	0	2	3	0
Edema	0	1	0	0	0	2	2	4
Fibrosis	0	1	0	0	0	1	1	4
Hemorrhage	1	2	2	0	0	1	2	4
Inflammation	0	0	0	0	0	0	2	3
Harderian gland: Number examined	10	10	2	3	6	4	10	10
Edema	0	0	0	0	0	0	0	1
Lacrimal gland: Number examined	10	10	2	3	6	4	10	10
Edema	0	0	0	0	0	0	0	1

(Continued)

2.6.7.7G Repeated-Dose Toxicity — Study Number: R087-TX-069 (Continued)

Daily Dose (mg/kg)		0 (Control)		10		30		100	
Number of Animals		M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Histopathology (Continued)									
Salivary gland:	Number examined	10	10	2	3	6	4	10	10
Edema		0	0	0	0	0	0	0	1
Catheter, exit:	Number examined	10	10	3	3	6	5	10	10
Edema		6	3	3	1	0	2	4	5
Fibrosis		7	8	3	3	5	4	8	10
Foreign body, hair shaft		1	2	0	0	1	0	1	0
Hemorrhage		1	0	2	2	0	1	1	4
Inflammation		4	5	1	2	4	3	5	8
Mineralization		0	1	0	0	0	0	1	1
Catheter, entrance:	Number examined	10	10	2	3	9	6	10	10
Edema		0	1	1	1	1	1	1	2
Fibrosis		9	10	2	2	9	5	8	9
Foreign body, hair shaft		1	0	0	0	1	0	1	1
Hemorrhage		1	0	1	1	1	0	2	2
Inflammation		6	5	0	1	4	3	7	3
Mineralization		4	5	0	1	4	4	3	0
Thrombus		0	1	0	1	2	1	1	6
Catheter, tip:	Number examined	10	10	4	4	9	10	10	10
Edema		0	0	0	0	1	1	2	4
Fibrosis		4	2	2	3	7	8	8	9
Hemorrhage		1	1	0	0	1	0	4	0
Inflammation		2	1	0	1	6	3	7	5
Mineralization		0	0	0	0	0	3	0	0
Thrombus		6	8	4	4	7	9	7	10
Skin:	Number examined	10	10	2	3	6	5	10	10
Exudate, acute		0	0	0	0	0	0	1	0
Mediastinum:	Number examined	0	0	0	0	0	0	1	0
Fibrosis/Hemorrhage		0	0	0	0	0	0	1	0
Pericardial sac:	Number examined	0	0	0	0	0	0	0	3
Bacterial colonies/Edema/Fibrosis/ Hemorrhage/Inflammation		0	0	0	0	0	0	0	3

2.6.7.7.J Repeated-Dose Toxicity **Report Title:** 4 -Week Bolus Intravenous Injection Toxicity Study with YM087 (CI-1025) in Dogs **Test Article:** Conivaptan hydrochloride

Species/Strain: Beagle Dogs **Duration of Dosing:** 4 Weeks **Study No.** R087-TX-072
Initial Age: 11-12 Months **Duration of Postdose:** None
Date of First Dose: 21 Sep 1998 **Method of Administration:** Intravenous, bolus at 4 mL/kg **GLP Compliance:** Yes
Vehicle/Formulation: Vehicle: [redacted] propylene glycol, [redacted] ethanol, and lactic acid sufficient to adjust pH to 3.3 ± 0.2. Diluent: 5% dextrose solution

Special Features: One female at 10 mg/kg was found dead on Day 3, and remaining five animals at 10 mg/kg were sacrificed on Day 16.
No Observed Adverse Effect Level: 2 mg/kg

Daily Dose (mg/kg)		0 (Control)		2		5		10	
Number of animals		M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Toxicokinetics:									
C_{max} (ng/mL):	Day 1	NA	NA	1440	1500	3727	3673	6783	8080
	Week 4 [a]	NA	NA	1467	1387	4320	3940	13633	9790 [b]
AUC_{0-24} (ng·hr/mL):	Day 1	NA	NA	13383	10520	48149	42433	102028	102077
	Week 4 [a]	NA	NA	13517	10141	52139	39555	211119	100109 [b]
Noteworthy findings									
Died or Sacrificed Moribund		0	0	0	0	0	0	0	1
Clinical Observations [c]									
Appears dehydrated		0	0	0	0	0	1	0	0
Swollen									
Limb-front-left		0	0	0	0	0	0	1	0
Limb-front-right		0	0	0	0	0	1	0	0
Limbs-all		0	0	0	0	0	0	2	1
Thin appearance		0	0	0	1	0	1	0	0
Tremor -entire body		0	0	0	0	0	1	0	1
Ataxia									
Moderate		0	0	0	0	0	1	1	0
Hypoactivity									
Moderate		0	0	0	0	0	1	0	0
Severe		0	0	0	0	0	1	0	0

NA = Not applicable.
a - Day 15 for 10 mg/kg dose group.
b - Data of 1 animal.
c - Number of animals affected.

Daily Dose (mg/kg)	0 (Control)		2		5		10	
Number of animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Clinical Observations [a] (Continued)								
Recumbent-sternal	0	0	0	0	0	0	0	1
Vocalization during dosing	0	0	0	0	0	0	0	1
Vomitus								
Yellow in color	0	0	0	0	0	1	0	0
Containing food	0	0	1	2	1	0	0	0
Excessive salivation	1	0	1	0	0	1	1	2
Appears to be cycling	0	0	0	1	0	1	0	0
Discolored feces-yellow in color	0	0	0	0	0	0	0	1
Mucoid feces	1	0	0	0	0	0	1	0
Non-formed feces	2	0	0	0	0	1	0	0
Clear discharge from eyes	0	0	0	1	0	0	0	0
Injected sclera-eye right	0	0	0	0	0	1	0	0
Body Weights (kg):								
Pretreatment	8.4	6.8	8.6	6.4	8.4	6.8	8.8	6.6
Week 1	8.2	6.6	8.5	6.0	8.3	6.6	8.6	6.3
Week 2	8.4	6.6	8.4	6.4	8.2	6.4	8.0	6.4
Week 3	8.5	6.6	8.6	6.5	8.4	6.8	NE	NE
Week 4	8.3	6.7	8.3	6.2	8.2	6.8	NE	NE
Food Consumption (g/day):								
Day 1	219	227	157	58	143	95	108	119
Day 9	247	244	266	163*	220	298	190	148
Day 16	251	150	236	187	388	279*	NE	NE
Day 21	236	194	267	203	253	343*	NE	NE
Day 28	307	220	134*	142	188	262	NE	NE
Day 29	241	201	302	242	341	375	NE	NE

NE = Not examined.
ANOVA: * - P<0.05
a - Number of animals affected.

(Continued)

2.6.7.7J Repeated-Dose Toxicity **Study No. R087-TX-072 (Continued)**

Daily Dose (mg/kg)	0 (Control)		2		5		10	
Number of animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Water Consumption (g/day):								
Day 1	898	766	2778	1492	2713	2472	2997	1906
Day 4	604	1328	2485*	904	2602*	1541	2433*	3253
Day 8	1422	616	1310	1694	2069	1366	2094	2715
Day 15	772	530	1156	761	1465	1064	NE	4547
Day 22	651	838	552	903	822	844	NE	NE
Day 29	735	1587	1082	1427	1105	1196	NE	NE
Electrocardiography/Blood pressure	-	-	-	-	-	-	-	-
Ophthalmoscopy	-	-	-	-	-	-	-	-
Hematology								
RBC (10^6/µL):								
Pretreatment (Day -7)	6.71	6.89	7.10	6.86	7.33	6.78	7.37	6.79
Pretreatment (Day -3)	6.61	7.08	7.02	6.93	7.27	6.39	6.88	6.78
Day 15	NE	NE	NE	NE	NE	NE	6.34	6.03
Day 23	6.33	6.38	6.70	6.04	6.64	6.12	NE	NE
Reticulocyte (%RBC):								
Pretreatment (Day -7)	0.1	0.2	0.3	0.4	0.3	0.3	0.2	0.2
Pretreatment (Day -3)	0.0	0.0	0.5	0.2	0.5	0.3	0.4	0.1
Day 15	NE	NE	NE	NE	NE	NE	0.7	1.1
Day 23	0.2	0.4	0.3	0.2	0.3	0.2	NE	NE
Reticulocyte (10^6/µL):								
Pretreatment (Day -7)	0.01	0.01	0.02	0.02	0.02	0.02	0.02	0.01
Pretreatment (Day -3)	0.00	0.00	0.03	0.01	0.04	0.02 *	0.03	0.01
Day 15	NE	NE	NE	NE	NE	NE	0.05	0.07
Day 23	0.01	0.03	0.02	0.01	0.02	0.01	NE	NE
Hemoglobin (g/dL):								
Pretreatment (Day -7)	15.0	15.5	16.0	16.5	16.3	15.6	16.9	15.3
Pretreatment (Day -3)	14.3	15.7	15.6	16.4	16.3	14.6	15.5	15.3
Day 15	NE	NE	NE	NE	NE	NE	14.4	13.7
Day 23	14.0	14.3	15.2	14.4	15.1	14.2	NE	NE

NE = Not examined.
ANOVA: * - P<0.05

Daily Dose (mg/kg)	0 (Control)		2		5		10	
Number of animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Hematology (Continued)								
PCV (%):								
Pretreatment (Day -7)	46.4	46.2	49.1	49.4	50.1	47.2	51.4	46.8
Pretreatment (Day -3)	44.9	48.4	48.7	50.5	49.9	45.0	47.4	47.0
Day 15	NE	NE	NE	NE	NE	NE	42.6	41.3
Day 23	42.8	43.2	45.4	42.3	44.8	42.4	NE	NE
Platelet (10^3/µL)::								
Pretreatment (Day -7)	308	365	286	274	266	336	275	346
Pretreatment (Day -3)	288	366	294	294	267	327	263	344
Day 15	NE	NE	NE	NE	NE	NE	305	507
Day 23	330	403	309	329	282	330	NE	NE
RDW (%):								
Pretreatment (Day -7)	13.3	13.5	13.7	12.8	12.9	13.7	13.4	13.6
Pretreatment (Day -3)	13.5	13.6	13.7	12.7	13.3	13.5	13.7	13.4
Day 15	NE	NE	NE	NE	NE	NE	13.5	13.8
Day 23	13.3	13.4	13.3	12.8	12.9	13.0	NE	NE
MPV (fl):								
Pretreatment (Day -7)	6.4	6.7	6.4	6.3	6.4	6.9	6.6	6.4
Pretreatment (Day -3)	6.5	6.8	6.4	6.8	6.4	6.9	6.7	6.7
Day 15	NE	NE	NE	NE	NE	NE	6.7	6.5
Day 23	6.0	6.5	6.0	6.2	6.0	6.7	NE	NE
PT (sec):								
Pretreatment (Day -7)	6.2	6.2	6.6	6.7	6.5	6.6	6.2	6.2
Pretreatment (Day -3)	6.3	6.2	6.1	6.2	6.5	6.4	6.3	6.1
Day 15	NE	NE	NE	NE	NE	NE	6.1	6.1
Day 23	6.3	6.2	6.5	6.3	6.3	6.4	NE	NE
APPT (sec):								
Pretreatment (Day -7)	11.0	13.9	12.0	13.3	11.8	13.4	10.9	12.8
Pretreatment (Day -3)	10.1	13.9	10.8	11.4	10.7	11.6	10.4	11.6
Day 15	NE	NE	NE	NE	NE	NE	10.0	11.5
Day 23	10.2	13.8	10.6	11.7	10.5	11.5	NE	NE

NE = Not examined.

(Continued)

2.6.7.7J Repeated-Dose Toxicity Study No. R087-TX-072 (Continued)

Daily Dose (mg/kg) Number of animals	0 (Control) M: 3	F: 3	2 M: 3	F: 3	5 M: 3	F: 3	10 M: 3	F: 3
Hematology (Continued)								
WBC (10^3/µL):								
Pretreatment (Day -7)	5.9	9.3	7.7	7.5	7.1	8.8	6.9	8.6
Pretreatment (Day -3)	7.2	8.6	7.5	6.8	6.9	8.5	7.0	8.5
Day 15	NE	NE	NE	NE	NE	NE	16.6	11.9
Day 23	6.7	7.9	8.1	7.9	10.3	9.7	NE	NE
Segmented neutrophils/ absolute (10^3/µL):								
Pretreatment (Day -7)	3.6	5.7	4.7	4.1	3.9	5.4	4.4	5.2
Pretreatment (Day -3)	4.3	5.3	4.6	4.0	3.8	5.5	4.1	5.1
Day 15	NE	NE	NE	NE	NE	NE	12.6	7.7
Day 23	4.0	4.7	5.0	4.6	6.7	6.3	NE	NE
Lymphocytes/ absolute (10^3/µL):								
Pretreatment (Day -7)	1.6	3.0	2.4	2.8	2.3	2.5	2.0	2.7
Pretreatment (Day -3)	2.2	2.7	2.2	2.3	2.3	2.3	2.3	2.5
Day 15	NE	NE	NE	NE	NE	NE	3.1	3.3
Day 23	2.2	2.8	2.6	2.9	2.8	2.8	NE	NE
Monocytes/ absolute (10^3/µL):								
Pretreatment (Day -7)	0.4	0.3	0.3	0.3	0.5	0.3	0.4	0.5
Pretreatment (Day -3)	0.6	0.4	0.4	0.4	0.5	0.3	0.4	0.7 *
Day 15	NE	NE	NE	NE	NE	NE	0.7	0.8
Day 23	0.4	0.2	0.3	0.2	0.5	0.4	NE	NE
Eosinophils/ absolute (10^3/µL):								
Pretreatment (Day -7)	0.1	0.2	0.2	0.2	0.2	0.5	0.1	0.3
Pretreatment (Day -3)	0.1	0.2	0.1	0.2	0.2	0.4	0.1	0.2
Day 15	NE	NE	NE	NE	NE	NE	0.1	0.2
Day 23	0.1	0.3	0.1	0.2	0.2	0.2	NE	NE

NE = Not examined.
ANOVA: * - P<0.05

Daily Dose (mg/kg) Number of animals	0 (Control) M: 3	F: 3	2 M: 3	F: 3	5 M: 3	F: 3	10 M: 3	F: 3
Hematology (Continued)								
Basophils/ absolute (10^3/µL):								
Pretreatment (Day -7)	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Pretreatment (Day -3)	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.1
Day 15	NE	NE	NE	NE	NE	NE	0.1	0.1
Day 23	0.0	0.0	0.1	0.0	0.1	0.1	NE	NE
M/E Ratio:								
Day 16	NE	NE	NE	NE	NE	NE	1.29	0.88
Day 31	1.13	0.83	0.69 *	1.04	1.27	1.28	NE	NE
Blood Chemistry								
Glucose (mg/dL):								
Pretreatment (Day -7)	89	97	94	91	92	96	99	84
Pretreatment (Day -3)	89	106	89	93	91	106	97	92 *
Day 15	NE	NE	NE	NE	NE	NE	95	84
Day 23	92	100	91	95	89	95	NE	NE
Urea nitrogen (mg/dL):								
Pretreatment (Day -7)	20	14	13	20	16	13	16	13
Pretreatment (Day -3)	15	18	13	26	15	16	15	18
Day 15	NE	NE	NE	NE	NE	NE	10	8
Day 23	15	12	10 *	14	12 *	13	NE	NE
Creatinine (mg/dL):								
Pretreatment (Day -7)	0.9	0.8	0.9	0.8	0.9	0.8	0.9	0.7
Pretreatment (Day -3)	0.9	0.8	0.8	0.8	0.9	0.8	0.9	0.8
Day 15	NE	NE	NE	NE	NE	NE	0.7	0.5
Day 23	0.9	0.8	0.8	0.8	0.9	0.8	NE	NE
ALP (U/L):								
Pretreatment (Day -7)	48	45	41	46	43	67	50	51
Pretreatment (Day -3)	44	49	37	42	38	59	45	47
Day 15	NE	NE	NE	NE	NE	NE	97	81
Day 23	54	42	37	40	48	56	NE	NE

NE = Not examined.
ANOVA: * - P<0.05

(Continued)

2.6.7.7J Repeated-Dose Toxicity — Study No. R087-TX-072 (Continued)

Daily Dose (mg/kg)	0 (Control)		2		5		10	
Number of animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Blood Chemistry (Continued)								
Total cholesterol (mg/dL):								
Pretreatment (Day -7)	147	223	134	133	143	168	171	183
Pretreatment (Day -3)	126	236	133	139	132	162	147	188
Day 15	NE	NE	NE	NE	NE	NE	205	191
Day 23	119	207	110	106 *	126	130 *	NE	NE
AST (U/L):								
Pretreatment (Day -7)	24	27	23	34	22	24	28	27
Pretreatment (Day -3)	29	24	24	33	27	24	27	25
Day 15	NE	NE	NE	NE	NE	NE	26	24
Day 23	31	31	31	40	30	31	NE	NE
ALT (U/L):								
Pretreatment (Day -7)	33	27	33	32	33	27	33	25
Pretreatment (Day -3)	36	27	36	31	34	25	33	27
Day 15	NE	NE	NE	NE	NE	NE	27	22
Day 23	30	27	27	27	30	24	NE	NE
LDH (U/L):								
Pretreatment (Day -7)	78	82	50	70	52	75	68	79
Pretreatment (Day -3)	107	68	82	70	91	66	52	51
Day 15	NE	NE	NE	NE	NE	NE	60	40
Day 23	111	83	84	60	83	61	NE	NE
Total protein (g/dL):								
Pretreatment (Day -7)	5.7	5.5	5.6	5.1	5.3	5.1	5.8	5.3
Pretreatment (Day -3)	5.4	6.0	6.0	5.4	5.6	5.4	5.7	5.8
Day 15	NE	NE	NE	NE	NE	NE	5.7	5.5
Day 23	5.4	5.5	5.6	5.0	5.6	5.2	NE	NE
Albumin (g/dL):								
Pretreatment (Day -7)	3.8	3.7	3.8	3.5	3.5	3.6	3.8	3.4
Pretreatment (Day -3)	3.6	3.9	3.9	3.7	3.6	3.7	3.7	3.6
Day 15	NE	NE	NE	NE	NE	NE	3.2	3.1
Day 23	3.7	3.8	3.8	3.4	3.5 *	3.4	NE	NE

NE = Not examined.
ANOVA: * - P<0.05

Daily Dose (mg/kg)	0 (Control)		2		5		10	
Number of animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Blood Chemistry (Continued)								
Globulin (g/dL):								
Pretreatment (Day -7)	1.9	1.8	1.8	1.6	1.7	1.5	2.0	1.9
Pretreatment (Day -3)	1.8	2.0	2.1	1.7	2.0	1.7	2.0	2.1
Day 15	NE	NE	NE	NE	NE	NE	2.5	2.4
Day 23	1.7	1.7	1.8	1.6	2.1	1.7	NE	NE
A/G Ratio:								
Pretreatment (Day -7)	2.05	2.14	2.21	2.24	2.05	2.46	1.94	1.85
Pretreatment (Day -3)	2.01	1.96	1.92	2.25	1.82	2.22	1.99	1.80
Day 15	NE	NE	NE	NE	NE	NE	1.34	1.32
Day 23	2.26	2.23	2.12	2.12	1.72	1.99	NE	NE
Calcium (mg/dL):								
Pretreatment (Day -7)	10.3	10.5	10.6	10.2	10.2	10.3	10.5	10.3
Pretreatment (Day -3)	9.8	10.6	10.3	10.3	9.9	10.2	10.0	10.6
Day 15	NE	NE	NE	NE	NE	NE	10.0	9.8
Day 23	10.1	10.4	10.4	9.8	10.3	9.8	NE	NE
Total bilirubin (mg/dL):								
Pretreatment (Day -7)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Pretreatment (Day -3)	0.1	0.1	0.1	0.2	0.1	0.2	0.1	0.1
Day 15	NE	NE	NE	NE	NE	NE	0.2	0.2
Day 23	0.0	0.1	0.1	0.0	0.1	0.1	NE	NE
Creatine kinase(U/L):								
Pretreatment (Day -7)	106	121	93	121	92	122	293	134
Pretreatment (Day -3)	135	117	121	112	116	126	137	106
Day 15	NE	NE	NE	NE	NE	NE	110	94
Day 23	169	105	158	161	171	107	NE	NE
Triglyceride (mg/dL):								
Pretreatment (Day -7)	32	40	22	30	25	34	33	36
Pretreatment (Day -3)	29	39	26	32	26	27	36	35
Day 15	NE	NE	NE	NE	NE	NE	40	31
Day 23	28	39	23	33	19	33	NE	NE

NE = Not examined.

(Continued)

2.6.7.7J Repeated-Dose Toxicity Study No. R087-TX-072 (Continued)

Daily Dose (mg/kg)	0 (Control)		2		5		10	
Number of animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Blood Chemistry (Continued)								
Inorganic phosphorus (mg/dL):								
Pretreatment (Day -7)	4.7	4.6	4.7	4.7	4.8	4.2	4.8	4.5
Pretreatment (Day -3)	4.3	4.5	4.6	4.5	4.3	4.1	4.4	4.5
Day 15	NE	NE	NE	NE	NE	NE	4.5	4.1
Day 23	4.6	4.1	4.9	4.4	4.7	4.3	NE	NE
GGT (U/L):								
Pretreatment (Day -7)	6	6	6	5	6	6	6	6
Pretreatment (Day -3)	4	5	5	4	4	5	5	5
Day 15	NE	NE	NE	NE	NE	NE	5	5
Day 23	5	4	4	5	5	4	NE	NE
Sodium (mEq/L):								
Pretreatment (Day -7)	149	146	147	147	149	147	149	146
Pretreatment (Day -3)	145	148	146	153	146	147	145	148
Day 15	NE	NE	NE	NE	NE	NE	148	147
Day 23	141	140	140	140	142	137	NE	NE
Potassium (mEq/L):								
Pretreatment (Day -7)	4.5	4.5	4.3	4.6	4.5	4.4	4.4	4.3
Pretreatment (Day -3)	4.4	4.4	4.3	4.4	4.5	4.4	4.4	4.4
Day 15	NE	NE	NE	NE	NE	NE	4.2	4.2
Day 23	4.3	4.4	4.3	4.3	4.4	4.0	NE	NE
Chloride (mEq/L):								
Pretreatment (Day -7)	115	112	112	114	114	113	114	113
Pretreatment (Day -3)	112	115	113	119	113	114	111	114
Day 15	NE	NE	NE	NE	NE	NE	114	113
Day 23	111	109	110	110	112	107	NE	NE

NE = Not examined.

Daily Dose (mg/kg)		0 (Control)		2		5		10	
Number of animals		M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Urinalysis									
Volume (mL):									
Day -8/-7	0-8 hr	68	128	101	137	10	139	165	55
	8-24 hr	41	46	65	165	31	44	69	75
Day -4/-3	0-8 hr	21	68	79	36	52	108	183	104
	8-24 hr	123	58	43	54	31	69	66	60
Day 14/15	0-8 hr	NE	NE	NE	NE	NE	NE	334	409
	8-24 hr	NE	NE	NE	NE	NE	NE	275	757
Day 22/23	0-8 hr	43	153	85	250	148	171	NE	NE
	8-24 hr	38	221	114	248	227 *	329	NE	NE
Osmolality (mOsm/kg):									
Day -8/-7	0-8 hr	1359	806	907	412	1574	1406	300	1080
	8-24 hr	1784	1695	1749	1252	1943	1616	1615	1797
Day -4/-3	0-8 hr	2263	1464	1638	1692	1712	905	743	647
	8-24 hr	1533	1690	2196	1946	2104	1637	1429	2004
Day 14/15	0-8 hr	NE	NE	NE	NE	NE	NE	500	337
	8-24 hr	NE	NE	NE	NE	NE	NE	606	164
Day 22/23	0-8 hr	1611	1001	633	299	501	481	NE	NE
	8-24 hr	2481	1635	754 *	529	435 *	532	NE	NE
Organ Weights									
Number examined		3	3	3	3	3	3	3	2
Terminal Body Weight (g)		8033.3	6400.0	8233.3	6133.3	7900.0	6366.7	7933.3	6150.0
Adrenal:	Absolute (g)	1.21	1.27	1.37	1.26	1.30	1.15	1.34	1.19
	Relative (%)	0.015	0.020	0.017	0.021	0.017	0.018	0.017	0.019
Brain:	Absolute (g)	71.2	64.8	69.2	69.3	76.9	69.2	77.3	67.5
	Relative (%)	0.89	1.02	0.84	1.14	0.98	1.10	0.98	1.10
Heart:	Absolute (g)	72.0	55.0	77.5	54.5	67.3	56.5	72.0	56.3
	Relative (%)	0.90	0.86	0.94	0.89	0.85	0.88	0.92	0.92
Kidney:	Absolute (g)	41.0	30.8	49.9	27.9	43.1	30.8	44.3	29.4
	Relative (%)	0.51	0.48	0.61	0.46	0.55	0.49	0.56	0.48

NE = Not examined.
ANOVA: * - P<0.05

(Continued)

2.6.7.7J Repeated-Dose Toxicity Study No. R087-TX-072 (Continued)

Daily Dose (mg/kg)		0 (Control)		2		5		10	
Number of animals		M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Organ Weights (Continued)									
Liver/ gallbladder:	Absolute (g)	203	167	191	156	204	178	231	176
	Relative (%)	2.5	2.6	2.3	2.5	2.6	2.8	2.9	2.9
Lung:	Absolute (g)	59.9	47.6	60.8	50.6	61.7	55.8	60.3	48.9
	Relative (%)	0.75	0.75	0.74	0.83	0.78	0.88	0.76	0.80
Submaxillary	Absolute (g)	8.5	6.1	8.2	5.4	8.6	6.6	9.0	5.5
salivary gland:	Relative (%)	0.11	0.10	0.10	0.09	0.11	0.10	0.11	0.09
Ovary:	Absolute (g)	NA	0.83	NA	0.97	NA	1.00	NA	0.76
	Relative (%)	NA	0.013	NA	0.016	NA	0.016	NA	0.012
Pituitary:	Absolute (g)	0.065	0.056	0.056	0.059	0.060	0.046	0.053	0.059
	Relative (%)	0.0008	0.0009	0.0007	0.0010	0.0008	0.0007	0.0007	0.0010
Prostate:	Absolute (g)	7.00	NA	6.15	NA	7.20	NA	6.16	NA
	Relative (%)	0.087	NA	0.075	NA	0.091	NA	0.079	NA
Spleen:	Absolute (g)	28.0	20.3	25.5	20.1	26.2	19.9	35.8	22.0
	Relative (%)	0.35	0.32	0.31	0.33	0.33	0.32	0.45	0.36
Testis/epididymis:	Absolute (g)	16.5	NA	14.7	NA	16.4	NA	15.8	NA
	Relative (%)	0.21	NA	0.18	NA	0.21	NA	0.20	NA
Thymus:	Absolute (g)	7.01	7.37	8.20	5.19	6.61	4.68	5.29	4.87
	Relative (%)	0.090	0.114	0.100	0.084	0.084	0.074	0.066	0.080
Thyroid/ parathyroid:	Absolute (g)	0.86	0.60	0.85	0.58	0.85	0.71	0.70	0.60
	Relative (%)	0.011	0.009	0.010	0.009	0.011	0.011	0.009	0.010
Uterus:	Absolute (g)	NA	4.76	NA	8.16	NA	7.55	NA	3.58
	Relative (%)	NA	0.071	NA	0.128	NA	0.114	NA	0.058
Gross Pathology									
Number examined		3	3	3	3	3	3	3	2
Injection site:									
Thickened		0	0	0	0	0	0	3	2
Liver:									
Mottled		0	0	0	0	0	0	1	1
Mammary:									
Thickened		0	1	0	0	0	1	0	1

NA = Not applicable.

Daily Dose (mg/kg)	0 (Control)		2		5		10	
Number of animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Gross Pathology (Continued)								
Ovary:								
Unequally sized	NA	1	NA	0	NA	1	NA	0
Enlarged	NA	0	NA	1	NA	0	NA	0
Thymus:								
Small	0	0	0	0	0	0	1	0
Thyroid:								
Unequally sized	0	0	0	0	1	0	0	0
Uterus:								
Wall, thickened	NA	1	NA	2	NA	1	NA	0
Vagina:								
Wall, thickened	NA	0	NA	1	NA	1	NA	0
Histopathology								
Number examined	3	3	3	3	3	3	3	2
Bone marrow, sternum:								
Necrosis, moderate	0	0	0	0	0	0	1	0
Kidney:								
Glomerulus, lipidosis	0	1	1	0	1	0	0	1
Inflammation, chronic	3	2	2	1	2	1	2	2
Papilla, microconcretion	3	3	3	3	3	2	3	2
Pyelitis	0	0	0	0	0	0	0	1
Liver:								
Inflammation, chronic	3	3	3	3	3	3	3	2
Pigment, Kupffer cells	0	1	0	1	0	1	1	0
Thymus:								
Depletion, lymphoid	0	0	0	0	0	0	1	0
Injection site:								
Inflammation, chronic	2	2	2	3	0	3	0	2
Inflammation, chronic, active	0	1	1	0	3	0	3	2
Intimal thickening	0	0	0	0	1	0	0	1
Thrombus	0	0	0	0	2	2	3	1
Hemorrhage	1	2	3	3	2	2	3	2
Edema	0	0	0	0	1	0	1	2

NA = Not applicable.

2.6.7.7L Repeated-Dose Toxicity **Report Title:** 4-week Continuous Intravenous Infusion Toxicity Study with YM087 (CI-1025) in Dogs **Test Article:** Conivaptan hydrochloride

Species/Strain: Beagle Dogs **Duration of Dosing:** 4 Weeks **Study No.** R087-TX-074
Initial Age: 11-12 Months **Duration of Postdose:** None
Date of First Dose: 23 Sep 1998 **Method of Administration:** Intravenous, infusion at 2 mL/kg/hr **GLP Compliance:** Yes
Vehicle/Formulation: Vehicle: [redacted] propylene glycol, [redacted] ethanol, and
Special Features: None lactic acid sufficient to adjust pH to 3.3 ± 0.2. Diluent: 5% dextrose solution
No Observed Adverse Effect Level: 10 mg/kg

Daily Dose[a] (mg/kg)	0 (Control)		2		10		20	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Toxicokinetics: (During Infusion)								
C_{ss} (ng/mL): Day 2	NA	NA	352	308	2923	3117	7413	6457
Day 28	NA	NA	505	334	5727	5007	21900	12273
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Clinical Observations								
Appears dehydrated	0	0	0	0	0	0	2	0
Thin appearance	0	1	0	0	0	0	3	2
Pale gums	0	0	0	0	0	0	0	1
Yellow gums	0	0	0	0	0	0	2	0
Yellow skin/Entire body	0	0	0	0	0	0	2	0
Eyes								
Yellow colored - appears jaundiced	0	0	0	0	0	0	2	0
Body Weights (kg):								
Day 1	8.2	6.9	8.1	6.7	8.5	7.2	8.1	6.9
Day 8	8.1	6.9	8.2	6.7	8.6	7.2	8.1	6.8
Day 15	7.9	7.0	8.3	6.8	8.6	7.3	7.8	6.5
Day 22	8.2	6.6	8.1	7.0	8.4	7.3	7.4	6.7
Day 29	8.1	6.6	7.9	6.8	8.2	7.1	6.6	6.3

NA = Not applicable.
a - Dose rates = 0.084, 0.416, and 0.834 mg/kg/hr, dose solution concentrations = 0.042, 0.208, and 0.417 mg/mL

Daily Dose (mg/kg)	0 (Control)		2		10		20	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Food Consumption (g/day):								
Day 1	212	237	133	245	170	171	207	86
Day 3	255	179	197	180	172*	205	134*	73
Day 6	259	227	230	292	246	214	168*	115
Day 14	276	176	253	255	307	251	98*	155
Day 16	323	190	238	314	321	305	91*	271
Day 20	221	182	212	235	247	213	66*	208
Day 24	252	215	223	277	314	271	44*	180
Day 27	337	323	285	397	341	356	83*	269
Day 29	162	76	201	222	209	289	46	73
Water Consumption (g/day):								
Day 1	740	338	1992	3170*	3272*	3036*	3051*	1901
Day 8	2467	257	1352	1198*	1325	1801*	1353	1020
Day 15	441	171	596	854*	857	1079*	360	1007*
Day 22	1232	309	603	679	778	1262	180	938
Day 29	492	277	426	357	426	916*	97	249
Electrocardiography	-	-	-	-	-	-	-	-
Hematology								
RBC (10^6/µL):								
Pretreatment (Week -3)	7.28	6.70	7.67	7.03	7.46	6.26*	7.15	6.23*
Pretreatment (Week -1)	7.12	5.85	7.01	6.62	7.13	6.06	6.54	6.21
Week 4	6.45	6.18	6.87	6.89	6.51	6.39	4.63*	5.80
Reticulocyte (% RBC):								
Pretreatment (Week -3)	0.6	0.2	0.4	0.1	0.2	0.2	0.6	0.1
Pretreatment (Week -1)	0.2	0.1	0.1	0.2	0.3	0.1	0.1	0.0
Week 4	0.2	0.5	0.4	0.3	0.3	0.4	0.3	0.9
Hematology (Continued)								
Reticulocyte (10^6/µL):								
Pretreatment (Week -3)	0.05	0.01	0.04	0.01	0.02	0.01	0.04	0.01
Pretreatment (Week -1)	0.01	0.01	0.01	0.01	0.03	0.01	0.01	0.00
Week 4	0.01	0.03	0.03	0.02	0.02	0.02	0.01	0.05

ANOVA: * - P<0.05

(Continued)

2.6.7.7L Repeated-Dose Toxicity Study No. R087-TX-074 (Continued)

Daily Dose (mg/kg)	0 (Control)		2		10		20	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Hemoglobin (g/dL):								
Pretreatment (Week -3)	16.6	15.4	17.6	16.3	17.5	14.6	16.4	14.0
Pretreatment (Week -1)	15.8	13.2	15.6	14.9	16.4	13.8	14.5	13.6
Week 4	14.5	14.0	15.4	15.5	14.9	14.6	10.1*	12.8
PCV (%):								
Pretreatment (Week -3)	50.8	47.2	53.7	49.4	53.3	44.6	50.3	43.7
Pretreatment (Week -1)	49.3	41.2	48.9	46.4	50.6	43.0	45.5	43.2
Week 4	43.4	42.7	46.2	46.7	44.7	43.9	30.7*	39.5
Platelets (10^3/µL):								
Pretreatment (Week -3)	282	384	261	321	272	377	262	329
Pretreatment (Week -1)	268	369	277	357	271	347	231	340
Week 4	298	375	248	328	321	317	147*	292
PT (sec):								
Pretreatment (Week -3)	7.5	6.3	6.7	6.2	7.1	6.4	6.8	6.5
Pretreatment (Week -1)	6.5	6.3	6.5	6.3	6.8	6.4	6.5	6.5
Week 4	6.3	6.4	6.4	6.4	6.6	6.3	6.6	6.3
APTT (sec):								
Pretreatment (Week -3)	12.5	10.6	13.1	11.2	10.7	10.7	10.3	10.7
Pretreatment (Week -1)	10.5	11.4	10.5	11.3	11.0	11.3	11.5	11.8
Week 4	10.8	13.2	10.2	11.1	10.7	11.8	10.5	11.0
WBC (10^3/µL):								
Pretreatment (Week -3)	10.2	8.5	10.5	8.7	9.7	10.4	9.5	12.8
Pretreatment (Week -1)	9.1	9.3	8.9	11.1	7.6	7.1	9.9	9.7
Week 4	9.9	8.6	9.0	12.4	10.6	11.0	12.9	11.1
Blood Chemistry								
Glucose (mg/dL):								
Pretreatment (Week -3)	81	87	86	85	84	86	79	87
Pretreatment (Week -1)	94	89	92	86	93	92	86	87
Week 4	91	89	96	81	90	93	64*	85

ANOVA: * - P<0.05

Daily Dose (mg/kg)	0 (Control)		2		10		20	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Blood Chemistry (Continued)								
BUN (mg/dL):								
Pretreatment (Week -3)	13	16	14	15	14	18	16	14
Pretreatment (Week -1)	11	11	10	9	10	14	9	9
Week 4	9	10	11	11	10	11	10	9
Creatinine (mg/dL):								
Pretreatment (Week -3)	0.8	0.7	0.9	0.8	0.9	0.8	0.9	0.7
Pretreatment (Week -1)	0.8	0.7	0.8	0.8	0.8	0.8	0.8	0.7
Week 4	0.9	0.8	0.9	0.8	0.9	0.9	0.6	0.8
ALP (U/L):								
Pretreatment (Week -3)	43	84	58	72	68	100	68	98
Pretreatment (Week -1)	34	53	43	45	56	66	52	80
Week 4	34	52	39	42	82*	61	672*	111*
Total cholesterol (mg/dL):								
Pretreatment (Week -3)	169	219	187	210	154	226	152	226
Pretreatment (Week -1)	131	172	149	149	138	168	127	191
Week 4	139	144	138	138	172	191	176	217
AST (U/L):								
Pretreatment (Week -3)	25	31	34	27	29	31	26	33
Pretreatment (Week -1)	32	36	34	35	34	37	32	36
Week 4	30	34	31	38	30	33	123	41
ALT (U/L):								
Pretreatment (Week -3)	26	24	30	25	29	19	23	23
Pretreatment (Week -1)	32	30	35	33	44	34	33	33
Week 4	33	25	33	28	28	27	122	37
LDH (U/L):								
Pretreatment (Week -3)	115	96	164	157	91	92	205	117
Pretreatment (Week -1)	81	95	66	154	58	67	67	111
Week 4	88	98	60	175	56	54	169*	84

ANOVA: * - P<0.05

(Continued)

2.6.7.7L Repeated-Dose Toxicity — Study No. R087-TX-074 (Continued)

Daily Dose (mg/kg) / Number of Animals	0 (Control) M: 3	F: 3	2 M: 3	F: 3	10 M: 3	F: 3	20 M: 3	F: 3
Blood Chemistry (Continued)								
Total protein (g/dL):								
Pretreatment (Week -3)	5.8	6.0	6.3	6.1	6.1	6.2	5.6	6.1
Pretreatment (Week -1)	5.4	5.5	5.9	5.6	5.8	5.6	5.3	5.7
Week 4	5.5	5.5	5.6	5.8	6.2	6.0	5.1	5.8
Albumin (g/dL):								
Pretreatment (Week -3)	3.7	3.5	3.9	3.8	3.9	3.7	3.6	3.5
Pretreatment (Week -1)	3.6	3.6	3.7	3.7	3.9	3.8	3.6	3.8
Week 4	3.5	3.6	3.5	3.6	3.4	3.6	1.9*	3.1
Globulin (g/dL):								
Pretreatment (Week -3)	2.1	2.4	2.4	2.3	2.2	2.5	2.0	2.6
Pretreatment (Week -1)	1.8	1.9	2.1	1.9	1.9	1.8	1.7	2.0
Week 4	2.0	1.9	2.2	2.2	2.7*	2.3	3.2*	2.7
A/G Ratio:								
Pretreatment (Week -3)	1.73	1.47	1.63	1.63	1.82	1.50	1.85	1.35
Pretreatment (Week -1)	1.96	1.95	1.75	2.04	2.08	2.07	2.20	1.92
Week 4	1.75	2.09	1.60	1.73	1.26*	1.58	0.60*	1.18
Calcium (mg/dL):								
Pretreatment (Week -3)	10.5	10.5	10.7	10.5	10.8	10.6	10.6	10.6
Pretreatment (Week -1)	9.9	9.9	10.3	9.9	10.4	10.0	9.9	10.2
Week 4	10.2	10.3	10.2	10.2	10.5	10.5	8.9*	10.3
Total bilirubin (mg/dL):								
Pretreatment (Week -3)	0.2	0.2	0.1	0.2	0.2	0.1	0.1	0.1
Pretreatment (Week -1)	0.2	0.1	0.1	0.1	0.2	0.2	0.2	0.1
Week 4	0.2	0.1	0.1	0.3	0.2	0.2	4.8	0.2
Creatinine kinase (U/L)::								
Pretreatment (Week -3)	141	160	188	165	137	158	172	144
Pretreatment (Week -1)	203	199	181	239	172	244	184	173
Week 4	133	152	124	311	115	128	143	206

ANOVA: * - P<0.05

2.6.7.7L Repeated-Dose Toxicity — Study No. R087-TX-074 (Continued)

Daily Dose (mg/kg) / Number of Animals	0 (Control) M: 3	F: 3	2 M: 3	F: 3	10 M: 3	F: 3	20 M: 3	F: 3
Blood Chemistry (Continued)								
Triglyceride (mg/dL):								
Pretreatment (Week -3)	36	44	47	43	34	43	40	51
Pretreatment (Week -1)	29	36	31	32	33	33	33	38
Week 4	23	33	23	27	28	32	72*	32
Inorganic phosphorus (mg/dL):								
Pretreatment (Week -3)	4.4	4.1	4.7	3.4	4.1	4.7	5.0	3.9
Pretreatment (Week -1)	4.1	4.5	4.8	4.1	4.8	4.1	4.2	4.4
Week 4	4.0	3.7	4.4	3.9	4.6	4.6	4.8	4.2
GGT (U/L):								
Pretreatment (Week -3)	5	7	7	6	6	7	5	5
Pretreatment (Week -1)	4	6	5	5	5	6	5	5
Week 4	4	4	4	4	4	5	11	4
Sodium (mEQ/L):								
Pretreatment (Week -3)	148	148	149	150	149	150	150	149
Pretreatment (Week -1)	145	146	145	147	146	146	149	146
Week 4	150	149	148	150	148	154	142	149
Potassium (mEQ/L):								
Pretreatment (Week -3)	4.5	4.6	4.8	4.6	4.6	4.5	4.8	4.1
Pretreatment (Week -1)	4.3	4.2	4.5	4.4	4.4	4.4	4.4	4.2
Week 4	4.5	4.2	4.4	4.2	4.1	4.2	3.9	4.0
Chloride (mEQ/L):								
Pretreatment (Week -3)	114	115	112	117	114	115	114	114
Pretreatment (Week -1)	113	114	112	116	113	115	117	113
Week 4	117	118	116	117	115	119	112	117

ANOVA: * - P<0.05

(Continued)

2.6.7.7L Repeated-Dose Toxicity Study No. R087-TX-074 (Continued)

Daily Dose (mg/kg) / Number of Animals		0 (Control) M: 3	0 (Control) F: 3	2 M: 3	2 F: 3	10 M: 3	10 F: 3	20 M: 3	20 F: 3
Urinalysis									
Volume (mL):									
Pretreatment (Week -3)		81	427	103	34	457	38	146	99
Pretreatment (Week -1)		193	190	278	96	383	213	242	358
Week 4		250	87	281	419*	282	509*	218	164
Osmolality (mOsm/kg):									
Pretreatment (Week -3)		1251	444	1580	1431	556	2744	1617	986
Pretreatment (Week -1)		1288	1593	1073	1400	832	2106	1088	977
Week 4		781	1604	612	887	974	415*	949	1005
Organ Weights									
Adrenal:	Absolute (g)	1.20	1.19	1.12	1.37	1.57	1.21	1.26	1.31
	Relative (%)	0.015	0.019	0.014	0.020	0.019	0.017	0.019	0.021
Brain:	Absolute (g)	73.6	73.0	70.9	67.3	69.0	62.6	71.0	71.7
	Relative (%)	0.93	1.14	0.91	1.00	0.83	0.87*	1.06	1.14
Heart:	Absolute (g)	81.7	58.6	73.8	69.6	83.2	63.7	68.2	67.5
	Relative (%)	1.03	0.92	0.95	1.04	1.00	0.88	1.01	1.07
Kidney:	Absolute (g)	44.6	33.1	40.0	31.4	42.7	32.4	44.7	35.0
	Relative (%)	0.56	0.52	0.51	0.47	0.52	0.45	0.67	0.56
Liver/gallbladder:	Absolute (g)	213	181	197	172	231	206	305*	242
	Relative (%)	2.7	2.8	2.5	2.5	2.8	2.8	4.6*	3.8*
Lung:	Absolute (g)	72.8	60.8	55.4	54.2	62.0	51.0	91.5*	69.7
	Relative (%)	0.91	0.96	0.71	0.80	0.75	0.70*	1.36*	1.10
Maxillary salivary gland:	Absolute (g)	9.0	7.9	8.4	8.4	9.2	8.6	7.9	7.1
	Relative (%)	0.11	0.12	0.11	0.12	0.11	0.12	0.12	0.11
Ovary:	Absolute (g)	NA	1.06	NA	1.16	NA	0.71	NA	0.72
	Relative (%)	NA	0.016	NA	0.018	NA	0.010	NA	0.011
Pituitary:	Absolute (g)	0.052	0.057	0.056	0.052	0.054	0.047	0.046	0.060
	Relative (%)	0.0007	0.0009	0.0007	0.0008	0.0007	0.0007	0.0007	0.0009
Prostate:	Absolute (g)	6.56	NA	4.07*	NA	4.70	NA	2.55*	NA
	Relative (%)	0.082	NA	0.052*	NA	0.057	NA	0.037*	NA
Spleen:	Absolute (g)	30.0	26.7	24.6	23.5	26.2	24.2	81.1	30.1
	Relative (%)	0.38	0.42	0.32	0.35	0.32	0.34	1.22	0.48

NA = Not applicable.
ANOVA: * - P<0.05

Daily Dose (mg/kg) / Number of Animals		0 (Control) M: 3	0 (Control) F: 3	2 M: 3	2 F: 3	10 M: 3	10 F: 3	20 M: 3	20 F: 3
Organ Weights (Continued)									
Testis/Epididymis:	Absolute (g)	15.4	NA	14.2	NA	15.1	NA	14.6	NA
	Relative (%)	0.19	NA	0.18	NA	0.18	NA	0.22	NA
Thymus:	Absolute (g)	3.77	3.91	3.78	3.46	3.78	4.21	3.09	2.59
	Relative (%)	0.048	0.061	0.049	0.050	0.044	0.059	0.045	0.041
Thyroid/parathyroid:	Absolute (g)	0.77	0.63	0.58	0.71	0.76	0.65	0.65	0.71
	Relative (%)	0.010	0.010	0.007	0.011	0.009	0.009	0.010	0.011
Uterus:	Absolute (g)	NA	4.20	NA	8.41	NA	2.68	NA	3.13
	Relative (%)	NA	0.064	NA	0.133	NA	0.037	NA	0.050
Gross Pathology									
Number examined		3	3	3	3	3	3	3	3
Lung:									
Pale		0	0	0	0	0	0	2	0
Mottled		0	0	0	0	0	0	3	1
Failure to collapse		0	0	1	0	0	0	0	0
Dark area		0	0	0	0	0	1	0	1
Spleen:									
Enlarged		0	0	0	0	0	0	3	0
Liver:									
Enlarged		0	0	0	0	0	0	2	1
Irregularly shaped		0	1	0	0	0	0	0	0
Kidney:									
Dark area		0	0	0	0	0	0	1	0
Enlarged		0	0	0	0	0	0	1	0
Thymus:									
Small		0	0	0	0	0	0	1	1
Testis:									
Soft		0	NA	0	NA	0	NA	1	NA
Prostate:									
Small		0	NA	0	NA	0	NA	1	NA

NE = Not examined. NA = Not applicable.

(Continued)

2.6.7.7L Repeated-Dose Toxicity Study No. R087-TX-074 (Continued)

Daily Dose (mg/kg)	0 (Control)		2		10		20	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Histopathology								
Number examined	3	3	3	3	3	3	3	3
Kidney:								
Degeneration, renal tubule	0	0	0	0	0	0	2	0
Congestion	0	0	0	0	0	0	2	0
Fibrosis	0	0	0	0	0	0	2	0
Concretion, papilla	3	3	3	3	3	3	3	3
Regeneration, renal tubule	0	0	1	0	1	0	0	1
Lipidosis, glomerulus	0	0	0	0	1	0	1	0
Lung:								
Pneumonitis	1	2	1	0	2	2	3	3
Inflammation, vascular	0	0	0	0	0	0	1	2
Hyperplasia, endthelium, artery	1	0	0	0	0	0	0	1
Embolus, artery	0	0	0	0	1	1	0	3
Spleen:								
Hematopoiesis, extramedullary	0	0	0	0	0	0	3	0
Lymphoid depletion	0	0	0	0	0	0	2	0
Hemorrhage, acute, capsular	0	0	0	0	0	0	1	0
Liver:								
Pigment	0	0	0	0	0	0	2	0
Dilation, sinusoidal	0	0	0	0	0	0	3	2
Hypertrophy, Kupffer cell	0	1	0	0	0	0	3	1
Cytoplasmic, alteration, hepatocyte	0	0	0	0	0	0	3	1
Hematopoiesis, extramedullary	0	0	0	0	0	0	3	0
Degeneration, centrilobular	0	0	0	0	0	0	2	0
Mineralization, capsule	0	1	0	0	0	0	0	0
Gallbladder:								
Pigment, mucosa	0	0	0	0	0	0	2	0
Stomach, gland:								
Concretion, mucosa, pylorus	1	2	2	2	2	2	3	3

NA = Not applicable.

2.6.7.7L Repeated-Dose Toxicity Study No. R087-TX-074 (Continued)

Daily Dose (mg/kg)	0 (Control)		2		10		20	
Number of Animals	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Histopathology (Continued)								
Duodenum:								
Distention, mucosal gland	3	2	1	2	1	1	3	2
Jejunum:								
Distention, mucosal gland	0	0	0	0	0	0	2	0
Ileum:								
Lymphoid depletion, Peyer's patch	0	0	0	0	0	0	2	1
Pancreas:								
Inflammation, peripancreatic fat	0	0	0	0	0	0	2	0
Cecum:								
Inflammation acute	0	0	0	0	0	0	1	0
Lymph node, mesenteric:								
Lymphoid depletion	0	0	0	0	0	0	3	1
Lymph node, other:								
Lymphoid depletion	0	0	0	0	0	0	2	0
Thymus:								
Lymphoid depletion	0	1	0	1	1	1	3	2
Cyst, embryonic duct remnant	2	0	2	3	2	1	2	1
Testis:								
Degeneration, seminiferous tubule	0	NA	0	NA	0	NA	2	NA
Prostate:								
Secretion decreased	0	NA	0	NA	0	NA	3	NA
Marrow sternum:								
Degeneration/necrosis	0	0	0	0	0	0	3	1
Catheter tip:								
Hyperplasia, endothelium	2	2	3	2	3	3	3	2
Inflammation, chronic	1	2	2	0	0	0	1	2
Hemorrhage, acute	2	1	2	1	0	0	1	0
Thrombus	1	1	2	1	0	1	1	0
Inflammation, vascular	0	0	0	0	0	0	0	1

NA = Not applicable.

Mouse and Rat Carcinogenicity Studies:

2.6.7.11A Carcinogenicity Study **Report Title:** 104-Week Carcinogenicity Gavage Study of YM087 in Mice **Test Article:** Conivaptan hydrochloride

Species/Strain: B6C3F1 Mice **Duration of Dosing:** 104 Weeks **Study No.** R087-TX-054
Initial Age: 5-6 Weeks **Method of Administration:** Gavage
Date of First Dose: 5 Jun 1997 **Vehicle/Formulation:** 0.5% Methylcellulose solution **GLP Compliance:** Yes
Treatment of Controls: Vehicle
Basis for High-Dose Selection: Toxicity-based endpoint.
Specific Features: None.

Daily Dose (mg/kg)	0 (Control)		1	3		10		30
Gender	M	F	F	M	F	M	F	M
Toxicokinetics: Week 53								
C_{max} (ng/mL)	NA	NA	32.9	157	191	771	1340	2880
AUC_{0-24} (ng·hr/mL)	NA	NA	117	509	628	3370	8725	21851
Number of Animals Survived:								
At Dosing Commencement	60	60	60	60	60	60	60	60
Week 26	60	60	60	58	58	59	60	59
Week 52	59	59	60	58	58	58	60	59
Week 78	57	57	58	54	54	57	56	58
Week 104	48	46	45	49	39	51	45	47
Terminal Sacrifice (Week 105)	48	45	43	48	38	51	45	47
Survival at Week 104 (%)	80	79	75	86	65†	85	75	78
Clinical Observations								
Distended abdomen	1	6	3	2	3	3	2	13
Swollen								
Ventral-abdominal, right	4	4	1	2	1	13	1	16
Ventral-abdominal, left	2	0	1	4	4	2	5	7
Perineal area	37	1	0	38	0	34	1	34
Body Weights (g) :								
Week 26	32.2	29.4	28.9	32.6	29.2	31.4	29.7	31.3
Week 52	39.4	36.3	35.4	38.3	34.8	37.4*	35.0	35.9*
Week 78	41.9	38.9	38.2	40.7	38.2	38.8*	37.1	37.1*
Week 104	38.7	36.6	35.6	38.8	36.4	38.2	36.3	38.3

NA = Not applicable.
Cox-Tarone binary regression methods or Gehan-Breslow nonparametric methods: †- P<0.05 Dunnett's Test: * - P<0.05

Daily Dose (mg/kg)	0 (Control)		1	3		10		30
Gender	M	F	F	M	F	M	F	M
Bodyweight Gain (g): Weeks 1-104	16.4	17.2	16.4	16.6	18.0	16.0	17.4	16.3
(% of Control)	-	-	95	101	105	98	101	99
Food Consumption (g/day):								
Week 25	6.5	6.2	6.3	6.7	6.4	6.6	6.3	6.5
Week 53	6.6	6.7	6.6	6.6	6.7	6.8	6.8	6.9
Week 77	6.1	6.5	6.3	6.0	6.4	6.4	6.3	6.5*
Week 104	6.3	6.7	6.5	6.1	7.2	6.7*	7.3*	7.5*
Water Consumption (mL/day):								
Week 26	6.0	6.3	7.3*	7.6*	11.1*	14.8*	22.4*	21.1*
Week 52	5.3	5.8	7.2*	7.5*	10.9*	15.0*	22.4*	24.8*
Week 78	5.8	6.5	7.0	7.6*	9.9*	15.1*	24.6*	27.0*
Week 104	6.4	6.5	7.2	9.0*	12.7*	19.9*	30.3*	32.5*
Number of Animals with Neoplastic Lesions:								
Adrenal, Cortex: Number Examined	60	60	59	60	60	60	60	60
Adenoma, Subcapsular Cell	2	1	1	0	1	0	0	2
Adrenal, Medulla: Number Examined	59	60	59	60	57	59	59	60
Pheochromocytoma	0	1	0	0	1	1	0	0
Bone, Femur: Number Examined	60	60	60	60	60	60	60	60
Osteosarcoma	0	0	0	0	1	0	0	0
Bone, Other: Number Examined	0	0	0	0	1	0	0	0
Osteosarcoma	0	0	0	0	1	0	0	0
Clitoral Gland: Number Examined	NA	0	1	NA	0	NA	1	NA
Carcinoma	NA	0	0	NA	0	NA	1	NA
Duodenum: Number Examined	58	59	57	57	55	58	56	59
Adenomatous Polyp	0	0	0	3	0	1	0	0
Harderian Gland: Number Examined	60	60	60	59	60	60	60	60
Adenoma	5	2	3	5	1	10	2	2
Carcinoma	1	0	1	0	0	0	2	0
Hematopoietic Neoplasia: Number Examined	60	60	60	60	60	60	60	60
Leukemia, Granulocytic	0	1	1	0	0	0	0	0
Leukemia, Mast Cell	0	1	0	0	0	0	0	0
Malignant Lymphoma, Lymphocytic	4	7	10	3	7	2	13	1
Sarcoma, Histiocytic	3	3	4	3	3	1	5	0

Dunnett's Test: * - P<0.05 (Continued)

2.6.7.11A Carcinogenicity Study Study No. R087-TX-054 (Continued)

Daily Dose (mg/kg)		0 (Control)		1	3		10		30
Gender		M	F	F	M	F	M	F	M
Number of Animals with Neoplastic Lesions:									
Kidney:	Number Examined	60	60	60	60	60	60	60	60
Adenoma, Tubular Cell		1	0	1	0	0	0	0	0
Papilloma, Transitional Cell		0	0	0	0	0	1	0	0
Liver:	Number Examined	60	60	60	60	60	60	60	60
Adenoma, Hepatocellular		10	9	6	7	5	8	3*	10
Carcinoma, Hepatocellular		9	3	2	10	3	3*	0	7
[Adenoma+Carcinoma]		19	12	8	17	8	11*	3*	17
Carcinoma, Bile Duct		0	0	0	0	1	0	0	0
Hemangioma		1	0	0	0	1	1	0	0
Hemangiosarcoma		0	0	1	5	0	1	0	0
Ito Cell Neoplasm		0	1	0	0	0	0	0	0
Sarcoma, NOS		0	0	1	0	0	0	0	0
Lung:	Number Examined	60	60	60	60	60	60	60	60
Adenoma, Bronchiolar-Alveolar		7	2	1	6	2	14	3	4
Carcinoma, Bronchiolar-Alveolar		7	3	0	2	2	0**	2	3
[Adenoma+Carcinoma]		14	5	1	8	4	14	5	7*
Mammary, Cranial:	Number Examined	NA	45	52	NA	56	NA	40	NA
Carcinoma		NA	2	0	NA	1	NA	0	NA
Marrow, Femur:	Number Examined	60	60	60	60	60	60	59	60
Hemangiosarcoma		0	1	0	0	0	0	0	0
Muscle, Other:	Number Examined	1	0	1	0	0	0	1	0
Rhabdomyosarcoma		0	0	0	0	0	0	1	0
Ovary:	Number Examined	NA	59	58	NA	58	NA	58	NA
Granulosa/Theca Cell Tumor		NA	0	0	NA	0	NA	1	NA
Papillary Cystadenoma		NA	1	0	NA	0	NA	0	NA
Teratoma		NA	0	0	NA	1	NA	0	NA
Pancreas:	Number Examined	60	60	60	60	59	60	59	60
Adenoma, Islet Cell		0	1	0	1	0	0	0	0

NA = Not applicable.
Dinse and Lagakos logistic prevalence methods and Cox-Tarone binary regression methods: * - P<0.05 ** - P<0.01

Daily Dose (mg/kg)		0 (Control)		1	3		10		30
Gender		M	F	F	M	F	M	F	M
Number of Animals with Neoplastic Lesions:									
Pituitary:	Number Examined	58	58	60	60	55	58	59	56
Adenoma		0	16	10	0	5*	1	8*	0
Skin, Other:	Number Examined	29	52	53	36	39	30	42	25
Squamous Cell Carcinoma		0	0	1	0	0	0	0	1
Spleen:	Number Examined	60	60	60	60	58	59	60	60
Hemangioma		0	0	1	0	0	0	1	0
Hemangiosarcoma		2	2	0	2	2	2	1	2
Stomach, Nonglandular:	Number Examined	60	60	60	60	59	59	59	60
Squamous Cell Carcinoma		1	0	0	0	0	0	0	0
Subcutaneous Tissue	Number Examined	1	3	3	6	3	3	1	0
Fibrosarcoma		1	1	1	2	3	2	1	0
Testis:	Number Examined	60	NA	NA	60	NA	60	NA	60
Benign Interstitial Cell Tumor		0	NA	NA	0	NA	1	NA	0
Thyroid	Number Examined	60	59	60	60	59	60	60	60
Follicular Cell Adenoma		0	0	0	1	0	1	0	0
Follicular Cell Carcinoma		0	0	0	1	0	0	0	0
Uterus:	Number Examined	NA	60	60	NA	59	NA	60	NA
Endometrial Stromal Polyp		NA	1	1	NA	2	NA	3	NA
Carcinoma		NA	0	1	NA	2	NA	1	NA
Hemangioma		NA	1	0	NA	0	NA	0	NA
Hemangiosarcoma		NA	0	1	NA	1	NA	1	NA
Leiomyoma		NA	1	0	NA	1	NA	1	NA
Number of Animals with Non-Neoplastic Lesions:									
Kidney:	Number Examined	60	60	60	60	60	60	60	60
Cyst		16	0	0	10	1	4**	5*	23
Increased Microconcretion, Tubule		5	0	0	0*	0	0*	0	1
Increased Pigment, Tubule		0	5	0*	0	3	0	31**	0
Pelvis, Dilatation		0	2	1	1	0	4	2	22**
Urinary Bladder:	Number Examined	60	59	58	60	59	59	60	60
Distention		1	0	0	2	1	7*	2	44**
Hyperplasia		1	0	0	1	0	5	0	35**

NA = Not applicable.
Dinse and Lagakos logistic prevalence methods and Cox-Tarone binary regression methods: * - P<0.05

2.6.7.11B Carcinogenicity Study **Report Title:** 104-Week Carcinogenicity Gavage Study of YM087 in Rats **Test Article:** Conivaptan hydrochloride

Species/Strain: F344 Rats **Duration of Dosing:** 104 Weeks **Study No.** R087-TX-047
Initial Age: Approximately 5 Weeks **Method of Administration:** Gavage
Date of First Dose: 18 Jun 1997 **Vehicle/Formulation:** 0.5% Methylcellulose solution **GLP Compliance:** Yes
Treatment of Controls: Vehicle
Basis for High-Dose Selection: Toxicity-based endpoint.
Specific Features: None.

Daily Dose (mg/kg)	0 (Control)		0.3	1		3		10		30
Gender	M	F	M	M	F	M	F	M	F	F
Toxicokinetics: Week 53										
C_{max} (ng/mL)	NA	NA	2.43	17.1	28.7	125	183	557	752	2080
AUC_{0-24} (ng·hr/mL)	NA	NA	22.3	103	193	956	1202	7017	7424	25546
Number of Animals Survived:										
At Dosing Commencement	60	60	60	60	60	60	60	60	60	60
Week 26	60	59	60	60	60	60	60	59	60	60
Week 52	60	58	60	60	57	60	58	58	60	59
Week 78	58	57	57	58	56	55	54	45	52	49
Week 90	52	57	50	57	54	47	50	38	42	36
Week 104	39	45	38	44	44	33	34	21	29	18
Terminal Sacrifice (Week 105)	39	45	38	42	44	32	34	19	29	17
Survival at Week 104 (%)	65	76	63	73	73	55	57††	35††	48††	31††
Clinical Observations										
Hunched posture	0	0	3	2	1	10	8	10	17	19
Thin appearance	3	2	7	10	4	22	16	40	30	35
Rough hair coat	3	1	6	4	3	14	6	22	17	23
Body Weights (g):										
Week 26	362	193	361	344*	189	321*	187*	297*	190	194
Week 52	421	216	415	401*	212	368*	209	327*	208*	213
Week 78	435	246	430	408*	238	369*	225*	317*	210*	206*
Week 104	398	270	392	374*	257	328*	229*	281*	211*	197*

NA = Not applicable.
Cox-Tarone binary regression methods or Gehan-Breslow nonparametric methods: †† - P<0.01 Dunnett's Test: * - P<0.05

Daily Dose (mg/kg)	0 (Control)		0.3	1		3		10		30
Gender	M	F	M	M	F	M	F	M	F	F
Bodyweight Gain (g): Weeks 1-104	287	180	287	268	168*	223*	142*	183*	123*	107*
(% of Control)	-	-	100	93	93	78	79	64	68	59
Food Consumption (g/day):										
Week 25	19	12	19	19	13	19	13*	19	14*	14*
Week 53	19	12	20	20	13*	19	13*	19	14*	14*
Week 78	21	15	22*	22*	16*	21	16	20	15	15
Week 104	19	14	20	19	14	19	15	18	14	15
Water Consumption (mL/day):										
Week 26	17.7	15.7	23.3*	52.1*	32.2*	108.7*	77.6*	160.6*	112.2*	138.5*
Week 52	18.8	15.7	25.4*	65.4*	40.2*	128.5*	91.2*	164.4*	113.4*	141.2*
Week 78	23.4	20.5	32.2*	81.6*	47.8*	151.4*	93.4*	176.7*	135.3*	149.7*
Week 104	23.9	20.5	38.3*	68.4*	45.5*	137.1*	80.7*	168.0*	122.1*	149.6*
Number of Animals with Neoplastic Lesions:										
Adrenal, Cortex: Number Examined	60	60	60	60	60	60	59	60	60	60
Adenoma	0	0	0	1	0	1	0	0	0	0
Carcinoma	0	0	0	0	1	0	0	0	0	0
Adrenal, Medulla: Number Examined	60	59	60	60	59	60	59	60	60	60
Pheochromocytoma	5	0	2	4	0	1	0	3	0	0
Complex Pheochromocytoma	1	0	0	1	0	0	0	0	0	0
Malignant Pheochromocytoma	0	1	0	2	0	0	0	1	0	1
Brain: Number Examined	60	60	60	60	60	60	60	60	60	60
Astrocytoma	1	0	2	1	0	0	0	0	0	0
Cavity,										
Abdominal: Number Examined	5	2	2	2	3	2	1	0	0	1
Mesothelioma	4	0	1	1	0	0	0	0	0	0
Clitoral Gland: Number Examined	NA	0	NA	NA	0	NA	0	NA	0	3
Adenoma	NA	0	NA	NA	0	NA	0	NA	0	1
Colon: Number Examined	57	58	58	57	60	59	58	54	58	56
Leiomyosarcoma	0	0	1	0	0	0	0	0	0	0
Eye: Number Examined	60	59	60	60	60	60	59	60	60	60
Melanoma, Iris	0	0	1	0	0	0	0	0	0	0

NA = Not applicable.
Dunnett's Test: * - P<0.05

(Continued)

2.6.7.11B Carcinogenicity Study Study No. R087-TX-047 (Continued)

Daily Dose (mg/kg)		0 (Control)		0.3	1		3		10		30
Gender		M	F	M	M	F	M	F	M	F	F
Number of Animals with Neoplastic Lesions:											
Harderian Gland:	Number Examined	60	60	60	60	60	60	60	60	60	60
Sarcoma		0	0	0	0	0	1	0	0	0	0
Head, Coronal:	Number Examined	1	0	2	2	0	1	0	0	0	1
Trichoepithelioma		0	0	0	1	0	0	0	0	0	0
Basal Cell Carcinoma		0	0	1	0	0	0	0	0	0	0
Carcinoma, Zymbal's Gland		0	0	1	0	0	0	0	0	0	0
Heart:	Number Examined	60	60	60	60	60	60	60	60	60	60
Schwannoma		0	0	1	1	0	0	0	0	0	0
Hematopoietic											
Neoplasia:	Number Examined	60	60	60	60	60	60	60	60	60	60
Leukemia, Largegranular Lymphocytic		16	12	15	15	11	7*	13	4**	5	4
Lymphoma		0	0	0	0	1	1	1	0	0	0
Sarcoma, Histiocytic		1	0	0	0	0	0	1	0	0	0
Ileum:	Number Examined	53	56	58	53	56	53	55	46	50	50
Adenocarcinoma		0	0	0	0	0	0	0	1	0	0
Kidney:	Number Examined	60	60	60	60	60	60	60	60	60	60
Adenoma, Tubular Cell		0	0	1	0	0	0	0	0	0	0
Papilloma, Transitional Cell		0	0	0	0	0	0	1	0	0	0
Nephroblastoma		0	1	0	0	0	0	0	0	0	0
Lipoma		1	0	0	0	1	0	0	0	0	0
Liposarcoma		0	0	0	1	0	0	0	0	0	0
Mesenchymal Tumor (Osteogenic)		0	0	0	0	0	0	1	0	0	0
Liver:	Number Examined	60	60	60	60	60	60	60	60	60	60
Adenoma, Hepatocellular		4	1	2	5	1	0*	1	3	1	0
Carcinoma, Hepatocellular		0	0	1	0	0	0	0	0	0	0
[Adenoma+Carcinoma]		4	1	3	5	1	0*	1	3	1	0
Lung:	Number Examined	60	60	60	60	60	60	60	60	60	60
Carcinoma, Bronchiolar-Alveolar		0	1	0	1	0	0	0	0	0	0
Mammary, Caudal:	Number Examined	NA	49	NA	NA	49	NA	54	NA	50	50
Fibroadenoma		NA	1	NA	NA	0	NA	0	NA	0	0

Dinse and Lagakos logistic prevalence methods and Cox-Tarone binary regression methods: * - P<0.05 ** - P<0.01

Daily Dose (mg/kg)		0 (Control)		0.3	1		3		10		30
Gender		M	F	M	M	F	M	F	M	F	F
Number of Animals with Neoplastic Lesions:											
Mammary, Cranial:	Number Examined	NA	52	NA	NA	47	NA	43	NA	48	50
Carcinoma		NA	0	NA	NA	1	NA	0	NA	0	0
Mammary, Male:	Number Examined	2	NA	4	2	NA	3	NA	0	NA	NA
Fibroadenoma		0	NA	1	1	NA	0	NA	0	NA	NA
Mammary, Other:	Number Examined	NA	8	NA	NA	6	NA	1	NA	2	1
Fibroadenoma		NA	5	NA	NA	4	NA	1	NA	1	0
Ovary:	Number Examined	NA	60	NA	NA	60	NA	60	NA	60	60
Granulosa/Theca Cell Tumor		NA	0	NA	NA	1	NA	1	NA	1	0
Pancreas:	Number Examined	60	60	60	58	60	60	60	60	60	60
Adenoma, Islet Cell		3	1	4	1	0	0	0	0	0	0
Carcinoma, Islet Cell		2	0	1	1	0	2	0	0	0	0
Parathyroid:	Number Examined	56	54	58	57	57	55	59	57	57	57
Adenoma		0	0	0	0	0	0	0	0	1	0
Pituitary:	Number Examined	59	60	59	60	60	60	60	60	59	59
Adenoma, Anterior Lobe		24	26	29	22	29	21	23	8	19	17
Adenoma, Intermediate Lobe		0	0	0	0	0	0	1	0	0	0
Carcinoma, Anterior Lobe		0	0	0	1	0	1	0	0	2	0
Prepeutial Gland:	Number Examined	2	NA	0	0	NA	1	NA	0	NA	NA
Adenoma		1	NA	0	0	NA	1	NA	0	NA	NA
Submaxillary Gland:	Number Examined	60	59	60	60	60	59	60	60	60	60
Carcinoma		0	0	0	0	0	1	0	0	0	0
Schwannoma		0	1	0	1	0	0	0	0	0	0
Skin, Other:	Number Examined	15	2	16	15	1	9	6	4	2	5
Papilloma		0	0	0	2	0	0	0	0	0	0
Squamous Cell Papilloma		1	0	3	0	0	0	0	1	1	0
Keratoacanthoma		3	1	5	5	0	1	0	1	0	0
Adenoma, Zymbal's Gland		1	0	0	0	0	0	0	0	0	0
Basal Cell Adenoma		0	0	0	0	0	0	1	0	0	0
Basal Cell Carcinoma		1	0	0	0	0	0	0	0	0	0

NA = Not applicable.
Dinse and Lagakos logistic prevalence methods and Cox-Tarone binary regression methods: * - P<0.05

(Continued)

2.6.7.11B Carcinogenicity Study Study No. R087-TX-047 (Continued)

Daily Dose (mg/kg)	0 (Control)		0.3	1		3		10		30
Gender	M	F	M	M	F	M	F	M	F	F
Number of Animals with Neoplastic Lesions:										
Spleen: Number Examined	60	59	60	60	60	60	60	60	60	59
Sarcoma	0	0	0	1	0	0	0	0	0	0
Stomach,										
Nonglandular: Number Examined	59	60	60	60	60	60	60	60	60	60
Papilloma	0	0	0	0	0	2	0	0	0	0
Squamous Cell Carcinoma	0	0	0	0	0	0	0	1	0	0
Subcutaneous										
Tissue: Number Examined	2	3	2	0	0	2	0	2	1	1
Fibroma	2	1	1	0	0	2	0	0	0	0
Fibrosarcoma	0	1	0	0	0	0	0	1	1	1
Rhabdomyosarcoma	0	0	0	0	0	0	0	1	0	0
Testis: Number Examined	60	NA	60	60	NA	60	NA	60	NA	NA
Benign Interstitial Cell Tumor	53	NA	53	57	NA	53	NA	43	NA	NA
Thymus: Number Examined	56	56	57	56	57	52	51	38	50	43
Thymoma	0	0	0	1	0	0	0	0	0	0
Thyroid: Number Examined	60	58	60	60	60	60	60	60	60	60
Follicular Cell Adenoma	0	0	1	1	0	1	0	0	0	0
"C" Cell Adenoma	2	3	4	7*	3	0	4	4	2	1
"C" Cell Carcinoma	9	3	7	7	3	2*	7	4	5	0
Urinary Bladder: Number Examined	60	59	60	60	60	60	60	59	60	60
Papilloma, Transitional Cell	0	0	0	1	0	0	0	0	0	0
Uterus: Number Examined	NA	60	NA	NA	60	NA	60	NA	60	60
Endometrial Stromal Polyp	NA	8	NA	NA	6	NA	10	NA	2	2
Endometrial Stromal Sarcoma	NA	1	NA	NA	0	NA	0	NA	1	0
Sarcoma	NA	0	NA	NA	0	NA	1	NA	0	0
Carcinoma	NA	1	NA	NA	3	NA	0	NA	0	0
Uterus, Cervix: Number Examined	NA	60	NA	NA	60	NA	60	NA	60	60
Granular Cell Tumor	NA	0	NA	NA	0	NA	1	NA	0	0
Endometrial Stromal Polyp	NA	0	NA	NA	1	NA	1	NA	1	0
Endometrial Stromal sarcoma	NA	0	NA	NA	1	NA	0	NA	0	1
Schwannoma	NA	0	NA	NA	1	NA	0	NA	0	0

Daily Dose (mg/kg)	0 (Control)		0.3	1		3		10		30
Gender	M	F	M	M	F	M	F	M	F	F
Number of Animals with Non-Neoplastic Lesions:										
Lung Number Examined	60	60	60	60	60	60	60	60	60	60
Foreign Body Pneumonia	6	0	3	11	2	$36^{\dagger *}$	$21^{\dagger\dagger}$	$49^{\dagger\dagger}$	$37^{\dagger\dagger}$	$48^{\dagger *}$
Esophagus Number Examined	60	60	60	60	59	60	60	60	60	60
Distended with Ingesta	1	0	1	2	1	4	$6^{\dagger}$	4	5^{*}	6^{*}
Trachea Number Examined	60	60	60	60	60	60	60	60	60	59
Exudate/Foreign Material (Ingesta)	2	0	1	1	1	3	2	3	4	$8^{*\dagger}$
Kidney Number Examined	60	60	60	60	60	60	60	60	60	60
Calculi, pelvis	48	57	49	$12^{\dagger *}$	59	$5^{\dagger *}$	$46^{*\dagger}$	$11^{\dagger\dagger}$	$40^{\dagger\dagger}$	$50^{\dagger}$
Hyperplasia, Pelvic Epithelium	51	45	54	$24^{\dagger\dagger}$	55^{*}	$2^{\dagger *}$	$27^{\dagger\dagger}$	$4^{\dagger *}$	$15^{\dagger\dagger}$	$15^{\dagger *}$
Stomach,										
Nonglandular Number Examined	59	60	60	60	60	60	60	60	60	60
Mineralization, Muscularis	0	0	1	$8^{*\dagger}$	0	$8^{\dagger\dagger}$	3	$19^{\dagger\dagger}$	2	$8^{*\dagger}$

NA = Not applicable.
Dinse and Lagakos logistic prevalence methods and Cox-Tarone binary regression methods: * - P<0.05
Cochran-Armitage Test and Fisher-Irwin Exact Test: † - P<0.05 †† - P<0.01

Oral and Intravenous Reproductive Toxicology Studies:

2.6.7.13A Reproductive and Developmental Toxicity - Fertility and Early Embryonic Development to Implantation

Report Title: Fertility Study (Segment I) of YM087 Administered Orally to Male Rats

Test Article: Conivaptan hydrochloride

Design similar to ICH 4.1.1: No
Species/Strain: SD Rats
Initial Age: 6 Weeks
Date of First Dose: 20 Jun 1994
Special Features: None
No Observed Adverse Effect Level:
F_0 Males: 1 mg/kg
F_1 Litters: 100 mg/kg

Duration of Dosing: M: 9 weeks prior to mating until the day before sacrifice
Day of Mating: Day 0
Day of C-Section: Day 20 of gestation
Method of Administration: Gavage
Vehicle/Formulation: 0.5% Methylcellulose solution

Study No. R087-TX-009

GLP Compliance: Yes

Daily Dose (mg/kg)		0 (Control)	1	10	100
F_0 Males	Number Evaluated	22	22	22	22
	Died or Sacrificed Moribund	0	0	0	1
	Clinical Observations				
	Hypoactivity	0	0	0	1
	Lateral position	0	0	0	1
	Necropsy Observations	-	-	-	-
	Body weights (g):				
	Week 0	222.8	230.1*	224.2	222.9
	Week 1	279.1	288.3	272.9	261.3**
	Week 3	370.7	387.5	358.5	336.7**
	Week 6	459.7	486.5	434.5	413.5**
	Week 9	511.1	542.4	474.2*	461.7**
	Food Consumption (g/day):				
	Week 1	27.3	28.2	24.8**	22.4**
	Week 2	30.0	30.8	28.2	27.3*
	Week 4	31.1	32.5	29.3	27.2**
	Week 7	29.6	31.1	27.2*	27.9
	Week 9	29.6	30.1	26.4**	26.8*
	No. of Males that Mated (%)	21 (95.5)	22 (100.0)	21 (95.5)	20 (95.2)
	No. of Fertile Males (%)	21 (100.0)	21 (95.5)	19 (90.5)	19 (95.0)

- No noteworthy findings.
Dunnett's Test or Scheffe's Test: * - P<0.05 ** - P<0.01

Daily Dose (mg/kg)		0 (Control)	1	10	100
F_0 Females	No. of Pregnant Females	21	21	19	19
	No. Aborted or with Total Resorption of Litter	0	1	1	0
	Mean No. Corpora Lutea	17.3	16.3	16.4	17.8
Litters	Mean No. Implantations	15.5	14.6	15.3	17.0
	% Preimplantation Loss [c]	10.44	10.50	6.73	4.44††
	Mean No. Live Conceptuses	15.0	13.6	14.8	16.5
	Dead Conceptuses (Post-implantation loss %)	10 (3.07)	21 (6.84†)	9 (3.09)	9 (2.79)
	Early Deaths	10	21	9	9
	Late Deaths	0	0	0	0
	Mean Fetal Body Weight (g) : Male	3.31	3.37	3.30	3.39
	Mean Fetal Body Weight (g) : Female	3.15	3.19	3.13	3.20
	Fetal Sex Ratios (M/F) [a]	0.86	1.12	1.14	0.90
	Fetal Anomalies:				
	Gross External [b]	0	1	0	1
	Visceral Anomalies [c]	2	1	0	4
	Skeletal Anomalies	0	NE	NE	0

NE = Not examined.
Chi-square Test: † - P<0.05 †† - P<0.01
a - Totaled value per group.
b - All gross external anomalies observed were considered unrelated to the treatment. These anomalies included vestigial tail, cleft lips and cleft palate.
c - All visceral anomalies observed were considered unrelated to treatment. These anomalies included dilatation of renal pelvis, dilatation of ureter, absence o eyeball and situs inversus.

2.6.7.13B Reproductive and Developmental Toxicity - Fertility and Early Embryonic Development to Implantation

Report Title: Effect of YM087 on the Estrous Cycle and Fertility in Rats

Test Article: Conivaptan hydrochloride

Design similar to ICH 4.1.1: Yes
Species/Strain: SD Rats
Initial Age: 9-10 Weeks
Date of First Dose: 22 Nov 1994
Special Features: None

Duration of Dosing: Regimen A: 2 weeks prior to mating, through GD7
Regimen B: 5 weeks
Day of Mating: Day 0
Day of C-Section: GD13
Method of Administration: Gavage
Vehicle/Formulation: 0.5% Methylcellulose solution

Study No. R087-TX-116

GLP Compliance: No

Daily Dose (mg/kg)		0 (Control)	1	10	100
F_0 Females	No. Evaluated (Regimen A/B)	6/6	6/6	6/6	6/6
	No. Died or Sacrificed Moribund[c]	0	0	0	0
	Clinical Observations[a]	-	-	-	-
	Necropsy Observations[a]	-	-	-	-
	Estrous Cycle[a]				
	Prolonged diestrus	0/12	0/12	10/12	12/12
	No. of Females Sperm-Positive (%)[b]	6 (100)	6 (100)	6 (100)	6 (100)
	No. of Pregnant Females (%)[b]	4 (66.7)	5 (83.3)	6 (100)	5 (83.3)
	Mean No. Corpora Lutea[b]	17.5	17.0	17.0	14.0
F_1 Fetuses	Mean No. Implantations[b]	13.8	15.6	17.0	13.0
	% Preimplantation Loss[b]	21.4	8.2	0.0	7.1
	Mean No. Live Conceptuses[b]	13.5	15.0	15.5	11.6
	Dead Conceptuses (Post-implantation loss %)[b]	1 (1.8)	3 (3.8)	9 (8.8)	7 (10.8)
	Early deaths (%)	1 (1.8)	3 (3.8)	9 (8.8)	7 (10.8)
	Late deaths (%)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

- No noteworthy findings. GD = Gestation day.
a - Examined in animals with regimen A and B
b - Examined in animals with regimen A

2.6.7.13C Reproductive and Developmental Toxicity - Fertility and Early Embryonic Development to Implantation

Report Title: Female Fertility Study (Segment I Study) of YM087 in Rats by Oral Administration

Test Article: Conivaptan hydrochloride

Design similar to ICH 4.1.1: Yes
Species/Strain: SD Rats
Initial Age: 9 Weeks
Date of First Dose: 20 Feb 1995
Special Features: None
No Observed Adverse Effect Level:
F_0 Females: 1 mg/kg
F_1 Litters: 1 mg/kg

Duration of Dosing: F: 2 weeks prior to mating, through GD7
Day of Mating: Day 0
Day of C-Section: GD20
Method of Administration: Gavage
Vehicle/Formulation: 0.5% Methylcellulose solution

Study No. R087-TX-010

GLP Compliance: Yes

		0 (Control)	1	10	100
F_0 Females	No. Evaluated	22	22	22	22
	No. Died or Sacrificed Moribund	0	0	1[a]	0
	Clinical Observations:				
	Hypoactivity	0	0	0	3
	Necropsy Observations	-	-	-	-
	Premating Body Weights	-	-	-	-
	Gestation Body Weights	-	-	-	-
	Premating Food Consumption (g)				
	Week 1	20.9	20.2	17.8**	15.2**
	Gestation Food Consumption (g)				
	GD4	26.1	25.8	23.1**	23.6**
	GD7	28.4	27.9	25.8**	26.2**
	GD10	29.4	30.3	27.9	30.1
	GD20	29.5	29.4	30.2	31.3
	Estrous Cycle				
	Prolonged diestrus	0	0	12	22
	Mean No. Days Prior to Mating	2.5	3.7	4.3	3.9
	No. of Females Sperm-Positive (%)	22 (100)	22 (100)	22 (100)	22 (100)
	No. of Pregnant Females (%)	22 (100)	22 (100)	20 (95.2)[b]	15 (68.2)[^]
	Mean No. Corpora Lutea	18.2	18.6	18.0	16.3

- No noteworthy findings. GD = Gestation day.
Dunnett's Test or Scheffe's Test: ** - P<0.01. Chi Square Test: ^ - p<0.05
a - Sacrificed due to intubation error (GD5), and showed esophageal perforation and dark reddening in the lung on necropsy.
b - One animal which was sacrificed on GD5 was excluded from evaluation.

Daily Dose (mg/kg)			0 (Control)	1	10	100
F_1 Fetuses	Mean No. Implantations		16.8	16.7	15.8	13.5
	% Preimplantation Loss		7.73	10.3	12.3[#]	17.1[^#]
	Mean No. Live Conceptuses		16.0	16.0	14.7	11.4*
	Dead Conceptuses (Post-implantation loss %)		18 (4.86)	16 (4.36)	22 (6.98)	32 (15.8)[^^]
	Early deaths (%)		18 (4.86)	16 (4.36)	22 (6.98)	32 (15.8)[^^]
	Late deaths (%)		0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	Mean Placental Weight (g):	Male	0.48	0.49	0.49	0.51
		Female	0.46	0.48	0.47	0.58**
	Mean Fetal Body Weights (g):	Male	3.24	3.13	3.43	3.44
		Female	3.16	2.99	3.23	3.29
	Fetal Sex Ratio (males/females)		1.08	1.01	0.92	0.97
	Fetal Anomalies					
	Gross External Anomalies					
	Fetuses Examined for External Anomalies		352	351	293	171
	Fetuses with Gross External Anomalies		1[a]	1[b]	1[c]	0
	Visceral Anomalies					
	Fetuses Examined for Visceral Anomalies		116	NE	NE	56
	No. Fetuses with Visceral Anomalies		0			1[d]
	Skeletal Anomalies					
	Fetuses Examined for Skeletal Anomalies		235	NE	NE	115
	No. Fetuses with Skeletal Anomalies		0			0
	No. Fetuses with Skeletal Variations		15[e]			4[f]
	No. Sternebrae		4.9			5.0
	No. Sacro-Caudal Vertebrae		7.2			7.3

NE = Not examined.
Dunnett's Test or Scheffe's Test: * - P<0.05 Chi Square Test: ^^ - p<0.01 ^ - p<0.05
a - Complication of brachyury, bilateral anophthalmia, acheiria, apodia and general edema were observed.
b - Micrognathia was observed and considered unrelated to the treatment.
c - Syndactyly of forelimbs was observed and considered unrelated to the treatment.
d - Dilated renal pelvis was observed and considered unrelated to the treatment.
e - Splitting or dumbbell shape of ossification centers of thoracic vertebral bodies, splitting of sternebrae, 14th ribs and shortening of 13th ribs were observed.
f - Splitting of ossification centers of thoracic vertebral bodies and splitting of sternebrae were observed and considered unrelated to the treatment.

2.6.7.13D Reproductive and Developmental Toxicity - Fertility and Early Embryonic Development to Implantation

Report Title: Additional Female Fertility Study (Segment I Study) of YM087 in Rats by Oral Administration (Reassessment of NOAEL)

Test Article: Conivaptan hydrochloride

Design similar to ICH 4.1.1: Yes
Species/Strain: SD Rats
Initial Age: 9-10 Weeks
Date of First Dose: 12 Nov 1996
Special Features: None
No Observed Adverse Effect Level:
F_1 Litters: 3 mg/kg

Duration of Dosing: F: 2 weeks prior to mating, through GD7
Day of Mating: Day 0
Day of C-Section: GD20
Method of Administration: Gavage
Vehicle/Formulation: 0.5% Methylcellulose solution

Study No. R087-TX-041

GLP Compliance: Yes

Daily Dose (mg/kg)		0 (Control)	3
F_0 Females	No. Evaluated	22	22
	No. Died or Sacrificed Moribund	0	0
	Clinical Observations	-	-
	Necropsy Observations	-	-
	Premating Body Weights (g):		
	1W	268.4	256.7*
	2W	284.6	269.1*
	Gestation Body Weights (g):		
	GD0	294.6	276.6**
	GD7	341.7	318.9**
	GD14	386.5	356.2**
	GD20	475.4	441.2**
	Premating Food Consumption (g):		
	1W	21.7	19.2**
	2W	23.1	20.7**
	Gestation Food Consumption (g):		
	GD7	30.7	27.7**
	GD14	33.0	30.4*
	GD20	31.7	30.1
	Estrous Cycle	-	-

- No noteworthy findings. GD = Gestation day.
Student's t-Test: ** - $p<0.01$ * - $p<0.05$

Daily Dose (mg/kg)		0 (Control)	3
F_0 Females	No. of Females Sperm-Positive (%)	21 (95.5)	22 (100)
	No. of Pregnant Females (%)	19 (90.5)	22 (100)
	Mean No. Corpora Lutea	18.5	17.4
F_1 Fetuses	Mean No. Implantations	17.1	16.0
	% Preimplantation Loss	7.67	7.85
	Mean No. Live Conceptuses	15.5	14.7
	Dead Conceptuses (Post-implantation loss %)	30 (9.23)	28 (7.95)
	Early deaths (%)	28 (8.62)	28 (7.95)
	Late deaths (%)	2 (0.62)	0 (0.00)
	Fetal Sex Ratio (males/female)	1.05	0.89
	Fetal Anomalies		
	Gross External Anomalies		
	Fetuses Examined for External Anomalies	295	324
	Fetuses with Gross External Anomalies	1[a]	0

a - Micrognathia

2.6.7.13E Reproductive and Developmental Toxicity - Fertility and Early Embryonic Development to Implantation

Report Title: Additional Female Fertility Study (Segment I Study) of YM087 in Rats by Oral Administration –The Effect of Administration Period on Fertility-

Test Article: Conivaptan hydrochloride

Design similar to ICH 4.1.1: Yes
Species/Strain: SD Rats
Initial Age: Pre-pregnancy dose study: 10 Weeks
Early pregnancy dose study: 12 - 13 Weeks
Date of First Dose:
Pre-pregnancy dose study: 31 Oct 1995
Early pregnancy dose study: 15 Nov 1995
Special Features: None

Duration of Dosing: Pre-pregnancy dose study: 2 weeks prior to mating until the day before successful mating
Early pregnancy dose study: GD0-7
Day of Mating: Day 0
Day of C-Section: GD14
Method of Administration: Gavage
Vehicle/Formulation: 0.5% Methylcellulose solution

Study No. R087-TX-011

GLP Compliance: Yes

Daily Dose (mg/kg)		0 (Control)	100	
Pre-pregnancy dose study				
F_0 Females	No. Evaluated	20	20	
	No. Died or Sacrificed Moribund	0	0	
	Clinical Observations:			
	Before Copulation: Polyuria	0	20	
	Gestation Period	-	-	
	Premating Body Weights	-	-	- No noteworthy findings.
	Gestation Body Weights	-	-	
	Premating Food Consumption (g):			
	Day 1-8	21.5	16.9**	
	Day 8-15	21.4	21.9	
	Gestation Food Consumption	-	-	
	Estrous Cycle			
	Prolonged diestrus	0	18	
	No. of Females Sperm-Positive (%)	20 (100)	20 (100)	
	No. of Pregnant Females (%)	20 (100)	16 (80.0)	
	Necropsy Observations	-	-	
	Mean No. Corpora Lutea	17.9	16.4	
	Mean No. Implantations	16.2	15.1	
	% Preimplantation Loss	10.1	9.1	
Pre-pregnancy dose study (Continued)				
F_0 Females	Mean No. Live Conceptuses	15.0	14.4	
	Dead Conceptuses (Post-implantation loss %)	23 (6.8)	10 (5.8)	
	Early deaths (%)	20 (6.0)	9 (3.7)	
	Late deaths (%)	3 (0.8)	1 (2.1)	
Early pregnancy dose study				
F_0 Females	No. Evaluated	20	19	
	No. Died or Sacrificed Moribund	0	2[a]	
	Clinical Observations:			
	Polyuria	0	19	
	Hypoactivity	0	4	
	Piloerection	0	3	
	Irregular respiration	0	3	
	Thin appearance	0	3	
	Dirty fur	0	3	
	Body Weights (g):			
	GD0	281	272	
	GD4	302	267**	
	GD7	312	283**	
	GD14	344	324**	
	Food Consumption (g):			GD = Gestation day.
	GD0-4	24.5	11.6**	
	GD4-7	25.9	20.4**	
	GD7-10	26.6	24.5*	
	GD10-14	26.6	29.6**	

a - Found dead before dosing on GD4 and 5 respectively with enlargement of the adrenals, atrophy of the thymus, or scattered dark red spots in the stomach.

Early pregnancy dose study (Continued)				
F_0 Females	Necropsy Observations	-	-	
	Mean No. Corpora Lutea	18.4	17.5	- No noteworthy findings.
	Mean No. Implantations	16.5	15.0	
	% Preimplantation Loss	9.7	13.3	
	Mean No. Live Conceptuses	15.6	12.3*	
	Dead Conceptuses (Post-implantation loss %)	18 (5.8)	46 (19.5)[#]	
	Early deaths (%)	17 (5.5)	43 (18.2)[#]	
	Late deaths (%)	1 (0.3)	3 (1.3)	

Student's t-Test or Aspin-Welch t-Test: ** - $p<0.01$ * - $p<0.05$
Mann-Whitney U-Test: [#] - $p<0.05$

2.6.7.13F Reproductive and Developmental Toxicity - Fertility and Early Embryonic Development to Implantation

Report Title: Additional Female Fertility Study (Segment I Study) of YM087 in Rats by Oral Administration –Assessment of the Reversibility after Pre-mating Treatment-

Test Article: Conivaptan hydrochloride

Design similar to ICH 4.1.1: Yes
Species/Strain: SD Rats
Initial Age: 10 Weeks
Date of First Dose: 26 Nov 1996
Special Features: None

Duration of Dosing: 2 weeks prior to mating
Day of Mating: Day 0
Day of C-Section: GD14
Method of Administration: Gavage
Vehicle/Formulation: 0.5% Methylcellulose solution

Study No. R087-TX-042

GLP Compliance: Yes

Daily Dose (mg/kg)		0 (Control)	100
Study I [a]			
F_0 Females	No. Evaluated	20	20
	No. Died or Sacrificed Moribund	0	1 [b]
	Clinical Observations:		
	Polyuria	0	20
	Premating Body Weights	-	-
	Gestation Body Weights	-	-
	Premating Food Consumption (g):		
	Day 1-8	22.5	18.3**
	Day 8-15	23.0	22.3
	Gestation Food Consumption	-	-
	Estrous Cycle		
	Prolonged diestrus	0	14
	Without estrous stage	0	13
	No. of Females Sperm-Positive (%)	20 (100)	19 (100)
	No. of Pregnant Females (%)	20 (100)	17 (89.5)
	Necropsy Observations	-	-
	Mean No. Corpora Lutea	18.7	17.2*

- No noteworthy findings. GD = Gestation day.
Student's t-Test or Aspin-Welch t-Test: ** - $p<0.01$ * - $p<0.05$
a - Mating was performed after 2-week administration.
b - This animal showed decreased amount of feces on dosing day 3, and showed a decrease in movements and emaciation and died on dosing day 8. Necropsy findings showed atrophy of the spleen and thymus.

Daily Dose (mg/kg)		0 (Control)	100
Study I [a]			
F_0 Females	Mean No. Implantations	17.5	15.8*
	% Preimplantation Loss	6.2	8.2
	Mean No. Live Conceptuses	16.3	14.4*
	Dead Conceptuses (Post-implantation loss %)	24 (6.9)	24 (9.0)
	Early deaths (%)	23 (6.6)	24 (9.0)
	Late deaths (%)	1 (0.3)	0 (0.0)
Study II [a]			
F_0 Females	No. Evaluated	20	20
	No. Died or Sacrificed Moribund	0	1 [b]
	Clinical Observations:		
	Polyuria	0	20
	Premating Body Weights	-	-
	Recovery Period Body Weights	-	-
	Gestation Body Weights	-	-
	Premating Food Consumption (g)		
	Day 1-8	22.7	18.0**
	Day 8-15	23.1	22.6
	Recovery Period Food Consumption	-	-
	Gestation Food Consumption	-	-
	Estrous Cycle		
	Prolonged diestrus	0	17 [c]
	Without estrous stage	0	11 [c]
	No. of Females Sperm-Positive (%)	20 (100)	18 (94.7)
	No. of Pregnant Females (%)	20 (100)	18 (100)
	Necropsy Observations	-	-
	Mean No. Corpora Lutea	18.6	18.6
	Mean No. Implantations	17.7	16.9
	% Preimplantation Loss	4.9	8.7
	Mean No. Live Conceptuses	15.5	15.1
	Dead Conceptuses (Post-implantation loss %)	43 (12.2)	33 (10.8)
	Early deaths (%)	38 (10.8)	30 (9.8)
	Late deaths (%)	5 (1.4)	3 (1.0)

- No noteworthy findings.
Student's t-Test or Aspin-Welch t-Test: ** - $p<0.01$
a - Mating was performed after 5-week withdrawal following 2-week administration.
b - This animal died on dosing day 3 with no clinical signs.
c - All animals were reversed within 2 weeks after start of withdrawal.

2.6.7.13G Reproductive and Developmental Toxicity – Fertility and Early Embryonic Development to Implantation

Report Title: Study of Fertility in Male Rats by Intravenous Injection of YM087

Test Article: Conivaptan hydrochloride

Design similar to ICH 4.1.1.: Yes
Species/Strain: SD (IGS) Rats
Initial Age: 10-11 Weeks
Date of First Dose: 28 Mar, 2000
Special Features: None
No Observed Adverse Effect Level:
F_0 Males: 0.5 mg/kg
F_1 Litters: 2.5 mg/kg

Duration of Dosing: M: 4 weeks prior to mating until sacrifice (59 days)
Day of Mating: Day 0
Day of C-Section: GD13
Method of Administration: Intravenous, bolus at 10 mL/kg
Vehicle/Formulation: Vehicle: [redacted] propylene glycol, [redacted] ethanol, and lactic acid sufficient to adjust pH to 3.3 ± 0.2. Diluent: 5% dextrose solution

Study No. R087-TX-088

GLP Compliance: Yes

Daily Dose (mg/kg)		0 (control)	0.5	1.25	2.5
Males	No. Evaluated	22	22	22	22
	No. Died or Sacrificed Moribund	0	0	0	0
	Clinical Observations				
	Swollen tail	10	12	15†	19††
	Necropsy Observations	-	-	-	-
	Body weight: Day 28[a]	444.4	447.4	444.1	431.6
	Body weight gain: Day 1-4	9.4	13.3	10.5	2.8*
	Day 1-60	152.2	156.0	153.7	130.1
	Food Consumption: Day 1-8	26.9	27.0	26.6	24.0**
	Food Consumption: Day 1-57	27.2	27.1	27.3	26.0
	Mean No. Days Prior to Mating	2.8	4.0	3.4	3.4
	No. of Males that Mated (%)	22 (100)	22 (100)	22 (100)	22 (100)
	No. of Fertile Males (%)	20 (90.9)	21 (95.4)	19 (86.4)	21 (95.4)

- No noteworthy findings. GD = Gestation day.
Dunnett's Test: * - P<0.05 ** - p<0.01
Chi-Square Test: † - P<0.05 †† - p<0.01

Daily Dose (mg/kg)		0 (control)	0.5	1.25	2.5
Female (untreated)	No. of Pregnant Females	20	21	19	21
	No. Died or Sacrificed Moribund	0	0	0	0
	Clinical Observations	-	-	-	-
	Localized alopecia (limbs)	0	0	3	1
	Necropsy Observations	-	-	-	-
	Dilation of renal pelvis (right)	1	0	0	1
	Gestation Body Weight: GD 13	329.4	327.0	330.8	326.7
	Gestation Body Weight gain: GD0-7	39.0	33.0	36.8	30.5**
	GD0-13	70.8	64.0	70.3	64.1
	Gestation Food Consumption: GD0-13	26.3	25.0	26.0	25.8
	No. Aborted or with Total Resorption of Litter	0	0	0	0
	Mean No. Corpora Lutea	19.2	18.8	19.0	18.7
	Mean No. Implantations	16.8	16.7	17.0	16.2
	% Preimplantation Loss[a]	12.5	11.4	10.5	13.0
	Mean No. Live Conceptuses	15.9	16.1	16.4	15.4
	Mean No. Resorption	1.0	0.6	0.6	0.8
	No. Dead Conceptuses	19	12	12	17
	% Postimplantaion Loss[a]	5.6	3.4	3.7	5.0

- No noteworthy findings. GD = Gestation day.
Dunnett's Test: * - P<0.05 ** - p<0.01
a - Totaled value per group.

2.6.7.13II Reproductive and Developmental Toxicity – Fertility and Early Embryonic Development to Implantation

Report Title: Study on Fertility and Early Embryonic Development to Implantation in Female Rats by Intravenous Injection of YM087

Test Article: Conivaptan hydrochloride

Design similar to ICH 4.1.1.: Yes
Species/Strain: SD (IGS) Rats
Initial Age: 11-12 Weeks
Date of First Dose: 10 Apr. 2000
Special Features: None
No Observed Adverse Effect Level:
F_0 Females: 0.5 mg/kg
F_1 Litters: 1.25 mg/kg

Duration of Dosing: F: 2 weeks prior to mating, through GD7
Day of Mating: Day 0
Day of C-Section: GD13
Method of Administration: Intravenous, bolus at 10 mL/kg
Vehicle/Formulation: Vehicle: [redacted] propylene glycol, [redacted] ethanol, and lactic acid sufficient to adjust pH to 3.3 ± 0.2. Diluent: 5% dextrose solution

Study No. R087-TX-089

GLP Compliance: Yes

Daily Dose (mg/kg)			0 (control)	0.5	1.25	2.5
Female	No. Evaluated		22	22	22	22
	No. Died or Sacrificed Moribund		0	0	0	0
	Clinical Observations:		-	-	-	-
	Necropsy Observations		-	-	-	-
	Premating Body Weight (g):	Day 15[a]	255.8	258.1	259.0	258.6
	Body Weight Gain (g):	Day 1-4	0.7	2.0	2.0	-0.4
		Day 4-8	0.4	1.4	1.5	4.8**
		Day 11-15[a]	2.0	0.6	4.0	-0.5
		Day 1-15[a]	5.8	9.6	10.5	9.2
	Gestation Body Weight (g):	GD13	318.1	314.8	320.0	315.6
	Premating Food Consumption (g):	Day 1-8	17.2	16.7	16.0**	15.7**
	Premating Food Consumption (g):	Day 1-15[a]	18.3	18.0	18.0	17.8
	Gestation Food Consumption (g):	GD0-13	23.1	23.3	24.0	23.6
	Mean No. Estrous Cycle/14 days		3.5	3.5	3.3	2.7*
	Rats with 6 or more consecutive days of diestrus		0	0	0	5**
	Mean No. Days Prior to Mating		2.2	2.1	1.9	2.0
	No. of Females Sperm-Positive (%)		22 (100)	22 (100)	22 (100)	22 (100)

- No noteworthy findings. GD = Gestation day.
Dunnett's Test: ** - p<0.01
a - Last value recorded before cohabitation.

Daily Dose (mg/kg)		0 (control)	0.5	1.25	2.5
Female	No. of Pregnant Females (%)	21 (95.4)	22 (100)	19 (86.4)	21 (95.4)
	No. Aborted or with Total Resorption of Litter	0	1	0	1
	Mean No. Corpora Lutea	18.0	16.2	16.0	15.0**
	Mean No. Implantations	15.8	13.6*	14.7	13.6
	% Preimplantation Loss[b]	11.9	16.0*	8.5	9.2
	Mean No. Live Conceptuses	15.3	13.2	13.9	11.8[^]
	Mean No. Resorption	0.5	0.4	0.8	1.8[^]
	No. Dead Conceptuses	11	9	15	37[^]
	% Postimplantaion Loss[b]	3.3	3.0	5.4	12.9**

Dunnett's Test: * - P<0.05 ** - p<0.01
Chi-Square Test: [^] - P<0.05 [^^] - p<0.01
a - Last value recorded before cohabitation.
b - Totaled value per group.

2.6.7.14A Reproductive and Developmental Toxicity - Effects on Embryo-Fetal Development | **Report Title:** Teratology Study of YM087 by Oral Administration to Rats: Effect on Fetuses | **Test Article:** Conivaptan hydrochloride

Design similar to ICH 4.1.3: Yes | **Duration of Dosing:** GD7-17 | **Study No.** R087-TX-012
Species/Strain: SD Rats
Initial Age: 13 Weeks at the Start of Mating | **Day of Mating:** Day 0 | **GLP Compliance:** Yes
Date of First Dose: 31 May 1994 | **Day of C-Section:** GD20
Special Features: None | **Method of Administration:** Gavage
No Observed Adverse Effect Level: | **Vehicle/Formulation:** 0.5% Methylcellulose solution
F_0 Females: 1 mg/kg
F_1 Litters: 1 mg/kg

Daily Dose (mg/kg)			0 (Control)	1	10	100
Dams	Toxicokinetics[a]:					
	C_{max} (ng/mL):	GD7	NA	13.1	616	4505
		GD17	NA	11.1	581	3328
	$AUC_{0\text{-}24}$ (ng·hr/mL):	GD7	NA	71.4	5514	68331
		GD17	NA	88.0	4628	39137
	No. Pregnant		23	21	23	21
	No. Died or Sacrificed Moribund		0	0	0	1[b] (GD11)
	No. Aborted or with Total Resorption of Liter		0	2	0	0
	Clinical Observations					
	Hypoactivity		0	0	0	3 (GD7, 10[b], 11[b])
	Necropsy Observations					
	Hemorrhage of lung		0	0	0	1[b]
	Body Weights (g):	GD7	318.7	317.3	319.9	319.7
		GD8	320.8	319.1	309.2	290.2**
		GD10	328.9	327.7	315.7	305.6*
		GD18	390.3	382.1	370.0	356.0*
		GD20	422.5	408.6	406.0	394.1

NA = Not applicable. GD = Gestation day.
Scheffe's Test: * - P<0.05 ** - P<0.01
a - From Study No. R087-TX-086, Retrospective Toxicokinetic Evaluations for Oral Dose Reproductive Studies of YM087 in Rats.
b - Sacrificed on GD11 (Intubation error on GD10).

Daily Dose (mg/kg)			0 (Control)	1	10	100
Dams	Food Consumption (g/day):	GD7	23.7	23.4	23.7	23.3
		GD8	24.7	22.1	12.7**	7.0**
		GD10	24.7	23.6	15.7**	12.6**
		GD18	25.9	23.8**	22.4**	19.8**
		GD20	26.1	25.3	26.7	26.1
	Mean No. Corpora Lutea		16.7	16.0	17.5	16.8
	Mean No. Implantations		15.7	13.8	15.8	15.4
Litters:	No. Litters Evaluated		23	21	23	21
	No. Live Fetuses		340	269	350	299
	Mean No. Live Fetuses		14.8	12.8	15.2	14.2
	% Postimplantation Loss		5.82	7.24	3.85	7.72
	No. Early Resorptions		6	13	5	11
	No. Late Resorptions		14	8	9	14
	No. Dead Fetuses		1	0	0	0
	Mean Fetal Body Weights (g):	Male	3.21	3.25	2.97**	2.85**
		Female	3.11	3.08	2.82**	2.73**
	Mean Placental Weight (g):	Male	0.47	0.50	0.49	0.47
		Female	0.47	0.48	0.47	0.46
	Fetal Sex Ratio (% males)(M/F)		1.09	1.01	0.85	0.86
	Fetal Anomalies					
	No. Fetuses with Gross External Anomalies[a]		0	0	2	2
	No. Fetuses with Visceral Anomalies[b]		1	3	1	1
	No. Fetuses with Skeletal Anomalies[c]		0	0	1	0
	Mean No. Sternebrae		5.4	5.3	4.9**	5.1*
	Mean No. Sacro-caudal Vertebrae		7.5	7.5	7.0**	6.9**

GD = Gestation day.
Scheffe's Test: * - P<0.05 ** - p<0.01
a - All gross external anomalies observed were considered unrelated to the treatment. These anomalies included cranioschisis, anury, anal atresia, and vestigial tail.
b - All visceral anomalies observed were considered unrelated to the treatment. These anomalies included undescended testis, dilatation of renal pelvis, and dilation of lateral ventricle.
c - Skeletal anomalies observed were complex malformation in one fetus and considered unrelated to the treatment. These anomalies included wavy ribs, and deformity of clavicle, scapula, humerus, radius, ulna and femur.

2.6.7.14B Reproductive and Developmental Toxicity – Effects on Pre-and Postnatal Development, Including Maternal Function

Report Title: Teratology Study of YM087 in Rats by Oral Administration: Assessment of the Effects on Offspring

Test Article: Conivaptan hydrochloride

Design similar to ICH 4.1.3: Yes
Species/Strain: SD Rats
Initial Age: 12-14 Weeks at the time of successful mating
Date of First Dose: 12 Jan 1996
Special Features: None
No Observed Adverse Effect Level:
F_0 Dams: 1 mg/kg
F_1 Litters: 10 mg/kg

Duration of Dosing: GD7-17
Day of Mating: Day 0
Method of Administration: Gavage
Vehicle/Formulation: 0.5% Methylcellulose solution
Litters Culled/Not Culled: Culled on day 4 of lactation

Study No. R087-TX-013
GLP Compliance: Yes

Daily Dose (mg/kg)			0 (Control)	1	10	100
F_0 Females	Toxicokinetics[a]:					
	C_{max} (ng/mL):	GD7	NA	13.1	616	4505
		GD17	NA	11.1	581	3328
	AUC_{0-24} (ng·hr/mL):	GD7	NA	71.4	5514	68331
		GD17	NA	88.0	4628	39137
	No. Pregnant		20	19	20	20
	No. Died or Sacrificed Moribund		0	1 (GD20)[b]	0	4 (GD8, 10, 13, 14)
	No. Aborted or with Total Resorption of Litter		0	0	0	0
	Clinical Observations					
	Polyuria		0	0	20 (GD7-17)	19 (GD7-17)
	Hypoactivity		0	0	0	3 (GD8-13)[c]
	Irregular Respiration		0	0	0	3 (GD9-13)[c]
	Emaciation		0	0	0	2 (GD10-14)[c]
	Tremor		0	0	0	1 (GD12)[c]
	Piloerection		0	0	0	2 (GD12-13)[c]

NA = Not applicable. GD = Gestation day.
a - From Study No. R087-TX-086, Retrospective Toxicokinetic Evaluations for Oral Dose Reproductive Studies of YM087 in Rats
b - Due to a dosing error.
c - These signs were observed in dead animals.

Daily Dose (mg/kg)			0 (Control)	1	10	100
F_0 Females	Clinical Observations					
	Red Soil Around the Eyes, Nose and/or Mouth		0	0	0	3 (GD9-14, 18)
	Prone Position		0	0	0	2 (GD13)[a]
	Absence of Righting Reflex		0	0	0	1 (GD13)[a]
	Necropsy Observations					
	Abdominal Cavity: Decreased of adipose tissue		0	0	0	1[b]
	Thymus: Atrophy		0	0	0	1[b]
	Heart: A grayish white region in the left ventricular outer wall		0	0	0	1[b]
	Spleen: Atrophy		0	0	0	1[b]
	Stomach: Retention of gas		0	0	0	1[b]
	Gestation Body Weight (g):	GD7	301	302	298	300
		GD8	303	305	294	263**
		GD18	380	386	370	344**
	Lactation Body Weight (g):	LD0	300	300	295	287
		LD11	345	341	333	324**
		LD22	322	324	318	309
	Gestation Food Consumption (g/day)	GD8	25.4	24.9	14.2**	5.2**
		GD18	29.4	28.8	26.6*	23.4**
		GD20	26.1	25.3	27.7	28.1
	Lactation Food Consumption (g/day)	LD0-4	33.5	29.9	33.5	34.1
		LD18-22	72.7	69.7	73.0	68.4
	Mean Duration of Gestation (days)		21.5	21.6	21.9†	21.9†
	Abnormal Parturition		0	0	0	0

GD = Gestation day. LD = Lactation day.
a - These signs were observed in dead animals.
b - These findings were observed in dead animals.
Dunnett's Test or Welch's t-Test: * - P<0.05 ** - P<0.01 Wilcoxon Rank Sum Test: † - P<0.05

(Continued)

2.6.7.14B Reproductive and Developmental Toxicity **Study No. R087-TX-013 (Continued)**

Daily Dose (mg/kg)				0 (Control)	1	10	100
F_1 Litters: (Preweaning)	No. Litters Evaluated			20	18	20	16
	Mean No. of Implantations			15.2	16.1	16.7	15.6
	Mean No. Pups/Litter			13.9	15.3	15.6	14.4
	Mean % Delivery Index/Litter [a]			88.8	95.1	93.1	92.5
	Mean No. Liveborn Pups/Litter			13.3	14.7	15.2	14.1
	Mean % Birth Index/Litter [b]			84.2	91.1	90.7	90.5
	No. of Litters with Stillborn Pups			5	3	4	3
	Postnatal Survival to Day 4 (Before culling)			264	256	296	222
	Mean % Viability Index/Litter [c]			99.6	97.0	97.6	99.1
	Postnatal Survival to Weaning			151	143	160	126
	Mean % Weaning Index/Litter [d]			99.3	99.3	100.0	98.4
	No. of Total Litter Losses			1	0	0	0
	Mean Body Weight (g):	Male	LD0	6.58	6.32	6.41	6.47
			LD4	10.87	10.21	10.27	9.93*
			LD7	17.7	16.5	16.8	16.1*
			LD14	34.4	32.6	33.4	32.0
			LD22	61.0	57.4	59.1	55.7**
		Female	LD0	6.24	5.86*	6.06	6.06
			LD4	10.29	9.52	9.81	9.66
			LD7	16.8	15.5	16.0	15.6
			LD14	33.0	31.3	32.4	30.8
			LD22	58.3	54.8	56.9	53.8*
	Pups Sex Ratios (% Male Proportion)			53.6	49.6	52.8	49.8

LD = Lactation day.
Dunnett's Test or Welch's t-Test: * - P<0.05 ** - P<0.01
a - (Number of pups/Number of implantation sites) × 100.
b - (Number of liveborn pups/number of implantation sites) × 100.
c - (Number of live pups on LD4/number of liveborn pups on LD0) × 100.
d - (Number of live pups on LD22/number of live pups on LD4) × 100

Daily Dose (mg/kg)			0 (Control)	1	10	100
F_1 Litters: (Preweaning)	Pups Clinical Observations		-	-	-	-
	Gross External Anomalies		0	0	0	1 [a]
	Pups Necropsy Observations:	LD4	-	-	-	-
		LD22	-	-	-	-
	Physical Development					
	% Pinna Unfolding:	LD4	100.0	100.0	100.0	100.0
	% Growth Abdominal Hair:	LD14	100.0	100.0	100.0	100.0
	% Eruption of Upper Incisor:	LD14	100.0	100.0	100.0	100.0
	% Eyelid Opening:	LD18	100.0	100.0	100.0	100.0
	Skeletal Anomalies					
	No. Sacral and Caudal Vertebrae:	Male	31.9	32.0	31.6	31.9
		Female	32.1	31.7	31.9	32.0
	No. Sternebrae:	Male	6.0	6.0	6.0	6.0
		Female	6.0	6.0	6.0	6.0

LD = Lactation day.
- - No noteworthy findings.
a - Multiple anomalies (Anal atresia and anury).

2.6.7.14B Reproductive and Developmental Toxicity **Study No. R087-TX-013 (Continued)**

Daily Dose (mg/kg)			0 (Control)	1	10	100
F_1 Males: (Postweaning)	No. Evaluated Postweaning in Behavior		19	18	20	16
	No. Died or Sacrificed Moribund		0	0	0	0
	Clinical Observations		-	-	-	-
	Necropsy Observations:	10W	-	-	-	-
	Body Weights (g):	D28	99	94*	96	91**
		D42	228	220	224	218*
		D70	423	407	423	412
	Sensory Functions	5W				
	% Visual Placing Response		100.0	100.0	100.0	100.0
	% Preyer's Reflex		100.0	100.0	100.0	100.0
	% Pupillary Reflex		100.0	100.0	100.0	100.0
	% Pain Response		100.0	100.0	100.0	100.0
	% Air Righting Reflex		100.0	100.0	100.0	100.0
	% Back Righting		100.0	100.0	100.0	100.0
	% Negative Geotaxis		100.0	100.0	100.0	100.0
	Motor Activity:	6W				
	Open Field Test		-	-	-	-
	Learning and Memory:	6-7W				
	Conditioned Avoidance Response		-	-	-	-
	No. Evaluated Postweaning in Reproductive Performance		19	18	20	16
	No. Died or Sacrificed Moribund		0	0	0	0
	Clinical Observations		-	-	-	-
	Necropsy Observations:	17-18W	-	-	-	-
	Genital Development					
	% Decent of Testis:	D35	100.0	100.0	100.0	100.0
	% Development of U-type Penis:	D56	100.0	100.0	100.0	100.0
	No. of Males that Mated		19	18	20	16
	No. of Fertile Males		18	17	19	16
F_1 Females: (Postweaning)	No. Evaluated Postweaning in Behavior		19	18	20	16
	No. Died or Sacrificed Moribund		0	0	0	0
	Clinical Observations		-	-	-	-
	Necropsy Observations		-	-	-	-
	Premating Body Weights (g):	D28	88	84*	86	83**
		D42	174	168	166*	166*
		D70	266	254*	253*	262
	Sensory Functions:	5W	-	-	-	-
	% Visual Placing Response		100.0	100.0	100.0	100.0
	% Preyer's Reflex		100.0	100.0	100.0	100.0
	% Pupillary Reflex		100.0	100.0	100.0	100.0
	% Pain Response		100.0	100.0	100.0	100.0
	% Air Righting Reflex		100.0	100.0	100.0	100.0
	% Back Righting		100.0	100.0	100.0	100.0
	% Negative Geotaxis		100.0	100.0	95.0	100.0
	Motor Activity:	6W				
	Open Field Test		-	-	-	-
	Learning and Memory:	6-7W				
	Conditioned Avoidance Response		-	-	-	-
F_1 Females: (Postweaning)	No. Evaluated Postweaning in Reproductive Performance		19	18	20	16
	No. Died or Sacrificed Moribund		0	0	0	0
	Clinical Observations		-	-	-	-
	Necropsy Observations		-	-	-	-
	Gestation Body Weight (g):	GD0	298	282	288	292
		GD7	333	318	321	329
		GD14	369	355	356	363
		GD20	449	435	437	443
	Genital Development					
	% Opening of Vagina:	D49	100.0	100.0	100.0	100.0
	No. of Rats in Cohabitation		19	18	20	16
	No. of Females Sperm-Positive		19	18	20	16
	No. of Pregnant Females		18	17	19	16
	Mean No. Corpora Lutea		18.2	16.8	16.9	17.5
	Mean No. Implantations		16.1	15.6	16.0	15.6
	Mean % Preimplantation Loss		11.6	6.7*	5.6**	11.1
F_2 Litters:	Mean No. Live Conceptuses / Litter		15.4	14.6	15.1	14.6
	No. Resorptions		12	18	17	14
	No. Dead Conceptuses		0	0	0	1
	% Postimplantation Loss		4.2	6.8	5.6	6.0
	Fetal Body Weights (g):	Male	4.12	3.99	3.95	4.17
		Female	3.85	3.76	3.74	3.90
	Placental Weights (g):		0.497	0.484	0.501	0.502
	Pups Sex Ratios (% Male Proportion)		48.0	50.4	52.3	46.2
	Fetal External Anomalies		0	0	0	0

- No noteworthy findings. GD = Gestation day. D = Day of after birth.
Chi-Square Test: * - P<0.05 ** - P<0.01

2.6.7.14C Reproductive and Developmental Toxicity – Effects on Embryo-Fetal Development

Report Title: Study for Effects of YM087 on Embryo-Fetal Development in Rats by Intravenous Injection

Test Article: Conivaptan hydrochloride

Design similar to ICH 4.1.3: Yes
Species/Strain: SD (IGS) Rats
Initial Age: 9-10 Weeks at the start of mating
Date of First Dose: 21 February 2000
Special Features: None
No Observed Adverse Effect Level:
F_0 Females: < 0.5 mg/kg
F_1 Litters: 2.5 mg/kg

Duration of Dosing: GD7-17
Day of Mating: Day 0
Day of C-Section: GD21
Method of Administration: Intravenous, bolus at 10 mL/kg
Vehicle/Formulation: Vehicle: [redacted] propylene glycol, [redacted] ethanol, and lactic acid sufficient to adjust pH to 3.3 ± 0.2. Diluent: 5% dextrose solution

Study No. R087-TX-092

GLP Compliance: Yes

Daily Dose (mg/kg)		0 (Control)	0.5	1.25	2.5
Dams/Does:	Toxicokinetics: AUC[a]: (ng-hr/mL): GD7	NA	317	1810	3803
	No. Pregnant	25	25	23	24
	No. Died or Sacrificed Moribund	0	0	0	0
	No. Aborted or with Total Resorption of Litter				
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Body Weight (g): GD18	359.2	357.4	354.6	356.7
	Body Weight Gain (g): GD7-18	+77.9	+79.0	+73.3	+77.8
	Food Consumption (g/day): GD7-10	23.2	21.1**	20.2**	19.0**
	GD10-12	24.0	22.3*	22.2*	21.4**
	GD7-18	24.9	23.6*	23.1**	22.7**
	Mean No. Corpora Lutea	17.3	16.7	17.2	16.7[b]
	Mean No. Implantations	14.5	15.4	15.2	15.2[b]

- No noteworthy findings. NA = Not applicable. GD = Gestation day.
Dunnett's Test or Satterthwaite Analysis: * - P<0.05 ** - p<0.01
a - From Study No. R087-TX-091.
b - One dam was removed due to delivery on day 21 of gestation.

Daily Dose (mg/kg)		0 (Control)	0.5	1.25	2.5
Litters:	No. Litters Evaluated	25	25	23	23
	No. Live Fetuses	348	371	344	335
	Mean No. Live Fetuses	13.9	14.8	15.0	14.6
	Mean % Postimplantation Loss	4.3	3.4	1.7	3.9
	No. Early Resorptions	15	13	6	12
	No. Late Resorptions	0	0	0	2
	No. Dead Fetuses	0	0	0	0
	Mean Fetal Sex Ratio (% males/litter)	50.8	51.3	50.4	51.5
	Mean Fetal Body Weight (g): Male	5.76	5.71	5.50**	5.68
	Female	5.52	5.38	5.28**	5.38
	Mean Placental Weight (g): Male	0.57	0.57	0.58	0.56
	Female	0.58	0.54	0.54	0.53
	No. Fetal Anomalies (%)				
	Gross External Anomalies[a]	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
	Visceral Anomalies[b]	2 (0.6)	10 (2.7)	5 (1.4)	6 (1.8)
	Skeletal Anomalies[c]	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)
	Degree of Ossification	-	-	-	-

- No noteworthy findings.
Dunnett's Test or Satterthwaite Analysis: * - P<0.05 ** - p<0.01
a - All gross external anomalies observed were considered unrelated to the treatment. These anomalies included exencephaly, protruding and absent tongue, low set pinna, depressed eye bulge, cleft snout, short tail, submaxillary agnathia, and gastroschisis.
b - All visceral anomalies observed were considered unrelated to the treatment. These anomalies included absent lobes in the lung (partial, one or more lobes), one or more lobes absent in the lung, microphthalmia, dilation of lateral and/or third ventricle, septal defect of heart, protruded liver, stomach, intestines, spleen and/or pancreas through abdominal wall, dilation of renal pelvis, and situs inversus.
c - All skeletal anomalies observed were considered unrelated to the treatment. These anomalies included ossific abnormalities (vertebral centernum, and ribs), small eye socket, short and fused mandibules.

2.6.7.14D Reproductive and Developmental Toxicity - Effects on Embryo-Fetal Development **Report Title:** Teratology Study of YM087 in Rabbits by Oral Administration **Test Article:** Conivaptan hydrochloride

Design similar to ICH 4.1.3: Yes
Species/Strain: New Zealand White Rabbits
Initial Age: 21 Weeks at the Start of Mating
Date of First Dose: 31 May 1994
Special Features: None
No Observed Adverse Effect Level:
F_0 Females: <0.2 mg/kg
F_1 Litters: 6 mg/kg

Duration of Dosing: GD6-18
Day of Mating: Day 0
Day of C-Section: GD29
Method of Administration: Gavage
Vehicle/Formulation: 0.5% Methylcellulose solution

Study No. R087-TX-014
GLP Compliance: Yes

Daily Dose (mg/kg)			0 (Control)	0.2	1	6
Dams:	Toxicokinetics[a]:					
	C_{max} (ng/mL)	GD6	NA	2.43	18.1	262
		GD18	NA	9.57	32.1	267
	AUC_{0-24} (ng·hr/mL)	GD6	NA	9.17	82.3	1046
		GD18	NA	40.5	244	1322
	No. Pregnant		18	17	15	14
	No. Died or Sacrificed Moribund		0	1 (GD9)	0	0
	No. Aborted or with Total Resorption of Litter		0	0	0	1 (GD28)
	Clinical Observations		-	-	-	-
	Necropsy Observations	Stenosis of small intestine (Hernia)	0	1	0	0
		Trichobezoar	0	0	0	1
	Body Weights (g)	GD6	4058	3994	4121	4141
		GD7	4057	3978	4078	4056
		GD12	4077	3982	4102	4053
		GD18	4113	3994	4111	4093
		GD29	4156	4023	4244	4195

- No noteworthy findings. NA = Not applicable. GD = Gestation day.
a - From Study No. R087-TX-087, Evaluation Study of Toxicokinetics in Pregnant Rabbits Administered YM087 Orally during the Period of Fetal Organogenesis.

Daily Dose (mg/kg)			0 (Control)	0.2	1	6
Dams:	Food Consumption (g/day):	GD6	157.1	151.2	149.7	162.7
		GD7	161.1	140.1**	130.4**	91.8**
		GD12	144.9	123.0	139.1	118.2
		GD18	122.6	105.1	117.7	110.4
		GD29	85.3	75.6	113.4	80.8
	Mean No. Corpora Lutea		9.4	9.9	10.3	10.9
	Mean No. Implantations		7.4	8.4	8.9	9.3
Litters:	No. Litters Evaluated		18	16	15	13
	No. Live Fetuses		123	123	116	115
	Mean No. Live Fetuses		6.8	7.7	7.7	8.8
	% Postimplantation Loss		8.21	8.21	13.43	4.96
	No. Early Resorptions		2	1	1	0
	No. Late Resorptions		3	5	8	4
	No. Dead Fetuses		6	5	9	2
	Mean Fetal Body Weights (g):	Male	39.13	38.88	39.50	37.49
		Female	37.98	37.23	36.92	35.26
	Mean Placental Weight (g):	Male	5.33	5.16	5.10	5.35
		Female	4.98	4.96	4.97	4.78
	Fetal Sex Ratio (M/F)		0.89	1.05	0.76	0.95
	Fetal Anomalies					
	No. Fetuses with Gross External Anomalies		0	0	0	0
	No. Fetuses with Visceral Anomalies[a]		3	2	3	0
	No. Fetuses with Skeletal Anomalies[b]		4	2	0	3
	Mean No. Sternebrae		5.8	6.0*	5.8	5.9
	Mean No. Sacro-caudal Vertebrae		19.6	19.7	19.5	19.4

GD = Gestation day
Scheffe's Test: * - P<0.05 ** P<0.01
a - All visceral anomalies observed were considered unrelated to the treatment. These anomalies were absence of middle lobe in lung.
b - All skeletal anomalies observed were considered unrelated to the treatment. These anomalies included fusion of sternebrae, nodulation of rib, absence of cervical vertebral body, absence of cervical vertebral arch, supernumerary of thoracic vertebral body, supernumerary of rib, fusion of rib, hypoplasia of thoracic vertebral body, hypoplasia of thoracic vertebral arch, supernumerary of thoracic vertebral arch, hypoplasia of rib.

2.6.7.14E Reproductive and Developmental Toxicity – Effects on Embryo-Fetal Development

Report Title: Study for Effects of YM087 on Embryo-Fetal Development in Rabbits by Intravenous Injection

Test Article: Conivaptan hydrochloride

Design similar to ICH 4.1.3: Yes
Species/Strain: New Zealand White Rabbits
Initial Age: Approx. 6 Months
Date of First Dose: 30 Jan 2000
Special Features: None
No Observed Adverse Effect Level:
F_0 Females: 3 mg/kg
F_1 Litters: 12 mg/kg

Duration of Dosing: GD6-18
Day of Mating: Day 0
Day of C-Section: GD29
Method of Administration: Intravenous bolus at 10 mL/kg
Vehicle/Formulation: Vehicle: [redacted]% propylene glycol, [redacted]% ethanol, and lactic acid sufficient to adjust pH to 3.3 ± 0.2. Diluent: 5% dextrose solution

Study No. R087-TX-094
GLP Compliance: Yes

Daily Dose (mg/kg)			0 (Control)	3	6	12
Dams/Does:	Toxicokinetics: C_{max} (ng/mL):	GD6	NA	1843	4203	8773
		GD18	NA	2820	3940	10423
	AUC_{0-24} (ng-hr/mL):	GD6	NA	2614	5885	24298
		GD18	NA	3458	5645	27413
	No. Pregnant		19	18	20	19
	No. Died or Sacrificed Moribund		0	1[a]	0	0
	No. Aborted or with Total Resorption of Litter		0	0	0	0
	Clinical Observations					
	Purple ears		0	3	6*	10**
	Abrasion of the ears		0	0	3**	0
	Purple and swollen ears		0	1	5	3
	Scab on the ears		0	0	3	1
	Necropsy Observations		-	-	-	-
	Body Weight (kg): GD6		3.79	3.77	3.78	3.80
	GD7		3.80	3.80	3.78	3.76
	GD18		3.98	3.97	3.96	3.93
	Body Weight Gain (kg): GD6 18		+0.18	+0.20	+0.18	+0.12
	Food Consumption (g/day): GD6–7		152.5	160.6	146.2	126.9
	GD7 8		155.4	153.3	140.6	123.4**
	GD6–18		147.7	145.3	136.4	130.6

- No noteworthy findings. NA = Not applicable. GD = Gestation day.
Dunnett's Test or Satterthwaite Analysis: * - P<0.05 ** - p<0.01 Chi-Square Test: * - P<0.05 ** - p<0.01
a - One animal was moribund sacrificed on day 7 of gestation as the result of a restraint accident.

Daily Dose (mg/kg)		0 (Control)	3	6	12
Dams/Does:	Mean No. Corpora Lutea	9.8	10.5	9.6	10.1
	Mean No. Implantations	9.4	9.7	9.0	8.5
Litters:	No. Litters Evaluated	19	18	20	19
	No. Live Fetuses	173	166	168	157
	Mean No. Live Fetuses	9.1	9.2	8.4	8.3
	Mean % Postimplantation Loss	2.7	5.0	5.8	1.9
	No. Early Resorptions	0	3	1	0
	No. Late Resorptions	6	6	11	4
	No. Dead Fetuses	0	0	0	0
	Mean Fetal Sex Ratio (% males)	53.3	51.1	47.3	53.0
	Mean Fetal Body Weight (g): Male	42.53	42.11	45.20	44.82
	Female	41.60	41.52	42.95	43.10
	Mean Placental Weight (g): Male	5.67	6.03	6.01	6.06
	Female	5.41	5.74	5.44	5.69
	No. Fetal Anomalies				
	Gross External [a] (malformation/variation)	3/0	2/1	0/0	1/0
	Visceral Anomalies [b]	1/4	1/4	0/0	0/1
	Skeletal Anomalies [c]	0/15	1/10	1/23	1/13
	Total Affected Fetuses (Litters)	18 (10)	16 (11)	24 (15)	15 (9)

Dunnett's Test or Satterthwaite Analysis: * - P<0.05 ** - p<0.01
a - All gross external anomalies observed were considered unrelated to the treatment. These anomalies included meningocele, anencephaly or absent facial papilla of the head, short or thread-like tail, protruded tongue, absence of the snout and eye, flexed forelimbs, and abdominal distention.
b - All visceral anomalies observed were considered unrelated to the treatment. These anomalies included circumcorneal hemorrhage of the eye, small brain, large heart, absence of intermediate lobe in the lungs.
c - All skeletal anomalies observed were considered unrelated to the treatment. These anomalies included irregular ossification of the skull (fusion, contained an internasal/intranasal, midline suture displaced, irregular suture and irregular suture (frontal) of the nose, fusion and incompletely ossification of the fronatals), absence and parietal contained a hole of the skull, angulated ala hyoid, fused centra, hemivertebra, asymmetric centrum, bifid centrum and unilateral ossified centrum of the thoracic vertebra, 9, 14 and 15 presence, fusion and misaligned of the caudal vertebrae, thickened, fusued and proximate ribs, fusion, asymmetry, (1st and 2nd) incomplete ossification of the sternal centra.

2.6.7.15A Reproductive and Developmental Toxicity – Effects on Pre-and Postnatal Development, Including Maternal Function

Report Title: Peri- and Postnatal Study (Segment III Study) of YM087 in Rats by Oral Administration

Test Article: Conivaptan hydrochloride

Design similar to ICH 4.1.2: Yes
Species/Strain: SD Rats
Initial Age: 10-12 Weeks (mating day)
Date of First Dose: 28 Nov 1996
Special Features: None
No Observed Adverse Effect Level:
F_0 Females: 1.0 mg/kg
F_1 Litters: 0.1 mg/kg

Duration of Dosing: GD17 - LD21
Day of Mating: Day 0
Method of Administration: Gavage
Vehicle/Formulation: 0.5% Methylcellulose solution
Litters Culled: 8 offspring (4 males and 4 females)

Study No. R087-TX-043
GLP Compliance: Yes

Daily Dose (mg/kg)		0 (Control)	0.1	0.3	1.0
F_0 Females:	No. Pregnant	24	24	24	24
	No. Died or Sacrificed Moribund	0	1[a]	0	0
	No. Aborted or with Total Res. of Litters	0	0	0	0
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Body Weight	-	-	-	-
	Food Consumption	-	-	-	-
	Mean Duration of Gestation (days)	21.9	22.0	22.0	21.9
	Abnormal Parturition	0	1[a]	0	0
	Gestation Index (%)	100	95.8	100	100
	Delivery Index (%)	93.1	93.6	90.6	88.0
F_1 Litters:	No. Litter Evaluated	24	23	24	24
(Preweaning)	Mean No. of Implantations	16.4	16.8	17.5	16.8
	Mean No. Pups/Litter	15.2	15.7	15.8	14.7
	Mean No. Liveborn Pups/Litter	14.8	15.4	13.5	13.6
	Mean No. Stillborn Pups/Litter	0.38	0.30	2.38**	1.13**

- No noteworthy findings. GD = Gestation day. LD = Lactation day.
Chi Square Test: ** - $p<0.01$
a - This animal showed piloerection, decreased movement and irregular respiration, and began to manifest the delivery sign on GD23 and died on GD25 without delivering a single pup.

Daily Dose (mg/kg)		0 (Control)	0.1	0.3	1.0
F_1 Litters:	Birth Index (%)	90.9	91.9	78.1[a]	81.4
(Preweaning)	Viability Index on LD4 (%)	99.5	99.5	84.4	88.0
	Weaning Index (%)	99.5	99.5	100	98.9
	Mean Body weight	-	-	-	-
	Pups Sex Ratio (% males): LD0	50.8	53.4	48.0	52.8
	Pups Clinical Observations				
	No milk in stomach	0	1	3	3
	Cold to touch	0	0	2	3
	Microphthalmia	0	0	0	1
	Pups Necropsy Observations	-	-	-	-
	Physical Development				
	Pinna Unfolding	-	-	-	-
	Hair Growth	-	-	-	-
	Incisor Eruption	-	-	-	-
	Eye Opening	-	-	-	-
	Sensory functions and motor coordination				
	Back righting	-	-	-	-
	Negative geotaxis	-	-	-	-
	Visual placing response	-	-	-	-
	Preyer's reflex	-	-	-	-
	Pain response	-	-	-	-
	Air righting reflex	-	-	-	-
	Skeletal Examination				
	No. fetuses examined	95	91	80	84
	No. fetuses with malformations (%)	1 (1.1)	0 (0.0)	3 (3.8)	2 (2.4)
	Absence of part of the frontal and parietal bones	1 (1.1)	0 (0.0)	1 (1.3)	0 (0.0)
	Absence of thoracic vertebrae	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
	Nodulated ribs	0 (0.0)	0 (0.0)	2 (2.5)	1 (1.2)

- No noteworthy findings. LD = Lactation day.
Wilcoxon Rank Sum Test: [a] - $p<0.05$

(Continued)

2.6.7.15A Reproductive and Developmental Toxicity **Study No. R087-TX-043 (Continued)**

Daily Dose (mg/kg)		0 (Control)	0.1	0.3	1.0
F_1 Litters: (Preweaning)	No. fetuses with variations (%)	10 (10.5)	12 (13.2)	11 (13.8)	15 (17.9)
	Cervical rib	4 (4.2)	5 (5.5)	7 (8.8)	10 (11.9)
	13th rib shortening	3 (3.2)	1 (1.1)	0 (0.0)	0 (0.0)
	Accessory sternebrae	2 (2.1)	5 (5.5)	2 (2.5)	2 (2.4)
	Lumbar rib	0 (0.0)	1 (1.1)	2 (2.5)	2 (2.4)
	5 lumbar vertebrae	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Sacralization	3 (3.2)	0 (0.0)	0 (0.0)	1 (1.2)
	No. sacral and caudal vertebrae				
	Male	32.3	32.8**	32.7*	32.7*
	Female	32.3	32.6	32.6	32.7*
	No. sternabrae				
	Male	6.0	6.0	6.0	6.0
	Female	6.0	6.0	6.0	6.0
F_1 Males: (Postweaning)	No. Evaluated Postweaning Per Litter	24	23	21	22
	No. Died or Sacrificed Moribund	0	0	0	0
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Body Weight	-	-	-	-
	Sensory Function	-	-	-	-
	Emotional test and Spontaneous Motility	-	-	-	-
	Conditioned Avoidance Response	-	-	-	-
	Genital Development	-	-	-	-
	No. of Males that Cohabitated	24	23	21	22
	No. of Males that Mated (%)	23 (95.8)	22 (95.7)	20 (95.2)	22 (100)
	No. of Fertile Males (%)	21 (91.3)	21 (95.5)	20 (100)	21 (95.5)
F_1 Females: (Postweaning)	No. Evaluated Postweaning	24	23	21	22
	No. Died or Sacrificed Moribund	0	0	0	0
	Clinical Observations	-	-	-	-

- No noteworthy findings.
Dunnett's Test or Welch t-Test (Bonferroni adjustment): * - P<0.05 ** - p<0.01

Daily Dose (mg/kg)		0 (Control)	0.1	0.3	1.0
F_1 Females: (Postweaning)	Necropsy Observations	-	-	-	-
	Body Weight (g)				
	4W after birth	93	94	96	95
	6W after birth	177	177	181	186*
	8W after birth	233	231	234	241
	10W after birth	268	270	269	277
	Gestation Body Weight	-	-	-	-
	Sensory Function	-	-	-	-
	Emotional test and Spontaneous Motility	-	-	-	-
	Conditioned Avoidance Response	-	-	-	-
	Genital Development	-	-	-	-
	No. of Females that Cohabitated	24	23	21	22
	No. of Females Sperm/Plug-Positive	23	22	20	22
	No. of Pregnant Females	21	21	20	21
	Copulation Index (%)	95.8	95.7	95.2	100
	Fertility Index (%)	91.3	95.5	100	95.5
	Mean No. Corpora Lutea	18.9	18.1	20.1	19.0
	Mean No. Implantations	17.8	17.1	16.9	17.8
	% Preimplantation Loss	5.8	5.5	15.7##	6.5
F_1 Litters:	Mean No. Live Conceptuses/Litter	16.6	16.1	15.7	16.7
	Mean No. Postimplantation loss (%)	24 (6.4)	21 (5.8)	24 (7.1)	24 (6.4)
	No. Early death (%)	24 (6.4)	20 (5.6)	24 (7.1)	24 (6.4)
	No. Late death (%)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
	Fetal Body Weight (g): Male	3.74	3.85	3.92	3.86
	Female	3.53	3.64	3.66	3.67
	Fetal Sex Ratio (% Males)	51.3	51.2	44.6	48.3
	Fetal External Anomalies (%)	2 (0.6)[a]	0 (0.0)	0 (0.0)	1 (0.3)[b]

- No noteworthy findings.
Dunnett's Test or Welch t-Test (Bonferroni adjustment): * - P<0.05 Chi Square Test: ## - p<0.01
a - One with omphalocele and one with multiple malformations (general edema, hypoplasia of genital tubecle and adactyly).
b - Omphalocele.

2.6.7.15B Reproductive and Developmental Toxicity – Effects on Pre-and Postnatal Development, Including Maternal Function

Report Title: Study for Effects of YM087 on Prenatal and Postnatal Development in Rats by Intravenous Injection. Including Maternal Function

Test Article: Conivaptan hydrochloride

Design similar to ICH 4.1.2: Yes
Species/Strain: SD (IGS) Rats
Initial Age: 12 Weeks at the Start of Mating
Date of First Dose:07 Mar 2000
Special Features: None
No Observed Adverse Effect Level:
F_0 Females: 0.5 mg/kg
F_1: 1.25 mg/kg
F_2: 1.25 mg/kg

Duration of Dosing: GD7-LD20
Day of Mating: Day 0
Method of Administration: Intravenous, bolus at 10 mL/kg
Vehicle/Formulation: Vehicle: [redacted]% propylene glycol, [redacted]% ethanol, and lactic acid sufficient to adjust pH to 3.3 ± 0.2. Diluent: 5% dextrose solution
Litters Culled/Not Culled: Not culled

Study No. R087-TX-091
GLP Compliance: Yes

Daily Dose (mg/kg)			0 (Control)	0.5	1.25	2.5
F_0 Females:	Toxicokinetics: C_{max} (ng/mL)	GD7	NA	156	459	933
		LD20	NA	131	372	693
	AUC_{0-24} (ng-hr/mL):	GD7	NA	317	1810	3803
		LD20	NA	203	541	1582
	No. Pregnant		25	25	23	24
	No. Died or Sacrificed Moribund		0	0	0	0
	No. Aborted or with Total Res. of Litters		0	0	0	0
	Clinical Observations		-	-	-	-
	Necropsy Observations		-	-	-	-
	Gestation Body Weight (g):	GD20	392.5	397.8	390.0	384.3
	Gestation Body Weight Gain (g):	GD0 - 20	135.4	141.5	133.5	127.8
	Lactation Body Weight (g):	LD21	337.6	345.5	342.7	335.5
	Lactation Body Weight Gain (g):	LD1 - 21	42.0	46.1	45.3	47.9
	Gestation Food Consumption (g/day):	GD0-7	22.0	22.3	22.3	21.6
		GD7-10	22.1	21.9	19.6**	18.0**
		GD18-20	23.4	24.3	22.2	21.1*
		GD0-20	22.6	23.1	22.1	21.4*

- No noteworthy findings. NA = Not applicable. GD = Gestation day. LD = Lactation day.
Dunnett's Test: * - P<0.05 ** - p<0.01

Daily Dose (mg/kg)			0 (Control)	0.5	1.25	2.5
F_0 Females:	Lactation Food Consumption (g/day):	LD4 - 7	45.9	45.4	46.0	43.2
		LD7 - 10	58.1	55.9	54.5	51.1**
		LD10 - 14	64.5	67.4	64.5	59.6*
		LD18 - 21	83.0	75.4*	79.9	74.8*
		LD1 - L21	60.8	59.3	59.3	56.2
	Mean Duration of Gestation (days)		22.6	22.6	22.8	22.8
	Abnormal Parturition		-	-	-	-
F_1 Litters: (Preweaning)	No. Litter Evaluated		25	25	23	24
	Mean No. of Implantations		16.2	16.2	15.6	16.3
	Mean No. Pups/Litter		15.4	15.5	14.8[c]	15.5
	% Delivery Index (Mean value per litter)[b]		95.0	93.0	93.8[c]	94.9
	Mean No. Liveborn Pups/Litter		15.4	15.0	14.5[c]	15.4
	Mean No. Stillborn Pups/Litter		0.0	0.3	0.2[a]	0.1
	No. of Litters with Stillborn Pups		1	4	3	1
	% Viability Index (Totaled value per group)[d]		99.0	95.7[+]	96.9[c]	94.1[++]
	% Weaning Index (Totaled value per group)[e]		99.5	98.3	99.4	95.4[++]
	No. of Total Litter Losses		0	0	0	0
	Mean Body Weight (g):	LD1	6.3	6.3	6.3[a]	6.1
		LD4	8.7	8.6	8.5	8.0**
		LD7	12.2	12.2	12.1	10.9**
		LD14	22.9	23.7	22.9	20.1**
		LD21	35.7	36.8	35.5	32.1*
	Pups Sex Ratio (% males):	LD1	43.8	51.0	53.3[a]	49.0
	Pups Clinical Observations		-	-	-	-

- No noteworthy findings. LD = Lactation day.
Dunnett's Test: * - P<0.05 ** - p<0.01 Kruskal-Wallis Test and Dunn's Test: + - P<0.05 ++ - p<0.01
a - Excludes values for one litter; four additional pups were delivered on day 2 of lactation.
b - (Number of live pups/number of implantation sites) x 100.
c - Excludes values for one litter; the number of pups exceeds the number of implantation sites.
d - (Number of live pups on LD4/number of live pups on LD1) x 100.
e - (Number of live pups on LD21/ number of live pups on LD4) x 100.

(Continued)

2.6.7.15B Reproductive and Developmental Toxicity **Study No. R087-TX-091 (Continued)**

Daily Dose (mg/kg)			0 (Control)	0.5	1.25	2.5
F1 Litters:	No. Litter Evaluated		25	25	23	24
	Pups Necropsy Observations (scheduled)		-	-	-	-
	No Milk in Stomach (unscheduled) [a]		0/(1+2)	2/(5+7)	3/(4+5)	9/(1+23)
	Reflex and Physical Development					
	Surface Righting [b] (%):	LD6	74.0	73.3	71.5	56.4**
		LD11	100.0	99.5	100.0	96.3**
		LD13	100.0	100.0	100.0	100.0
	Pinna Unfolding [b]		-	-	-	-
	Hair Growth [b]		-	-	-	-
	Incisor Eruption [b]		-	-	-	-
	Inclined Plane [b] (%):	LD10	81.5	80.5	74.6	65.8*
		LD15	100.0	100.0	100.0	100.0
	Eye Opening [b]		-	-	-	-
	Acoustic Startle [b] (%):	LD14	98.3	87.8*	92.3	79.4**
		LD17	100.0	100.0	100.0	97.6*
		LD20	100.0	100.0	100.0	100.0
	Air Righting [b] (%):	LD17	67.3	59.8	59.6	47.1**
		LD21	99.0	96.3	96.7	94.1
	Pupil Constriction [b]		-	-	-	-

- No noteworthy findings. LD = Lactation day.
Kruskal-Wallis Test and Dunn's Test: * - P<0.05 ** - p<0.01
a - Number of pups affected / (number of stillborns + number of pups found dead)
b - Mean % of pups meeting the criterion for the developmental landmark tested on each day postpartum.

Daily Dose (mg/kg)			0 (Control)	0.5	1.25	2.5
F1 Males: (Postweaning)	No. Evaluated Postweaning Per Litter		25	25	23	24
	No. Died or Sacrificed Moribund (or Missing)		1 [a]	1 [b]	0	1 [c]
	Clinical Observations		-	-	-	-
	Necropsy Observations		-	-	-	-
	Mean Body Weight (g):	PD1	42.0	42.5	41.0	38.0*
		PD15	143.2	135.9	139.3	130.1**
		PD36	339.0	323.0	333.5	313.6**
		PD43	387.2	372.4	384.0	364.0
		Precohabitation (100 - 104 days of age)	559.1	549.6	555.7	535.4
		Termination (160 - 164 days of age)	666.4	656.0	673.6	644.8
	Preputial Separation (Mean days postpartum)		45.8	46.4	45.3	47.3* [d]
	Motor Activity		-	-	-	-
	Functional Observation Battery		-	-	-	-
	Learning and Memory		-	-	-	-
	No. of Males that Cohabitated		25	24 [e]	23	23 [e]
	Mean No. Days Prior to Mating		4.7	3.5	3.0	3.9
	No. of Males that Mated (%)		21 (84.0)	23 (95.8)	23 (100.0)	20 (87.0)
	No. of Fertile Males (%)		20 (95.2)	19 (82.6)	18 (78.3)	18 (90.0)

- No noteworthy findings. PD = Postweaning day.
Dunnett's Test: * - P<0.05 ** - p<0.01 Chi-Square Test: * - P<0.05 ** - p<0.01
a - One animal was found dead on PD119.
b - One animal was missing on PD1.
c - One animal had an accidental death on PD8 (caught in feeder when cage was closed).
d - With preputial separation co-varied with day 43 body weights, the analyses were not significant.
e - Excludes values for rats that were not assigned to cohabitation because there were no available female rats.

2.6.7.15B Reproductive and Developmental Toxicity Study No. R087-TX-091 (Continued)

Daily Dose (mg/kg)		0 (Control)	0.5	1.25	2.5
F_1 Females: (Postweaning)	No. Evaluated Postweaning	25	24 [a]	23	24
	No. Died or Sacrificed Moribund	0	0	0	1 [b]
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Mean Body Weight (g): PD1	40.1	40.4	40.1	36.2*
	PD15	124.8	124.2	125.0	114.9**
	PD36	227.5	220.4	226.3	208.9**
	PD57	279.6	273.2	283.3	256.2**
	PD78	311.0	304.0	319.6	289.8*
	Precohabitation (100 - 104 days of age)	321.2	311.0	324.8	297.5
	Gestation Body Weight Change (g): GD0-21	+169.0	+158.4	+175.6	+168.4
	Vaginal Patency (Mean days postpartum)	32.6	32.5	33.0	33.6 [††] [c]

- No noteworthy findings. PD = Postweaning day. GD = Gestation day.
Dunnett's Test: * - P<0.05 ** - p<0.01 Chi-Square Test: [†] - P<0.05 [††] - p<0.01
a - Exclude values for one animal that was missing on PD1.
b - One animal had an accidental death on PD8 (caught in feeder when cage was closed).
c - With vagina patent co-varied with day 36 body weights, the analyses were not significant.

Daily Dose (mg/kg)		0 (Control)	0.5	1.25	2.5
F_1 Females:	No. Evaluated Postweaning	25	25 [a]	23	24 [b]
	Motor Activity	-	-	-	-
	Functional Observation Battery	-	-	-	-
	Learning and Memory	-	-	-	-
	No. of Females that Cohabitated	25	24	23	23
	Mean No. Days Prior to Mating	5.6	3.7	3.0	4.6
	No. of Females Sperm/Plug-Positive	22	24	23	21
	No. of Pregnant Females	21	20	18	19
	Copulation Index (%)	88.0	100.0	100.0	91.3
	Fertility Index (%)	95.4	83.3	78.3	90.5
	No. of Females Pregnant and Caesarean-Sectioned on Days 21 of Gestation	21	20	17 [c]	19
	No. of Litters with Total Resorption	0	1	0	0
	Mean No. Corpora Lutea	19.3	17.4	19.4	17.3
	Mean No. Implantations	15.5	14.0	16.6	15.0
	% Preimplantation Loss (Totaled value per group)	19.8 (80/405)	19.2 (67/348)	14.3 [††] (47/329)	12.8 [††] (42/328)

- No noteworthy findings.
Chi-Square Test: [†] - P<0.05 [††] - p<0.01
a - Exclude values for one animal that was missing on PD1.
b - Exclude values for one animal that had an accidental death on PD8 (caught in feeder when cage was closed).
c - One dam was removed due to delivery on day 21 of gestation.

Daily Dose (mg/kg)		0 (Control)	0.5	1.25	2.5
F_1 Litters:	Mean No. Live Conceptuses/Litter	14.8	13.5	15.6	14.3
	No. Dead Conceptuses	0	0	0	0
	Mean No. Resorptions	0.6	0.6	0.9	0.7
	Mean No. Early Resorptions	0.6	0.6	0.9	0.7
	Mean No. Late Resorptions	0	0	0	0
	% Postimplantaion Loss (Totaled value per group)	4.0	3.9	5.7	4.9
	Fetal Body Weight (g): Male	5.32	5.50	5.41	5.41
	Female	5.11	5.17	5.12	5.11
	Fetal Sex Ratio (% Males)	46.2	52.0	48.2	47.4
	Fetal External Anomalies				
	Edema of body or neck	0/312	0/270	0/266	2/272
	Protruding tongue	0/312	0/270	0/266	1/272
	Depressed eye bulge	0/312	1/270	0/266	0/272
	Low set ears	0/312	1/270	0/266	0/272

2.6.7.17E Mechanistic Study - Reproductive and Developmental Toxicity

Report Title: Effects on Plasma Hormone Concentration in Female Rats Treated with YM087 Orally

Test Article: Conivaptan hydrochloride

Species/Strain: SD Rats
Initial Age: 10 Weeks (at the randomization)
Date of First Dose: 14 March 1995
Special Features: None

Duration of Dosing: 7 Days
Method of Administration: Gavage
Vehicle/Formulation: 0.5% Methylcellulose solution

Study No. R087-TX-018

GLP Compliance: Yes

Daily Dose (mg/kg)			Untreated (Estrus Control)	Untreated (Pseudopregnancy Control) [a]	100 [b]
F_0 Females	Total No. Evaluated		25	30	50
	No. Animals (Blood Sampling Date)		25 (Estrus) [c]	30 (Day 6 of Pseudopregnancy) [d]	20 (Day 1 of Dosing) [e] 30 (Day 7 of Dosing) [f]
	Died or Sacrificed Moribund		0	0	0
	Clinical Observations		-	-	-
	Estrous Cycle: Prolongation of Diestrus		NA	30	30 [g]
	Plasma Hormone Concentration [h]				
	Progesterone (ng/mL)	3 hr after dosing (Day 1)	9.4	NA	204.8**
		6 hr	15.4	NA	296.4**
		12hr	15.1	NA	240.0**
		24 hr	24.6	NA	111.6
		-1 hr after dosing (Day 7)	NA	76.9	45.9
		3 hr after dosing (Day 7)	NA	78.5	128.7*
		10 hr	NA	79.2	188.6**
		12 hr	NA	66.8	236.6*
		15 hr	NA	75.8	225.2

- No Noteworthy Findings. NA = Not applicable.
Student's t- Test or Welch's Test: * - P<0.05 ** - P<0.01

a - Pseudopregnancy was induced by physical stimulation of the cervix using a glass rod in the evening of the day on which proestrus was indicated. The next day was regarded as day 0 of pseudopregnancy.
b - Conivaptan hydrochloride were administered once a day at 9:00 for 7days starting on the day on which estrus was indicated.
c - Blood samples were collected from 5 animals each at 9:00, 12:00, 15:00 and 21:00 on the day of estrus, and at 9:00 on the day of metestrus.
d - Blood samples were collected from 5 animals each at 6:00, 8:00, 12:00, 19:00, 21:00 and 24:00 on day 6 of pseudopregnancy.
e - Blood samples were collected from 5 animals each on day 1 of dosing at 12:00 (3 hours after dosing), 15:00 (6 hours after dosing) and 21:00 (12 hours after dosing), and at 9:00 (24 hours after dosing) on the following morning.
f - Blood samples were collected from 5 animals each on day 7 of dosing at 6:00 (before dosing), 8:00 (before dosing), 12:00 (3 hours after dosing), 19:00 (10 hours after dosing), 21:00 (12 hours after dosing) and 24:00 (15 hours after dosing).
g - All animals dosed for 7 days showed prolonged diestrus.
h - The plasma concentrations were determined by radioimmunoassay.

Daily Dose (mg/kg)			Untreated (Estrus Control)	Untreated (Pseudopregnancy Control) [a)]	100 [b)]
F_0 Females	Total No. Animals		25	30	50
	AVP (pg/mL)	3 hr after dosing (Day 1)	0.93	NA	70.80**
		6 hr	0.91	NA	70.94**
		12hr	0.74	NA	36.49**
		24 hr	0.55	NA	15.29
		-1 hr after dosing (Day 7)	NA	0.44	1.71
		3 hr after dosing (Day 7)	NA	0.73	7.01*
		10 hr	NA	0.69	8.38**
		12 hr	NA	0.44	10.07
		15 hr	NA	0.62	14.00*

- No noteworthy findings. NA = Not applicable.
Student's t- Test or Welch's Test: * - P<0.05 ** - P<0.01

2.6.7.17F Mechanistic Study - Reproductive and Developmental Toxicity

Report Title: Effect of YM087 on Plasma Progesterone Concentration in Female Rats by Single Oral Administration - Additional Study on Low Dose-

Test Article: Conivaptan hydrochloride

Species/Strain: SD Rats
Initial Age: 15 Weeks (at randomization)
Date of First Dose: 14 Apr 1997
Special Features: None

Duration of Dosing: 1 day
Method of Administration: Gavage
Vehicle/Formulation: 0.5% Methylcellulose solution

Study No. R087-TX-044

GLP Compliance: Yes

Daily Dose (mg/kg) [a]		0 (Control)	3	10
F_0 Females	Total No. Evaluated	25 [b]	20 [c]	20 [c]
	Died or Sacrificed Moribund	0	0	0
	Clinical Observations	-	-	-
	Plasma Hormone Concentration [d]			
	Progesterone (ng/mL)			
	0 hr (before dosing)	22.0	NA	NA
	3 hr after dosing	13.9	58.2	170**
	6 hr after dosing	23.9	44.5	137*
	12 hr after dosing	26.2	30.8	157*
	24 hr after dosing	21.2	19.9	14.3

- No noteworthy findings. NA = Not applicable.
Dunnett's Test or Dunnett's Type-Rank-Sum Test: * - P<0.05 ** - P<0.01
a - Conivaptan hydrochloride were administered once at 9:00 on the day on which estrus was indicated.
b - Blood samples were collected from 5 animals each at 0 hours (before dosing), 3 hours, 6 hours, 12 hours and 24 hours after dosing.
c - Blood samples were collected from 5 animals each at 3 hours, 6 hours, 12 hours and 24 hours after dosing.
d - The plasma concentrations were determined by radioimmunoassay (Study No. R087-TX-078).

2.6.7.17G Mechanistic Study - Reproductive and Developmental Toxicity

Report Title: Effect on Plasma Progesterone Concentration in Female Rats Treated with YM087 Orally

Test Article: Conivaptan hydrochloride

Species/Strain: SD Rats
Initial Age: 17-18 Weeks
Date of First Dose: 18 Mar 1996
Special Features: None

Duration of Dosing: 1 Day
Method of Administration: Gavage
Vehicle/Formulation: 0.5% Methylcellulose solution

Study No. R087-TX-019

GLP Compliance: No

Daily Dose (mg/kg) [a]		0 (Control)	100
F_0 Females	Total No. Evaluated	20 [b]	15 [c]
	Plasma Hormone Concentration [d]		
	Progesterone (ng/mL)		
	0 hr (before dosing)	11.7	NA
	3 hr after dosing	12.1	291.5**
	6 hr after dosing	19.4	346.0**
	12 hr after dosing	17.1	285.7**
	Corticosterone (ng/mL)		
	0 hr (before dosing)	644	NA
	3 hr after dosing	713	912
	6 hr after dosing	943	991
	12 hr after dosing	758	921
	ACTH (pg/mL)		
	0 hr (before dosing)	186	NA
	3 hr after dosing	305	863**
	6 hr after dosing	255	508
	12 hr after dosing	157	175

NA = Not applicable.
Student's t-Test or Welch's Test: ** - P<0.01
a - Conivaptan hydrochloride were administered once at 9:00 on the day on which estrus was indicated.
b - Blood samples were collected from 5 animals each at 9:00, 12:00, 15:00, and 21:00 on the dosing day.
c - Blood samples were collected from 5 animals each at 12:00, 15:00, and 21:00 on the dosing day.
d - The plasma concentrations were determined by radioimmunoassay.

Daily Dose (mg/kg) [a]		0 (Control-OVX)	0 (Control-ADX)	100 (OVX)	100 (ADX)	100 (OVX+ADX)
F_0 Females	Total No. Evaluated	4 [b]	5 [b]	5 [b]	5 [b]	5 [b]
	Plasma Hormone Concentration [c]					
	Progesterone (ng/mL)	10.0	3.3	89.6**	5.2	0.7

Student's t-Test or Welch's Test: ** - P<0.01
a - Animals were ovariectomized (OVX) and/or adrenoectmized (ADX) with either between 8:00 and 9:00 a.m. on the day of estrus. Conivaptan hydrochloride was administered once at 10 to 60 min after the ovariectomy and/or adrenoectomy.
b - Blood samples were collected from 5 animals at 6 hours after dosing but 1 sample in Control-OVX group was lost because of the damage of the sample bottle.
c - The plasma concentrations were determined by radioimmunoassay.

2.6.7.17II Mechanistic Study - Reproductive and Developmental Toxicity | **Report Title:** In Vitro Effect of YM087 on Rat Adrenocortical Cells in Primary Culture | **Test Article:** Conivaptan hydrochloride

Primary Culture System: Female SD Rats, Adrenal Cortex
Initial Age: 11 Weeks (at the extirpation of adrenal glands)
Conditioned Medium: DMEM/F12 containing 15% Horse Serum and 2.5% Fetal Bovine Serum
Date of Exposure: 26 Jun 2002
Vehicle: DMSO-DMEM/F12 (Conivaptan hydrochloride), and sterilized water-DMEM/F12 (ACTH and AVP)
Special Features: None

Study No. R087-TX-102
GLP Compliance: No

Group[a]	Control	Conivaptan hydrochloride	AVP
Concentrations[b]: Conivaptan hydrochloride (μg/mL)	0	4.5	0
AVP (pg/mL)	0	0	100
Hormone Concentrations[c]			
Progesterone (ng/mL):			
0.5 hr after exposure	0.62	0.53	0.53
1 hr after exposure	1.06	0.80	1.19
3 hr after exposure	2.38	2.22	2.08
6 hr after exposure	4.27	6.53	4.14
12 hr after exposure	4.85	17.00	4.49
24 hr after exposure	6.23	35.32	6.24
Corticosterone[c,d] (ng/mL):			
0.5 hr after exposure	0.0	0.0	0.0
1 hr after exposure	0.0	0.0	0.0
3 hr after exposure	0.0	0.0	0.0
6 hr after exposure	14.4	4.7	13.7
12 hr after exposure	18.5	0.0	8.6
24 hr after exposure	41.6	2.7	42.8

ACTH: Adrenocorticotropic Hormone. AVP: Arginine-Vasopressin
a - The final concentration of DMSO in each culture well was 0.5 %.
b - Final concentrations in each culture well
c - The concentrations were determined by radioimmunoassay (Study No. R087-TX-107).
d - Values less than the limit of quantification [redacted] were regarded as zero in calculation of mean.

Group[a]	Control (ACTH)	Conivaptan hydrochloride			AVP
Concentrations[b]: Conivaptan hydrochloride (μg/mL)	0	0.15	1.5	4.5	0
ACTH (pg/mL)	1000	1000	1000	1000	1000
AVP (pg/mL)	0	0	0	0	100
Hormone Concentrations[c]					
Progesterone (ng/mL):					
0.5 hr after exposure	12.82	19.01	13.71	10.39	16.91
1 hr after exposure	29.27	37.93	40.12	38.95	32.41
3 hr after exposure	74.62	83.36	113.71	101.35	78.48
6 hr after exposure	43.24	125.90	125.11	118.11	63.34
12 hr after exposure	39.63	91.90	153.51	159.73	43.26
24 hr after exposure	10.21	53.29	77.98	69.26	11.59
Corticosterone[c,d] (ng/mL):					
0.5 hr after exposure	17.3	10.8	0.0	0.0	23.1
1 hr after exposure	35.6	16.4	9.7	0.0	38.0
3 hr after exposure	112.6	47.3	26.7	20.3	133.6
6 hr after exposure	173.1	131.5	49.4	34.9	274.0
12 hr after exposure	270.5	101.2	70.0	45.5	354.1
24 hr after exposure	190.4	128.4	51.2	27.5	210.6

ACTH: Adrenocoriticotoropic Hormone. AVP: Arginine-Vasopressin
a - The final concentration of DMSO in each culture well was 0.5 %.
b - Final concentrations in each culture well.
c - The concentrations were determined by radioimmunoassay.
d - Values less than the limit of quantification [redacted] were regarded as zero in calculation of mean.

2.6.7.17I Mechanistic Study- Reproductive and Developmental Toxicity

Report Title: Oral (Gavage) Dosage-Range and Comparative Sensitivity Study of YM087 in Brattleboro (*di/di*) and Long-Evans Female Rats

Test Article: Conivaptan hydrochloride

Species/Strain: Brattleboro Rats and Long-Evans Rats
Initial Age: 12 Weeks
Date of First Dose: 5 Jul 2000
Special Features: None
Duration of Dosing: F: Day 1 through 15 and 44 through 58
Method of Administration: Gavage
Vehicle/Formulation: 0.5% Methylcellulose solution
Study No. R087-TX-083
GLP Compliance: Yes
No Observed Adverse Effect Level: F_0 Females: <10 mg/kg

Daily Dose (mg/kg)		Brattleboro Rats 0 (Control)	10	30	100	Long-Evans Rats 0 (Control)	10	30	100
Females:	Toxicokinetics[a]: Day 1								
	Cmax (ng/mL)	NA	NA	2508	6050	NA	NA	2368	3982
	AUC_{0-24} (ng·hr/mL)	NA	NA	20489	63459	NA	NA	23279	62088
	Mean Plasma Progesterone Concentration[#] (ng/mL)								
	Predosage	5.428	NA	5.144	4.056	5.882	NA	6.386	5.714
	3 hr postdosage	7.100	NA	12.634	15.318	6.784	NA	62.804**	87.106**
	6 hr postdosage	10.534	NA	37.522*	43.066*	14.336	NA	54.704**	199.276**
	9 hr postdosage	13.282	NA	13.450	41.504*	6.254	NA	29.176**	106.750**
	12 hr postdosage	5.216	NA	19.628**	32.218**	6.232	NA	47.058**	72.650**
	24 hr postdosage	6.562	NA	11.552	8.410	11.712	NA	16.360	23.968
	No. Evaluated	10	10	10	10	10	10	10	10
	No. Died or Sacrificed Moribund	0	1[b]	0	1[c]	0	1[d]	0	2[e]

NA = Not applicable.
Dunnett's Test: * - p<0.05 ** - p<0.01

a - From Study No. R087-TX-084 (Determination of Plasma YM087 and Progesterone Levels in Brattleboro (*di/di*) and Long-Evans Female Rats Given a Single Oral (Gavage) Dosage of YM087)
b - One animal was found dead on day 58; the cause of death could not be determined, but is not considered related to the test article.
c - One animal was moribund sacrificed on day 3. This rat had repetitive chewing, ataxia, hypersensitivity, coldness to touch, decreased motor activity, dehydration and hunched posture. Water consumption was severely reduced.
d - One animal was found dead on day 58. This rat was injured on day 57 (the rat fell to the floor).
e - One animal had an accidental death during predose blood collection on day 58. Another animal was moribund sacrificed on day 6. This rat had ataxia, chromorhinorrhea, chromodacryorrhea, a red substance on the fore and hindpaws, and urine-stained abdominal fur, decreased motor activity, coldness to touch, hunched posture and dehydration. Water consumption was severely reduced.

Daily Dose (mg/kg)		Brattleboro Rats 0 (Control)	10	30	100	Long-Evans Rats 0 (Control)	10	30	100
Females:	Body Weights (g):								
	Day 1	194.4	194.7	194.4	195.6	234.6	231.8	230.0	231.1
	Day 16	208.9	210.9	220.5	220.2	249.7	242.1	241.5	248.8
	Day 44	221.9	222.6	230.5	230.4	267.1	257.4	256.1	267.0
	Day 58	233.0	236.1	251.6*	259.3**	270.8	263.6	261.7	272.2
	Food Consumption (g/day):								
	Day 1-5	14.4	13.3	14.1	14.3	16.3	13.7**	11.0**	10.6**
	Day 8-12	13.9	13.6	14.7	14.3	16.0	16.6	17.0	18.2**
	Day 12-15	15.9	14.6	16.8	17.3	19.1	14.9**	16.6	17.7
	Day 44-51	15.4	14.5	15.1	15.5	16.8	13.4[##]	13.2[#]	12.4[##]
	Day 51-58	15.3	15.5	16.0	16.1	16.4	17.0	16.7	18.5**
	Water Consumption (g/day):								
	Day 1-5	188.2	232.4**	237.3**	221.8**	23.0	115.2[##]	144.4[##]	166.9[##]
	Day 5-8	192.3	195.8	187.4	172.4	21.1	114.8**	171.0**	211.0**
	Day 8-12	202.0	184.9	174.8	158.6**	25.9	90.3**	151.3**	185.5**
	Day 12-16	204.4	181.0	158.1**	141.6**	20.4	98.2**	127.4**	147.3**
	Day 16-22	214.7	179.9**	170.7**	173.4**	22.2	20.6	25.8	24.6
	Day 22-29	229.0	234.9	239.0	241.5	23.3	21.2	23.5	25.2
	Day 44-47	237.9	263.8**	266.2**	268.9**	22.1	117.2**	169.4**	207.4**
	Day 47-51	243.9	230.4	231.2	218.6	22.9	108.0**	154.1**	205.2**
	Day 51-55	241.6	200.4**	195.0**	176.6**	22.6	113.6**	157.5**	182.2**
	Day 55-58	240.0	192.9**	179.3**	167.4**	20.4	105.2**	137.1**	164.7**

Dunnett's Test: * - p<0.05 ** - p<0.01
Satterthwaite Analysis for Populations with Independent Standard Deviations with Bonferroni Adjustment: [#] - p<0.05 [##] - p<0.01

(Continued)

2.6.7.17I Mechanistic Study **Study No. R087-TX-083 (Continued)**

Daily Dose (mg/kg)			Brattleboro Rats 0 (Control)	10	30	100	Long-Evans Rats 0 (Control)	10	30	100
Females:	Water Consumption/Urine Volume/Urine Osmolality:									
	Predosage	Water Consumption (mL)	183.1	197.6	178.9	192.4	25.7	25.7	23.3	23.5
		Urine Volume (mL)	155.4	174.9	155.7	175.2	8.5	6.9	6.4	8.0
		Urine Osmolality (mOsmol/kg)	136.3	127.1	128.8	123.3	1879.5	2117.7	2003.0	1795.0
	Days 1-2	Water Consumption (mL)	187.4	270.0$^{\ddagger\#}$	272.1$^{\#\#}$	233.9	23.4	121.9**	152.0**	165.6**
		Urine Volume (mL)	159.2	246.9$^{\ddagger\#}$	249.9$^{\#\#}$	219.9	9.5	99.3**	122.0**	147.7**
		Urine Osmolality (mOsmol/kg)	133.9	86.4$^{\#\#}$	79.8$^{\ddagger\#}$	95.1$^{\#}$	2339.2	194.9**	137.3**	112.6**
	Days 7-8	Water Consumption (mL)	206.7	214.0	188.7	175.3*	23.3	121.0**	186.1**	227.4**
		Urine Volume (mL)	184.5	189.4	164.4	150.3*	11.7	99.1**	149.3**	194.1**
		Urine Osmolality (mOsmol/kg)	127.7	127.8	144.1*	153.3**	1768.3	215.2**	142.5**	122.6**
	Days 14-15	Water Consumption (mL)	183.0	175.8	153.1	138.1	21.8	96.4$^{\#\#}$	118.4$^{\#\#}$	147.4$^{\#\#}$
		Urine Volume (mL)	172.1	149.9	128.0**	110.6**	9.0	81.8$^{\#\#}$	94.9‡‡	126.6$^{\#\#}$
		Urine Osmolality (mOsmol/kg)	128.1	148.9	178.9**	198.6**	1935.4	334.0**	220.4**	204.3**
	Days 44-45	Water Consumption (mL)	192.1	258.0	274.2$^{\#}$	284.0$^{\#}$	18.7	137.3**	175.1**	199.1**
		Urine Volume (mL)	168.0	250.1‡	252.9$^{\#\#}$	265.7$^{\#\#}$	5.1	107.5**	153.1**	183.0**
		Urine Osmolality (mOsmol/kg)	142.2	85.9**	79.9**	82.8**	1951.8	183.7**	125.5**	110.7**
	Days 50-51	Water Consumption (mL)	244.6	222.3	216.5	206.6	22.0	115.8**	152.8**	221.6**
		Urine Volume (mL)	206.4	195.4	181.7	171.1	5.5	85.3**	126.6**	196.9**
		Urine Osmolality (mOsmol/kg)	117.5	127.4	136.8	138.8	1937.5	241.6**	184.7**	133.8**
	Days 57-58	Water Consumption (mL)	227.3	178.2**	178.3**	161.6**	19.4	104.4**	129.3**	160.8**
		Urine Volume (mL)	196.6	158.3**	147.8**	145.8**	5.2	79.3**	109.1**	144.0**
		Urine Osmolality (mOsmol/kg)	120.1	152.2**	158.7**	184.1**	1902.0	270.8	206.5	188.7

Dunnett's Test: * - p<0.05 ** - p<0.01
Satterthwaite Analysis for Populations with Independent Standard Deviations with Bonferroni Adjustment: ‡ - p<0.05 $^{\#\#}$ - p<0.01

Daily Dose (mg/kg)		Brattleboro Rats 0 (Control)	10	30	100	Long-Evans Rats 0 (Control)	10	30	100
Females:	Predosage Estrous Stages:								
	Estrous Stages/14 days	2.6	2.8	2.8	2.8	3.2	3.3	3.2	3.5
	Rats with 6 or More Consecutive Days of Diestrus	1	0	0	0	0	0	0	0
	Rats with 6 or More Consecutive Days of Estrus	0	0	0	0	0	0	0	0
	First Dosage Estrous Stages[a]:								
	Estrous Stages/14 days	2.6	2.6	2.7	1.7*	3.9	3.7	2.5**	2.1**
	Rats with 6 or More Consecutive Days of Diestrus	1	1	4	4	0	1	4	2
	Rats with 6 or More Consecutive Days of Estrus	1	0	0	0	0	0	0	0
	Recovery Estrous Stages:								
	Estrous Stages/29 days	5.4	5.7	6.1	5.9	6.5	6.6	6.9	6.6
	Rats with 6 or More Consecutive Days of Diestrus	2	3	0	1	1	1	0	1
	Rats with 6 or More Consecutive Days of Estrus	0	1	0	0	0	0	0	0
	Second Dosage Estrous Stages[a]:								
	Estrous Stages/14 days	3.3	2.6	1.9**	0.9**	3.7	2.8	1.9**	2.0**
	Rats with 6 or More Consecutive Days of Diestrus	0	3	2	8**	0	1	3	4
	Rats with 6 or More Consecutive Days of Estrus	0	0	0	0	1	0	0	0

Dunnett's Test: * - p<0.05 ** - p<0.01
a - The first dosage period occurred on days 1-15 of study and the second dosage period occurred on days 44-58 of study.

2.6.7.17J Mechanistic Study - Reproductive and Developmental Toxicity

Report Title: Variation of Plasma Progesterone Concentration in Female Rats Treated with YM087 from 2 Weeks Prior to Cohabitation through Day 7 of Gestation

Test Article: Conivaptan hydrochloride

Species/Strain: SD Rats
Initial Age: 13-14 Weeks
Date of First Dose: 25 Nov 1998
Special Features: None
Vehicle/Formulation: 0.5% Methylcellulose solution

Duration of Dosing: F: 14 days prior to cohabitation through GD7
Day of Mating: Day 0
Day of C-Section: GD7 or 8
Method of Administration: Gavage

Study No. R087-TX-079
GLP Compliance: No

Daily Dose (mg/kg)			0 (Control)	100
Females:	Mean Plasma Progesterone Concentration (ng/mL)			
	Day 1	0 hr	12.2±7.4	10.6±5.0
		3 hr	3.7±5.4	202.7±50.3**
		6 hr	22.0±10.3	413.3±67.8**
		12 hr	26.1±10.7	167.8±80.4*
		24 hr	61.7±33.5	385.6±294.8
	Day 7	3 hr	NA	157.0±64.2**
		6 hr	NA	452.0±53.7**
		12 hr	NA	148.2±68.0*
		24 hr	NA	170.4±139.7
	Day 14	3 hr	NA	143.7±141.7
		6 hr	NA	293.3±252.7
		12 hr	NA	77.9±57.1
		24 hr	NA	232.2±141.6
	GD0	3 hr	8.0±5.6	51.3±27.4*
		6 hr	14.5±18.3	236.5±140.6*
		12 hr	10.6±7.3	132.0±98.3*
		24 hr	10.0±5.2	54.1±64.0

NA = Not applicable. GD = Gestation day.
Student's t-Test or Welch method: * - P<0.05 ** - P<0.01

Daily Dose (mg/kg)			0 (Control)	100
Females:	Mean Plasma Progesterone Concentration (ng/mL)			
	GD3	3 hr	61.6±9.7	157.3±54.6**
		6 hr	65.8±17.3	199.8±144.0*
		12 hr	74.8±9.9	88.5±47.5
		24 hr	75.8±17.7	51.1±26.7
	GD7	3 hr	85.1±13.6	216.2±41.5*
		6 hr	142.4±30.1	427.3±180.7*
		12 hr	94.4±9.5	134.9±89.9
		24 hr	142.7±27.3	63.7±49.9**
	No. Evaluated		52	72
	No. Died or Sacrificed Moribund		1[a]	1[a]
	Clinical Observations		-	-
	No. Prolonged Diestrus[b]		4/42	62/62
	Mean No. Days Prior to Mating		2.46	3.87
	No. of Females Sperm-Positive (%)		39/42[c] (92.8)	39/42[c] (92.8)
	No. of Pregnant Females (%)		34/38[d] (89.4)	23/39[d] (58.9)
	Mean No. Corpora Lutea		17.6	17.9
	Mean No. Implantations		16.5	14.4
	Mean % Preimplantation Loss		6.3	19.2

- No noteworthy findings. GD = Gestation day.
Student's t-Test or Welch method: * - P<0.05 ** - P<0.01
a - Accidental death.
b - No. of animals with 3 or more consecutive days of diestrus / No. of evaluated.
c - No. of animals with successful copulation / No. of paired animals.
d - No. of pregnant animals / No. of animals with successful copulation.

2.6.7.17K Mechanistic Study- Reproductive and Developmental Toxicity

Report Title: Measurement of Plasma Progesterone Concentration in Females Rats Following Subcutaneous Infusion of Progesterone Using the Osmotic Pump

Test Article: Progesterone

Species/Strain: SD Rats
Initial Age: 10-11 Weeks
Date of First Dose: 26 Jul 1999
Special Features: None

Duration of Dosing: 7 Days
Method of Administration: Subcutaneous infusion
Vehicle/Formulation: Propylene glycol

Study No. R087-TX-080

GLP Compliance: No

Daily Dose (µg/hr)		0 (Control)	30	100	300	600
Females:	No. Evaluated	5	5	5	5	5
	No. Prolonged Diestrus	0	0	3	5	5
	Mean Plasma Progesterone Concentration (ng/mL)					
	24 hr after the start of administration	32.7	54.3	86.0	148.9	93.7
	48 hr after the start of administration	44.0	70.0	107.1	195.3	260.9

2.6.7.17L Mechanistic Study- Reproductive and Developmental Toxicity

Report Title: Measurement of Plasma Progesterone Concentration in Female Rats Following Single Subcutaneous Administration of Progesterone

Test Article: Progesterone

Species/Strain: SD Rats
Initial Age: 10 Weeks
Date of First Dose: 07 Feb 2000
Special Features: None

Duration of Dosing: 1 Day
Method of Administration: Subcutaneous
Vehicle/Formulation: Sesame oil

Study No. R087-TX-081

GLP Compliance: No

Daily Dose (mg/kg)		0 (Control)	3	10	30	60
Females:	No. Evaluated	10	10	10	10	10
	Mean Plasma Progesterone Concentration (ng/mL)					
	1 hr after administration	18.7	73.4	229.8	572.9	1467.0
	3 hr after administration	17.8	62.3	149.4	456.8	794.8
	6 hr after administration	41.2	84.7	171.6	510.3	731.3
	12 hr after administration	27.0	36.9	65.0	217.7	342.6
	24 hr after administration	60.9	58.0	57.3	217.9	230.8

2.3.7.17M Mechanistic Study - Reproductive and Developmental Toxicity

Report Title: Study of Fertility and Preimplantation Embryonic Development in Female Rats Treated with Progesterone

Test Article: Progesterone

Design similar to ICH 4.1.1: Yes
Species/Strain: SD Rats
Initial Age: 10 Weeks
Date of First Dose: 21 Mar 2000
Special Features: None
No Observed Adverse Effect Level:
F_0 Females: <10 mg/kg
F_1 Litters: 30 mg/kg

Duration of Dosing: F: 14 days prior to cohabitation and GD0-7
Day of Mating: Day 0
Day of C-Section: GD13
Method of Administration: Subcutaneous
Vehicle/Formulation: Sesame oil

Study No. R087-TX-082

GLP Compliance: Yes

Daily Dose (mg/kg)			0 (Control)	10	30
Females:	Mean Plasma Progesterone Concentration[a] (ng/mL)				
	Day 1 3 hr[b]		10.68	87.38	161.32
	GD0 3 hr[b]		5.30	31.66	116.87
	No. Evaluated		20	20	20
	No. Died or Sacrificed Moribund		0	0	0
	Clinical Observations		-	-	-
	Necropsy Observations		-	-	-
	Premating Body Weight (g):	Day 1	251.5	249.0	249.3
		Day 4	254.2	259.7	265.3**
		Day 7	259.8	269.2*	279.7**
		Day 14	272.5	295.2**	308.4**
	Gestation Body Weight (g):	GD0	279.1	299.3**	313.3**
		GD6	309.7	323.2*	334.1**
		GD13	340.3	356.5*	368.6**
	Premating Food Consumption (g/day):	Day 4	18.6	19.4	20.3**
		Day 7	20.4	21.9	23.3**
		Day 11	20.7	22.8**	24.6**
		Day 14	19.8	23.0**	24.4**

- No noteworthy findings. GD = Gestation day.
Dunnett's Test: * - P<0.05 ** - p<0.01
a - From Study No. R087-TX-103 (Measurement of Plasma Progesterone Concentration in the Study of Fertility and Preimplantation Embryonic Development in Female Rats Treated with Progesterone).
b - Time after dosing.

Daily Dose (mg/kg)			0 (Control)	10	30
Females:	Gestation Food Consumption (g/day)		-	-	-
	No. Prolonged Diestrus		0	20	20
	Mean No. Days Prior to Mating		2.1	3.1*	4.3**
	No. of Females Sperm-Positive (%)		20 (100.0)	20 (100.0)	20 (100.0)
	No. of Pregnant Females (%)		19 (95.0)	20 (100.0)	19 (95.0)
	No. Aborted or with Total Resorption of Litter		0	0	0
	Mean No. Corpora Lutea		17.7	18.4	18.9
	Mean No. Implantations		15.3	16.2	16.5
	% Preimplantation Loss		13.69	11.72	13.06
	Mean No. Live Conceptuses		14.1	14.7	14.5
	No. of Postimplantation Loss:	Total (%)	22 (7.59)	31 (9.57)	37 (11.82)
		Early (%)	5 (1.72)	15 (4.63)[#]	11 (3.51)
		Resorb (%)	17 (5.86)	16 (4.94)	26 (8.31)
		Dead (%)	0 (0.00)	0 (0.00)	0 (0.00)

- No noteworthy findings.
Dunnett's Test: * - p<0.05 ** - p<0.01
Chi-Square Test: # - p<0.05

2.6.7.17N Mechanistic Study - Reproductive and Developmental Toxicity

Report Title: Study of Fertility and Embryonic Development in Rats: Effects of Progesterone Administration from 14 Days prior to Cohabitation through the Day before Successful Mating

Test Article: Progesterone

Species/Strain: SD Rats
Initial Age: 10-11 Weeks
Date of First Dose: 12 Mar 2002
Special Features: None
No Observed Adverse Effect Level:
F_0 Females: <30 mg/kg
F_1 Litters: <30 mg/kg

Duration of Dosing: F: 14 days prior to cohabitation through the day before successful mating
Day of Mating: Day 0
Day of C-Section: GD13
Method of Administration: Subcutaneous
Vehicle/Formulation: Sesame oil

Study No. R087-TX-100

GLP Compliance: Yes

Daily Dose (mg/kg)			0 (Control)	30	100
Females:	Mean Plasma progesterone concentration[a] (ng/mL)				
	Day 1 1 hr[b]		22.18	169.38	445.13
	3 hr[b]		16.35	218.93	621.88
	Day 14 1 hr[b]		21.56	209.41	351.62
	3 hr[b]		13.56	203.19	519.80
	No. Evaluated		20	20	20
	No. Died or Sacrificed Moribund		0	0	0
	Clinical Observations		-	-	-
	Necropsy Observations		-	-	-
	Premating Body Weight (g)	Day 4	254.6	264.9*	264.4
		Day 8	260.4	279.8**	278.0**
		Day 14	268.6	299.7**	295.4**
	Gestation Body Weight (g)		-	NA	NA
	Premating Food Consumption (g/day)	Day 3	18.6	20.4**	20.8**
		Day 7	18.7	21.2**	20.9**
		Day 13	17.7	21.9**	20.5**
	Gestation Food Consumption (g/day)		-	NA	NA

- No noteworthy findings. NA = Not applicable. GD = Gestation day.
Dunnett's Test: * - p<0.05 ** - p<0.01
a - From Study No. R087-TX-105 (Measurement of Plasma Progesterone Concentration in the Study of Fertility and Embryonic Development in Female Rats Treated with Progesterone).
b - Time after dosing.

Daily Dose (mg/kg)			0 (Control)	30	100
Females:	No. Evaluated		20[a]	20[a]	20[a]
	No. of Prolonged Diestrus		0	20	20
	Mean No. Days Prior to Mating		1.9	1.5	1.5*
	No. of Females Sperm-Positive (%)		20 (100.0)	20 (100.0)	19 (95.00)
	No. of Pregnant Females (%)		16 (80.00)	0 (0.00)[##]	0 (0.00)[##]
	No. Aborted or with Total Resorption of Litter		0	NA	NA
	Mean No. Corpora Lutea		14.3	NA	NA
	Mean No. Implantations		12.6	NA	NA
	% Preimplantation Loss		11.79	NA	NA
	Mean No. Live Conceptuses		12.2	NA	NA
	No. of Postimplantation Loss	Total (%)	7 (3.47)	NA	NA
		Early (%)	3 (1.49)	NA	NA
		Resorb (%)	4 (1.98)	NA	NA
		Dead (%)	0 (0.00)	NA	NA

NA = Not applicable.
Dunnett's Test: * - p<0.05
Fisher's Exact Test: # - p<0.05 ## - p<0.01
a - To induced mating behavior in animals treated with progesterone, 25 µg/kg of 17ß-estradiol dissolved in sesame oil was given subcutaneously once daily during cohabitation period. Control animals were treated with 17ß-estradiol in the same manner at the proestrus stage during the cohabitation period.

2.6.7.17O Mechanistic Study - Reproductive and Developmental Toxicity

Report Title: Study of Early Embryonic Development to Implantation in Female Rats: Effects of Progesterone Administration from Days 0 to 7 of Gestation

Test Article: Progesterone

Species/Strain: SD Rats
Initial Age: 12 Weeks at the start of cohabitation
Date of First Dose: 5 Mar 2002
Special Features: None
No Observed Adverse Effect Level:
F_0 Females: 30 mg/kg
F_1 Litters: <30 mg/kg

Duration of Dosing: F: GD0-7
Day of Mating: Day 0
Day of C-Section: GD13
Method of Administration: Subcutaneous
Vehicle/Formulation: Sesame oil

Study No. R087-TX-101

GLP Compliance: Yes

Daily Dose (mg/kg)			0 (Control)	30	100
Dams/Dose:	Mean Plasma Progesterone Concentration[a] (ng/mL)				
	GD0 1 hr[b]		9.11	468.91	479.81
	3 hr[b]		6.11	192.19	515.39
	GD7 1 hr[b]		49.43	301.15	452.87
	3 hr[b]		60.05	231.44	589.92
	No. Evaluated		17	20	19
	No. Died or Sacrificed Moribund		0	0	0
	Clinical Observations		-	-	-
	Necropsy Observations		-	-	-
	Gestation Body Weight (g):	GD0	269.5	266.0	266.0
		GD6	293.9	291.3	286.8
		GD7	296.4	293.0	288.0
		GD13	329.1	326.9	321.4
	Gestation Food Consumption (g/day):	GD6	22.9	23.0	20.7*
		GD7	22.7	22.6	21.1
		GD13	25.1	25.5	24.6

- No noteworthy findings. GD = Gestation day.
Dunnett's Test: * - p<0.05
a - From Study No. R087-TX-106 (Measurement of Plasma Progesterone Concentration in the Study of Preimplantation Embryonic Development in Female Rats Treated with Progesterone).
b - Time after dosing.

Daily Dose (mg/kg)			0 (Control)	30	100
	No. Aborted or with Total Resorption of Litter		0	0	0
	Mean No. Corpora Lutea		17.1	17.7	18.4
	Mean No. Implantations		15.9	15.1	15.8
	% Preimplantation Loss		7.22	14.45**	13.75**
	Mean No. Live Conceptuses		15.4	13.3	13.7
	No. of Postimplantation Loss	Total (%)	9 (3.33)	37 (12.25)**	40 (13.29)**
		Early (%)	2 (0.74)	6 (1.99)	9 (2.99)
		Resorb (%)	7 (2.59)	31 (10.26)**	29 (9.63)**
		Dead (%)	0 (0.00)	0 (0.00)	2 (0.66)

Chi-Square Test: ** - p<0.01

2.6.7.17P Mechanistic Study - Reproductive and Developmental Toxicity

Report Title: Single Oral Dose Toxicity Study of YM087 During Estrous Cycle and Pregnancy, and after Parturition in Rats

Test Article: Conivaptan hydrochloride

Design similar to ICH 4.1.1: No
Species/Strain: SD Rats
Initial Age: Non-pregnant: 12-13 Weeks
Pregnant and postpartum: 11 Weeks
Date of First Dose: 25 June 1996
Special Features: None

Duration of Dosing: Pregnant: GD7
Postpartum: Day of completion of parturition
Day of Mating: Day 0
Day of Necropsy or C-Section: Non-pregnant: 14 days after dosing
Pregnant: GD20
Postpartum: 14 days after parturition
Method of Administration: Gavage
Vehicle/Formulation: 0.5% Methylcellulose solution

Study No. R087-TX-020

GLP Compliance: Yes

Daily Dose (mg/kg)		10	30	100	300	1000
Non-pregnant	No. Evaluated	NA	NA	NA	NA	10
	No. Died or Sacrificed Moribund					0
	Clinical Observations					
	Hypoactivity					10
	Body weight: Decrease					10
	Necropsy Observations					-
Pregnant	No. Evaluated	NA	NA	10	10	9
	No. Died or Sacrificed Moribund			0	1 [a]	3 [b]
	Clinical Observations					
	Hypoactivity			10	9 [c]	6 [c]
	Ptosis			-	-	2 [c]
	Body weight: Decrease			10	10	10
	Cesarean section			-	-	-

- No noteworthy findings. GD = Gestation day. NA = Not applicable.
a - Hypoactivity and ptosis from the day of dosing and 2 day after dosing, respectively, and moribund sacrificed 3 days after dosing (GD10).
b - Hypoactivity and ptosis from the day of dosing and 1 day after dosing, respectively, and moribund sacrificed 3 days after dosing (GD10).
c - Excluding the died or moribund sacrificed animals.

Daily Dose (mg/kg)		10	30	100	300	1000
Postpartum	No. Evaluated	10	10	10	NA	NA
	No. Died or Sacrificed Moribund	0	1 [a]	4 [b]		
	Clinical Observations:					
	Hypoactivity	-	-	1 [c]		
	Body weight: Decrease	7	9	8		
	Parturition and Nursing	-	-	-		
	Necropsy Observations	-	-	-		

- No noteworthy findings. NA = Not applicable.
a - Hypoactivity from 1 day after dosing and died 2 days after dosing.
b - One animal showed decreased hypoactivity from 1 day after dosing and sacrificed due to moribund 2 days after dosing. Other one animal showed hypoactivity, and prone position and ptosis from 1 day and 2 days after dosing, respectively, and sacrificed due to moribund 3 days after dosing. Other 2 animals showed hypoactivity, and prone position, ptosis or convulsion from 1 day and 2 days after dosing, respectively, and died 3 days after dosing.
c - Excluding the died or moribund sacrificed animals.

Special Toxicology Studies:

2.6.7.16 Local Tolerance Study **Test Article:** Conivaptan hydrochloride

Species/ Strain	Method of Administration	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
2.6.7.16A Vascular Irritation Test					
NZW Rabbit	Intravenous	Five-fold dilution of formulation with propylene glycol/EtOH(1 mg/mL): 0.05 mL, injected into posterior auricular vein, and retained 3 min for 8 days	3F	No treatment-related local vascular irritation was observed.	R087-TX-095
NZW Rabbit	Intravenous	Formulation with glycerin (0.5 mg/mL): 0.05 mL, injected into posterior auricular vein, and retained 3 min for 8 days	3F	No treatment-related local vascular irritation was observed.	R087-TX-028
2.3.7.16B Muscular Irritation Test					
NZW Rabbit	Intramuscular	Formulation with glycerin (0.5 mg/mL): 1 mL, injected into vastus lateralis muscle	3F (necropsied on 2 days after injection), 3F(necropsied on 14 days after injection)	No treatment-related local intramuscular irritation was observed.	R087-TX-029
2.6.7.16C Skin Irritation Test					
NZW Rabbit	Dermal	Bulk: 0.5 g/animal	3F	No dermal response was observed at any time during 72 hr observation period	R087-TX-026
2.6.7.16D Eye Irritation Test					
NZW Rabbit	Ocular	Bulk: 100 mg/animal (flushed with lukewarm saline/unflushed after exposure)	3F	Unflushed group: Iris hyperemia was observed at 1hr after exposure, but disappeared by 2hr after exposure. Minimal conjunctival redness, chemosis and discharge were observed, but the changes disappeared by the day after exposure. Judgment: minimally irritating. Flushed group: No abnormalities were observed. Judgment: Non-irritating.	R087-TX-025
NZW Rabbit	Ocular	Formulation with glycerin (0.5 mg/mL): 100 µL/animal (flushed with lukewarm saline/unflushed after exposure)	3F	No abnormalities were observed in cornea, iris or conjunctiva in both flushed or unflushed groups. Judgment: Non-irritating.	R087-TX-027

Species/ Strain	Method of Administration		Duration of Dosing	Doses (mg/animal)	Gender and No. per Group	Noteworthy Findings	Study Number
2.6.7.17A Anaphylaxis Test							
Guinea pigs (Hartley)	ASA	Sensitization: Subcutaneous	3 times with 1-week interval	0.05, 1 (with FCA)	10M [c]	Negative	R087-TX-021
		Challenge: Intravenous	2 weeks after the final sensitization	Conivaptan HCl: 0.1 Conivaptan HCl-GPSA [b]: 5			
	PCA	Sensitization: Intradermal		Sera sampled in ASA test: 0.1 mL /site	4M [a] (recipient)	Negative	
		Challenge: Intravenous	24 hr later	Conivaptan HCl: 0.1 Conivaptan HCl-GPSA [b]: 5			
2.6.7.17B Delayed Type Dermal Sensitization Assay							
Guinea pigs (Hartley)		Sensitization: Subcutaneous	3 times with 1-week interval	0, 0.125, 5 (with FCA)	5F	0.05, 0.15 mg/mL: No skin reaction. 0.5 mg/mL: Erythema due to primary irritation was noted in all groups.	R087-TX-057
		Challenge: Intradermal	2 weeks after the final sensitization	0, 0.05, 0.15, 0.5 mg/mL, 0.1mL/site			

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
2.6.7.17C Hemolysis Test						
Human Blood	*In Vitro*	-	Five-fold dilution of formulation with propylene glycol/EtOH (1 mg/mL)	5 samples	When added 0.1 mL of blood to 1 mL of test formulation, hemolysis occurred. When added 1 mL of blood to 0.1 mL test formulation, no hemolysis occurred.	R087-TX-096
Human Blood	*In Vitro*	-	Formulation with glycerin (0.5 mg/mL)	5 samples	When added to 0.1 mL of blood, 1 mL of both test solution and placebo caused hemolysis. This hemolysis was considered due to glycerin formulation. When 0.2 mL of formulation was added to 2 mL of blood, mimic the clinical dosing situation, both test formulation and placebo did not cause hemolysis.	R087-TX-030
2.6.7.17D CFU Assay						
Bone marrow cells from F344 Rat	*In Vitro* CFU-E and CFU-GM assay	CFU-E: 2 days, CFU-GM: 4 or 8 days	1, 2.5, 5, 10, 25, 50, 100 µg/mL	3 cultures	Cytotoxic effect (LD_{50} value) CFU-E: 30.7 µg/mL CFU-GM (Neutrophil): 12.9 µg/mL CFU-GM (Macrophage): 11.3 µg/mL	R087-TX-098
Bone marrow cells from beagle dog	*In Vitro* CFU-E and CFU-GM assay	CFU-E: 2 days, CFU-GM: 4 or 8 days	1, 2.5, 5, 10, 25, 50, 100 µg/mL	3 cultures	Cytotoxic effect (LD_{50} value) 10-20 µg/mL in each assay	R087-TX-097

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Marked aquaresis mediated via the V_2 receptor was observed in studies with conivaptan in mice, rats and dogs. Decreased body weight in repeat dose studies can be attributed to the increased water consumption, decreased food consumption and increased urine output. An extensive toxicology program has been performed with conivaptan including oral and intravenous (bolus, infusion) routes in acute and repeat dosing conditions in several species. Conivaptan is not genotoxic, carcinogenic or teratogenic in animals. Target organ toxicity includes: bone marrow in dogs, hepato- and renal toxicity in rat and dog, effects on estrus cycle and reproduction in rats and vascular irritation in rats, rabbits and dogs and adrenal gland in rat. The bone marrow toxicity consisting of focal/multifocal necrosis and degeneration, decreased erythroblastic islands, myeloid hyperplasia, hypocellularity and fibrosis occurred at systemic exposures only at high sustained exposures (>40X the therapeutic exposure for durations of exposure beyond one week of dosing). These findings were reversed following a 6 week drug recovery phase as part of a 13 week oral dog toxicity study. This suggests limited clinical risk. Likewise hepatotoxicity occurs at high exposures given for durations greater than 1 week. Liver findings included: elevated enzymes, bile duct hyperplasia, sinusoidal dilatation, hepatocyte hypertrophy, inflammation, jaundice, cholestasis, hepatocyte necrosis at 40X therapeutic exposures. Slight increases in liver enzymes, hepatocellular hypertrophy and hepatocyte necrosis were observed in a one week IV rat study at 15X therapeutic exposure which was the lowest exposure for these findings. Exposures >5X therapeutic exposure are generally needed to see even slight increases in liver enzymes. Renal tubular degeneration is observed in rats at exposures 4X therapeutic exposure after one week IV dosing along with elevations in BUN suggesting some clinical relevance. However the indicated patient population might be expected to have underlying renal pathology consistent with this finding. Thus renal function would likely be monitored in this patient population during clinical use. It should be noted that the exposures described in animal studies are based on a clinical AUC=3580 ng h/ml which is an averaged value for a 20 mg bolus on day 1 followed by continuous IV infusion at 40 mg/day for 4 days in healthy volunteers. Clinical PK has not been provided in SIADH patients.

Effects on estrus cycles and reproduction in rats occurred at doses comparable to human clinical exposure. Conivaptan caused delayed parturition and physical and function developmental deterioration in offspring. Conivaptan is contraindicated during pregnancy and lactation based on these findings. The impaired ability to nurse and lactate were attributed to conivaptan inhibition of oxytocin receptors (Ki ~ 44 nM; ~24 mg/ml) Distribution studies in pregnant rats reveals placental (2-3X higher than maternal plasma levels) and milk transfer (maximal at 1 h post dose IV and reaches 2-3X higher than plasma levels) of conivaptan. Tissue levels in the fetuses <10% of maternal plasma concentrations but clearance was much slower (even after 24h post IV dose fetal levels were 39% of the Cmax) and accumulation in the fetus is possible. The sponsor attributes the prolonged estrus and adrenal hypertrophy/hyperplasia to the effect of conivaptan on steroidogenesis. Conivaptan increases progesterone, AVP and ACTH after ≥10 mg/kg oral doses in rats and decreases corticosterone via inhibition of 21-

hydroxylase; which converts progesterone to 11-deoxycorticosterone. Negative feedback results in secretion of pituitary ACTH with decreased plasma corticosterone resulting in stimulation of progesterone from the adrenal cortex. The ACTH is implicated in the adrenal hypertrophy/hyperplasia observed in the toxicology studies. Distribution studies reveal elevated conivaptan in rat adrenal glands relative to the plasma which may implicate a direct effect in addition. Adrenal findings occur as early as 4-weeks in rat at 2.5 mg/kg IV infusion (at therapeutic exposures) however the finding appears in the one-year oral dog toxicity study at 20 mg/kg (exposures >25X therapeutic exposure).
Tissue distribution studies in rats show testicular exposure to conivaptan is greater than plasma exposure although rats did not have histopathology and tissue distribution studies were not performed in dogs. In the 4-week continuous IV infusion study in dogs, 2/3 males given 20 mg/kg had mild-slight multi-focal degeneration of seminiferous tubules, immature sperm and epididymal vasculitis. The sponsor attributes this finding to deteriorating health of the two dogs. Exposures in these dogs were >30X therapeutic exposure the NOAEL for the study provides a 3X safety margin relative to clinical exposures. This finding was not observed in a 1 week continuous IV infusion study in dogs at higher exposures. No changes in male fertility were observed in rat reprotoxicity studies at doses up to 2.5 mg/kg/day. This finding only occurs with relatively high, prolonged (>1 week) exposures and is not likely to be clinically relevant.

Administration of conivaptan PG/EtOH clinical formulation is recommended in large veins typically used for humans to minimize the significant vascular irritation observed in nonclinical studies. The degree of inflammation was severe enough to terminate a 4 week rat IV infusion and dog IV bolus study.

Conivaptan was not mutagenic or carcinogenic in a series of studies designed to address this potential.

Unresolved toxicology issues (if any): none

Recommendations: Approvable

Suggested labeling: See page 3

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes___ No___

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/s/

Fred Alavi
9/22/04 11:40:53 AM
PHARMACOLOGIST
Pharmtox review of Vaprosil (conivaptan, NDA 21-697)
PharmTox review of conivaptan NDA 21-697

Karen Davis-Bruno
9/22/04 12:01:44 PM
PHARMACOLOGIST