CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203284Orig1s000

PHARMACOLOGY REVIEW(S)

Comments on N203284 Ravicti glycerol phenyl butyrate

From A. Jacobs, AD

Date: Dec 10, 2012

1. I concur that there are no pharm/tox approval issues and that the pregnancy category should be C. I concur with the Team leader that the nonstatistically significant tail effects in rat fetuses could be eliminated from the labeling
2. I have conveyed other comments to the Team leader and they will be addressed as appropriate

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/s/

ABIGAIL C JACOBS
12/10/2012

ADDENDUM TO PHARMACOLOGY TEAM LEADER MEMORANDUM FOR NDA 203,284 DATED DECEMBER 10, 2012

In the Pharmacology/Toxicology review by Dr. Ke Zhang (dated November 28, 2012), the following recommendation appears in the evaluation of the proposed labeling:

13.2 Animal Toxicology and/or Pharmacology

Evaluation: The sponsor omitted this section from the proposed labeling. However, in the label for Buphenyl (sodium phenylbutyrate), the following paragraph is included under "PRECAUTIONS":

"Neurotoxicity of Phenylacetate in Animals"
"When given subcutaneously to rat pups, 190–474 mg/kg phenylacetate caused decreased proliferation and increased loss of neurons, and it reduced CNS myelin. Cerebral synapse maturation was retarded, and the number of functioning nerve terminals in the cerebrum was reduced, which resulted in impaired brain growth. Prenatal exposure of rat pups to phenylacetate produced lesions in layer 5 of the cortical pyramidal cells; dendritic spines were longer and thinner than normal and reduced in number."

Since phenylacetate is a major metabolite of glycerol phenylbutyrate, the same information should be included in the label for Ravicti.

Recommended Version:

13.2 Animal Toxicology and/or Pharmacology

Neurotoxicity of Phenylacetate in Animals

When given subcutaneously to rat pups, 190–474 mg/kg phenylacetate caused decreased proliferation and increased loss of neurons, and it reduced CNS myelin. Cerebral synapse maturation was retarded, and the number of functioning nerve terminals in the cerebrum was reduced, which resulted in impaired brain growth. Prenatal exposure of rat pups to phenylacetate produced lesions in layer 5 of the cortical pyramidal cells; dendritic spines were longer and thinner than normal and reduced in number.

Comments:

Dr. Zhang provided a reasonable argument for including this animal data in the Ravicti label, and I concurred with all of Dr. Zhang's labeling recommendations in my Team Leader memorandum. However, I have reconsidered my view on this issue. First, it should be noted that the animal data summary, which originates from the Buphenyl® label, was based on data from an unidentified publication (see Pharmacology/

Toxicology review of NDA 20,572 and 20,573 dated April 23, 1996). The study methods were not described in this review. However, the data summary in the Buphenyl® label does indicate that the active metabolite, phenylacetate (PAA), which is known to be neurotoxic, was injected subcutaneously in rat pups and presumably in pregnant rats for the prenatal exposure evaluation.

The subcutaneous dosing of PAA in this study may have produced plasma levels higher than that achievable through oral administration of glycerol phenylbutyrate at an equivalent dose. Therefore, the relevance of the study results to the risk of neurotoxicity with orally administered glycerol phenylbutyrate is unknown. Furthermore, given that no detailed information about the study methods is available, the suitability of this data for inclusion in the Ravicti label is uncertain. Based on these considerations, it is appropriate to omit this nonclinical information in the Ravicti label.

Recommendations:

The nonclinical information from the Buphenyl® label, as shown above, should not be included in the Ravicti label.

_____ _____

David B. Joseph, Ph.D. Date
Pharmacology Team Leader
Division of Gastroenterology and Inborn Errors Products

cc:
NDA 203,284
DGIEP
DGIEP/PM
DGIEP/Dr. Joseph
DGIEP/Dr. Zhang
DGIEP/Dr. Blank
DGIEP/Dr. Griebel

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/s/

DAVID B JOSEPH
01/31/2013

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

FROM: David B. Joseph
Pharmacology Team Leader

DATE: December 10, 2012

SUBJECT: NDA 203,284 (SD # 1 dated December 23, 2011)

Sponsor: Hyperion Therapeutics Inc.

Drug Product: Ravicti™ (glycerol phenylbutyrate)

Comments:

1. Ravicti™ (glycerol phenylbutyrate) is a (b) (4)) for oral administration, and is indicated for adjunctive therapy for chronic management of adult and pediatric patients with UCDs (urea cycle disorders). Glycerol phenylbutyrate is a triglyceride containing three molecules of 4-phenyl-butyric acid (PBA) linked to a glycerol backbone. The drug is metabolized to PBA and then PAA (phenylacetic acid), which is conjugated with glutamine to form PAGN (phenylacetylglutamine). PAGN is excreted in urine, thereby acting as a substitute for urea by mediating nitrogen excretion. Glycerol phenylbutyrate and sodium phenylbutyrate (Buphenyl®) are metabolized to the same active metabolite (PAA), therefore both drugs share the same mechanism of action. Buphenyl® is approved for adjunctive therapy in the chronic management of adult and pediatric patients with UCDs.

2. In the 2-year rat carcinogenicity study, glycerol phenylbutyrate produced an increased incidence of pancreatic acinar cell adenoma, carcinoma and combined adenoma or carcinoma, and Zymbal's gland carcinoma in both male and female rats, and thyroid follicular cell adenoma, carcinoma and combined adenoma or carcinoma, adrenal cortical combined adenoma or carcinoma, uterine endometrial stromal polyp and combined polyp or sarcoma in female rats.

3. Glycerol phenylbutyrate and its major metabolites are not genotoxic. Therefore, the drug-induced tumors in rats appear to be mediated by a non-genotoxic mechanism(s). A common mechanism for induction of thyroid follicular cell tumors in rodents is through hepatic microsomal enzyme induction (Capen, Toxicologic Pathology, 25(1), pg. 39-48, 1997). The metabolites PBA and PAA were shown to be P450 enzyme inducers in cultured human hepatocytes, and hepatocellular hypertrophy (indicative of enzyme induction) was observed in mice and monkeys in

repeat-dose toxicity studies with glycerol phenylbutyrate. Although thyroid tumors occurred in rats in the 2-year carcinogenicity study, the available data from all rat studies does not clearly indicate whether glycerol phenylbutyrate or its metabolites produce enzyme induction. The Sponsor did not provide any study that evaluated enzyme induction in rats. However, a dose-dependent increase in liver weight occurred in the 3-month oral toxicity study in rats (up to 31% in females), but this effect was not associated with histological findings. Although hepatocellular hypertrophy was not observed in rats, the increased liver weight is consistent with enzyme induction. Therefore, the weight of evidence from rats and other species suggests that the thyroid tumors in rats were secondary to hepatic enzyme induction, a mechanism that does not appear to be relevant to the risk of thyroid tumor development in humans (Capen, Toxicologic Pathology, 25(1), pg. 39-48, 1997). However, in the absence of additional studies (e.g. hepatic enzyme induction in rats, effects on TSH levels in rats), a final conclusion cannot be made regarding the mechanism of the thyroid follicular cell tumors produced by glycerol phenylbutyrate.

Recommendations:

There are no nonclinical issues which preclude the approval of Ravicti™. I concur with Dr. Zhang's recommendation for approval, and his recommendations for labeling revisions.

_____ _____

David B. Joseph, Ph.D. Date
Pharmacology Team Leader
Division of Gastroenterology and Inborn Errors Products

cc:
NDA 203,284
DGIEP
DGIEP/PM
DGIEP/Dr. Joseph
DGIEP/Dr. Zhang
DGIEP/Dr. Blank
OND IO/Dr. Jacobs

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/s/

DAVID B JOSEPH
12/10/2012

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	203,284
Supporting document/s:	000
Applicant's letter date:	December 23, 2011
CDER stamp date:	December 23, 2011
Product:	Ravicti™ / glycerol phenylbutyrate
Indication:	Urea cycle disorders
Applicant:	Hyperion Therapeutics
	South San Francisco, CA
Review Division:	Division of Gastroenterology and Inborn Errors
	Products (DGIEP)
Reviewer:	Ke Zhang, Ph.D.
Supervisor/Team Leader:	David Joseph, Ph.D.
Division Director:	Donna Griebel, M.D.
Project Manager:	Jessica Benjamin

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 203,284 are owned by Hyperion Therapeutics or are data for which Hyperion Therapeutics has obtained a written right of reference. Any information or data necessary for approval of NDA 203,384 that Hyperion Therapeutics does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 203,284.

TABLE OF CONTENTS

1. Executive Summary

1.1 Introduction

Glycerol phenylbutyrate is a triglyceride containing three molecules of 4-phenylbutyric acid (PBA) linked to a glycerol backbone. Glycerol phenylbutyrate is hydrolyzed by lipases in the GI tract to glycerol and PBA following oral administration. PBA is then absorbed and metabolized to phenylacetic acid (PAA), which is subsequently conjugated with glutamine in the liver and kidneys to form phenylacetylglutamine (PAGN). PAGN is excreted in urine, thereby eliminating two moles of nitrogen on molar basis. Thus, PAGN is utilized as an alternate means for metabolic disposal of nitrogen waste in patients with genetic defects in their urea cycle. Buphenyl (sodium phenylbutyrate) is approved for treatment of urea cycle disorders. The current sponsor seeks market approval for glycerol phenylbutyrate as adjunctive therapy for chronic management of adult and pediatric patients ≥ 6 years of age with urea cycle disorders.

1.2 Brief Discussion of Nonclinical Findings

Ravicti™ (glycerol phenylbutyrate) is a [redacted] (b) (4)) for oral administration. Glycerol phenylbutyrate was tested as a neat liquid in the nonclinical studies. The results of the repeated-dose oral toxicity studies revealed that the central nervous system was the target organ of toxicity based on clinical signs including hypoactivity, impaired equilibrium, ptosis, and shallow or labored respiration in mice, hypoactivity, impaired equilibrium, and rigid muscle tone in rats, and hypoactivity, impaired equilibrium, hunched posture, recumbency, labored respiration, and tremor in monkeys. Histopathologic examination revealed hepatocellular hypertrophy in 13-week oral toxicity studies in mice and monkeys and in the 52-week oral toxicity study in monkeys. Minimal to mild periductal mixed cellular infiltrates in liver were observed in a neonatal rat toxicity study after 7 weeks of treatment.

Glycerol phenylbutyrate was not genotoxic in the Ames test, the *in vitro* chromosomal aberration test, or the *in vivo* rat micronucleus test. The metabolites PBA, PAA, PAGN, and phenylacetylglycine (PAG) were not genotoxic in the Ames test or the *in vitro* chromosomal aberration test.

Glycerol phenylbutyrate was not tumorigenic in the 26-week carcinogenicity study in Tg.rasH2 mice at oral doses of 600 and 1000 mg/kg/day. In the 2-year carcinogenicity study in rats, glycerol phenylbutyrate increased the incidence of

pancreatic acinar cell adenoma, carcinoma and combined adenoma or carcinoma, and Zymbal's gland carcinoma in both male and female rats, and thyroid follicular cell adenoma, carcinoma and combined adenoma or carcinoma, adrenal cortical combined adenoma or carcinoma, uterine endometrial stromal polyp and combined polyp or sarcoma in female rats. The exposure multiples which produced tumors were 4.7 in male rats and 8.4 in female rats relative to adult patients, and 3 in male rats and 5.5 in female rats relative to pediatric patients.

Glycerol phenylbutyrate did not have adverse effects on fertility or reproductive function in rats at oral doses up to 0.9 g/kg/day, but did produce an increase in the number of non-viable embryos at 1.2 g/kg/day in the fertility and general reproduction toxicity study in rats.

Glycerol phenylbutyrate had no adverse effects on embryo-fetal development in the oral developmental Segment II toxicity study in rabbits. In the oral developmental Segment II toxicity study in rats, the most common fetal effect was the presence of a cervical rib at the 7th cervical vertebra in the drug-treated rats. This effect was dose-dependent. Increased resorptions and reduced litter size were observed in the neonatal rat toxicity study.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical standpoint, the NDA application is approvable for the proposed indication.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Sponsor's Version:

8.1. Pregnancy

Pregnancy Category C

(b) (4)

(b) (4)

Evaluation: The animal to human exposure ratios should be calculated using the combined AUCs for PBA and PAA, given that the human AUCs for these metabolites are similar. The incidence of cervical ribs at the 7th cervical vertebra in rat fetuses should be stated since this effect was dose-dependent and statistically significant. The description of (b) (4) should be deleted, since these findings were not statistically significant and occurred with low incidence. Adverse embryo-fetal effects (i.e. increased resorptions and reduced litter size) that were observed only in the reproduction phase of the neonatal rat toxicity study should also be stated.

Recommended Version:

8.1. Pregnancy

Pregnancy Category C

The potential for glycerol phenylbutyrate to cause teratogenic effects was studied in rats and rabbits. Oral administration of glycerol phenylbutyrate up to 350 mg/kg/day in rabbits produced maternal toxicity, but no effects on embryo-fetal development. In rats, oral doses of 650 mg/kg/day and higher produced maternal toxicity and adverse effects on embryo-fetal development including reduced fetal weights, and cervical ribs at the 7th cervical vertebra. The dose of 650 mg/kg/day in rats is approximately 5.7 times the dose of 6.87 ml/m^2/day in adult patients, based on combined AUCs for PBA and PAA. No adverse effects were observed in rat fetuses at 300 mg/kg/day (1.9 times the dose of 6.87 ml/m^2/day in adult patients, based on combined AUCs for PBA and PAA). In a neonatal rat study with daily dosing performed on post partum day 2 through mating and pregnancy after maturation, embryotoxicity (increased resorptions) occurred at 650 mg/kg/day and litter size was reduced at 900 mg/kg/day. There are no adequate and well-controlled studies in pregnant women. Ravicti should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Sponsor's Version:

(b) (4)

Evaluation: The description of tumor incidences in rats should be changed to conform to the conclusions of the FDA review of the rat carcinogenicity study. The animal to human exposure ratios should be calculated using the combined AUCs for PBA and PAA, given that the human AUCs for these metabolites are similar. The exposure ratios for both adult and pediactric patients should be stated.

Recommended Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 26-week study in transgenic (Tg.rasH2) mice, glycerol phenylbutyrate was not tumorigenic at doses up to 1000 mg/kg/day. In a two-year study in Sprague-Dawley rats, glycerol phenylbutyrate caused a statistically significant increase in the incidence of pancreatic acinar cell adenoma, carcinoma and combined adenoma or carcinoma at 650 mg/kg/day in males (4.7 times the dose of 6.87 ml/m^2/day in adult patients, based on combined AUCs for PBA and PAA) and 900 mg/kg/day in females (8.4 times the dose of 6.87 ml/m^2/day in adult patients, based on combined AUCs for PBA and PAA). The incidence of the following tumors was also increased in female rats at 900 mg/kg/day: thyroid follicular cell adenoma, carcinoma and combined adenoma or carcinoma, adrenal cortical combined adenoma or carcinoma, uterine endometrial stromal polyp and combined polyp or sarcoma. The dose of 650 mg/kg/day in male rats is 3 times the dose of 7.45 ml/m^2/day in pediatric patients, based on combined AUCs for PBA and PAA. The dose of 900 mg/kg/day in female rats is 5.5 times the dose of 7.45 ml/m^2/day in pediatric patients, based on combined AUCs for PBA and PAA.

Mutagenesis

Glycerol phenylbutyrate was not genotoxic in the Ames test, the *in vitro* chromosomal aberration test in human peripheral blood lymphocytes, or the *in vivo* rat micronucleus test. The metabolites PBA, PAA, PAGN, and phenylacetylglycine were not genotoxic in the Ames test or *in vitro* chromosome aberration test in Chinese hamster ovary cells.

Impairment of Fertility

Glycerol phenylbutyrate had no effect on fertility or reproductive function in male and female rats at oral doses up to 900 mg/kg/day. However, the number of non-viable embryos was increased at 1200 mg/kg/day (approximately 7 times the dose of 6.87 ml/m^2/day in adult patients, based on combined AUCs for PBA and PAA).

13.2 Animal Toxicology and/or Pharmacology

Evaluation: The sponsor omitted this section from the proposed labeling. However, in the label for Buphenyl (sodium phenylbutyrate), the following paragraph is included under "PRECAUTIONS":

"Neurotoxicity of Phenylacetate in Animals"
"When given subcutaneously to rat pups, 190–474 mg/kg phenylacetate caused decreased proliferation and increased loss of neurons, and it reduced CNS myelin. Cerebral synapse maturation was retarded, and the number of functioning nerve terminals in the cerebrum was reduced, which resulted in impaired brain growth. Prenatal exposure of rat pups to phenylacetate produced lesions in layer 5 of the cortical pyramidal cells; dendritic spines were longer and thinner than normal and reduced in number."

Since phenylacetate is a major metabolite of glycerol phenylbutyrate, the same information should be included in the label for Ravicti.

Recommended Version:

13.2 Animal Toxicology and/or Pharmacology

Neurotoxicity of Phenylacetate in Animals

When given subcutaneously to rat pups, 190–474 mg/kg phenylacetate caused decreased proliferation and increased loss of neurons, and it reduced CNS myelin. Cerebral synapse maturation was retarded, and the number of functioning nerve terminals in the cerebrum was reduced, which resulted in impaired brain growth. Prenatal exposure of rat pups to phenylacetate produced lesions in layer 5 of the cortical pyramidal cells; dendritic spines were longer and thinner than normal and reduced in number.

2 Drug Information

2.1 Drug

Trade Name: Ravicti™

Code Name: HPN-100

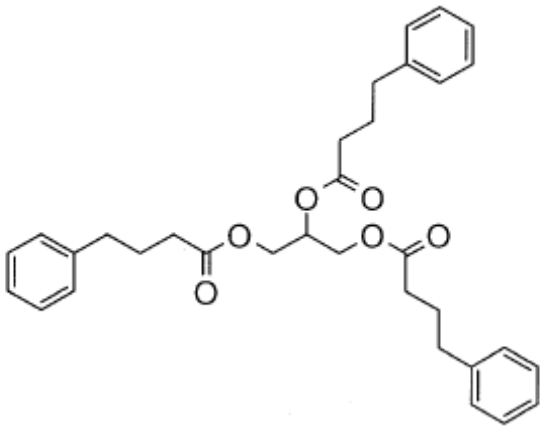
Chemical Name: Glycerol phenylbutyrate (GPB) / Glyceryl Tri-(4-phenylbutyrate) (GT4P)

Note: The code name, HPN-100, and abbreviations for the drug name, GPB and GT4P, are used in this review interchangeably.

Molecular Formula/Molecular Weight:

Molecular formula: $C_{33}H_{38}O_6$ **Relative Molecular Mass:** 530.67

Structure or Biochemical Description:



Pharmacologic Class: Nitrogen scavenging agent for hyperammonemia

2.2 Relevant INDs, NDAs, and DMFs: IND 73,480

2.3 Drug Formulation

Ravicti™ is a [redacted] for oral administration. It is colorless to pale yellow, and odorless. There are [redacted]

2.4 Comments on Novel Excipients: None

2.5 Comments on Impurities/Degradants of Concern: None

2.6 Proposed Clinical Population and Dosing Regimen

The proposed indication for Ravicti is adjunctive therapy for chronic management of adult and pediatric patients ≥ 6 years of age with urea cycle disorders involving deficiencies of the following enzymes: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) or arginase (ARG) as well as the mitochondrial transporter ornithine translocase (hyperornithinemia–hyperammonemia–homocitrullinuria [HHH] syndrome, also referred to as ornithine translocase deficiency).

The recommended starting dose for an adult is [redacted] divided into 3 doses. The recommended starting dose for pediatric patients is summarized in a table below taken from the sponsor's label.

Table 1: Recommended Starting Dose for Pediatric Patient (6-17 years of age)

BSA	Recommended Starting Dose
[redacted]	

The recommended dosing range for both adults and patients 6-17 years of age is 4.5 to 11.2 mL/m^2/day (5.0 to 12.4 g/m^2/day). Total daily dose is not to exceed 17.5 mL (19.3 g).

Regulatory Background

Glycerol phenylbutyrate (Ravicti™) was developed under IND 73,480. In the pre-NDA meeting on December 7, 2010, the sponsor agreed to submit final study reports of all required nonclinical studies, including the statistical analysis of the tumor datasets from the rat and mouse carcinogenicity studies, in the NDA submission. All needed study reports are submitted to this NDA (see below).

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology

Safety pharmacology

Overview			Test Article: Phenylacetic Acid (PAA), 4-phenylbutryic acid (PBA), Glycerol Phenylbutyrate (GPB)[1]			
Type of Study	**Test System**	**Method of Administration**	**Testing Facility**	**Study Number**	**Location Vol.**	**Page**
Safety Pharmacology						
Cardiovascular: hERG assay	HEK293 Transfected cells[a,c]	*In vitro*	(b) (4)	501209-1[b]		
Cardiovascular: Myocardial clamp	Rabbit myocytes[a,c]	*In vitro*		700109-1[b]		
Cardiovascular: Arrhythmogenic potential via the Carlsson Model	Rabbit[d]	Oral		283-0801[b]		
Cardiovascular	Cynomolgus Monkey[d]	Oral		UCY 004/053064[b]		
Central Nervous System & Respiration	Cynomolgus Monkey[d]	Oral		UCY 003/052669[b]		

hERG= human ether-a-go-go related gene, HEK293= human embryonic kidney cells, line 293
[a] Test article=phenylacetic acid (PAA)
[b] Study report contains a GLP Compliance statement
[c] Test article=4-phenylbutryic acid (PBA)
[d] Test article=glycerol phenylbutyrate (GPB), formerly referred to as glyceryl tri-(4-phenylburyate) (GT4P)

Pharmacokinetics

Table 2.4-2: Pharmacokinetic and Metabolism Studies Conducted with GPB

Type of Study	Species	Route	Dose/Form	Study Number
Absorption	Monkey	Oral	0.6 g/kg of GPB (neat)	UCY 002/043564
Absorption	Monkey	Oral	0.6 g/kg of ^{14}C-GPB	UCY 0008
Absorption	Monkey	Oral	0.6 g PBA equivalents/kg	CFU0007
Distribution	Monkey	Oral	0.6 g/kg of ^{14}C-GPB	UCY0008
Protein binding	Rat, mouse, dog, rabbit, monkey, human	*In vitro*	1–1000 µg/mL ^{14}C-PBA, 5–1000 µg/mL ^{14}C-PAA or 1–250 µg/mL ^{14}C-PAGN	CFU0003
Metabolism	Rat, mouse, dog, rabbit, monkey, human	*In vitro*	1 µM–10 mM of ^{14}C-PBA	PAJ 005
Pancreatic lipase activity against GPB	Recombinant human PTL, PLRP2, colipase, and CEL purified from yeast	*In vitro*	0.5 mL of GPB	Lowe2009
Metabolism	Monkey	Oral	0.6 g/kg of ^{14}C-GPB	UCY0008
Metabolism–induction	Human hepatocytes	*In vitro*	0.0287–8.6 mM PBA, or 0.069–20.7 mM PAA	CFU0004
Metabolism–inhibition	Human liver microsomes	*In vitro*	5 mM GPB or PBA	CFU0005

Table 2.4-2: Pharmacokinetic and Metabolism Studies Conducted with GPB (Continued)

Type of Study	Species	Route	Dose/Form	Study Number
Drug–drug interaction: *in vitro* enzymatic hydrolysis of GPB	Human plasma Human liver microsomes Human intestinal microsomes Purified porcine lipase in simulated intestinal fluid	*In vitro*	9.4 or 25 µM of GPB	A3091-11
Excretion	Monkey	Oral	0.6 g/kg of GPB (neat)	UCY 002/043564
Excretion	Monkey	Oral	0.6 g/kg of ^{14}C-GPB	UCY0008
Other: hydrolysis of GPB and [redacted] (b) (4)	Simulated intestinal fluid	*In vitro*	GPB: 100–100000 µM [redacted] (b) (4)	A5195

GPB = glycerol phenylbutyrate; PBA = phenylbutyrate; PAA = phenylacetic acid; 14C = carbon radiolabel; PTL = pancreatic triglyceride lipase; PLRP2 = pancreatic lipase related protein 2; CEL = carboxyl ester lipase.

Toxicology

Table 2.4-3: Toxicology Studies Conducted with GPB

Type of Study	Species	Route	GPB Doses (g/kg/day)	Dosing Duration	Study Number
Single dose	Rats	Oral	0.45–4.5	1 day	(b) (4) 510001
	Monkeys	Oral	0.45–6.5	1 day	(b) (4) 510003
Repeated dose	Mice	Oral	0.60, 0.90, 1.20, 1.50, 2.00	5 days	(b) (4)
			0.65, 0.90, 1.2, 2.0	14 days	(b) (4) -510007
			M: 0.60, 0.90, 1.20 F: 0.90, 1.50, 2.00	28 days	(b) (4)
			0.65, 0.90, 1.2	13 weeks	(b) (4) 510008
	Rats	Oral	0.65, 0.9, 1.2	14 days	510002
			0.65, 0.9, 1.2	13 weeks	510009
			0.65, 0.9, 1.2	26 weeks	671001
	Monkeys	Oral	1.0, 2.5, 3.5, 5.0, 10	14 days	7602-105
			0.75, 1.25, 1.75	13 weeks	(b) (4) 510010
			0.7, 1.1, 1.5	52 weeks	(b) (4) -671002
Genotoxicity GPB: Ames assay	*S. typhimurium*	*In vitro*	10–5000 µg/plate	NA	7602-100
Chromosomal aberration	Human lymphocytes	*In vitro*	82.4–500 µg/mL	NA	7602-101
Micronucleus	Rats	Oral	0.5, 1.0, 2.0	1 day	7602-102
Carcinogenicity	Tg.rasH2 mice	Oral	0.6, 1.0	26 weeks	(b) (4)
	CD(SD) rats	Oral	M: 0.07, 0.21, 0.65 F: 0.1, 0.3, 0.9	24 months	(b) (4) 671007
Reproduction and fertility	Rats	Oral	0.65, 0.9, 1.2	See [a]	MQY00011
Developmental	Rats	Oral	0.65, 0.9, 1.2, 1.5 [b]	GD 7–17	MQY00007
			0.3, 0.65, 0.9	GD 7–17	MQY00008
	Rabbits	Oral	0.2, 0.4, 0.6 [b]	GD 7–19	MQY00009
			0.15, 0.25, 0.35	GD 7–19	MQY00010
Peri-/Postnatal	Rats	Oral	0.3, 0.6, 0.9	GD 7–LD 20	MQY00012

Table 2.4-3: Toxicology Studies Conducted with GPB (Continued)

Type of Study	Species	Route	GPB Doses (g/kg/day)	Dosing Duration	Study Number
Neonatal/Juvenile	Rats	Oral	0.65, 0.9, 1.2, and 1, 2, 4, 6	PND 2–15; and PND 2–34	QBU00006
			0.65, 0.9, 1.2	PND 2–50; and PND 2–127/129 (M); or PND 2–GD 20 (F)	QBU00007

GPB = glycerol phenylbutyrate; GD = gestation day; LD = lactation day; NA = not applicable; PND = postnatal day.
[See a] Male: 28 days prior to mating through sacrifice; Female: 15 days prior to mating through gestation day 7
[b] Dose range–finding study

Table 2.4-4: Toxicology Studies Conducted with PBA, PAA, and PAGN

Test Article	Type of Study	Species	Route	Test Article Concentration	Study Number
PBA	Ames assay	*S. typhimurium* and *E. coli*	*In vitro*	1.5, 5.0, 15, 50, 150, 500, 1500, and 5000 µg/plate	(b) (4)
PAA				1.5, 5.0, 15, 50, 150, 500, 1500, and 5000 µg/plate	
PAGN				1.5, 5.0, 15, 50, 150, 500, 1500, and 5000 µg/plate	
PAG				1.5, 5.0, 15, 50, 150, 500, 1500, and 5000 µg/plate	
PBA	Chromosomal aberration	Human peripheral blood lymphocytes	*In vitro*	210 to 1640 µg/mL	
PBA		Chinese hamster ovary cells	*In vitro*	450 to 1640 µg/mL	
PAA				116 to 1360 µg/mL	
PAGN				520 to 2643 µg/mL	

PAA = phenylacetic acid; PAG = phenylacetylglycine; PAGN = phenylacetylglutamine; PBA = phenylbutyrate

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

The following pharmacology reviews under IND 73,480 and this NDA were referenced. Full reviews are included in this review verbatim:

1. Pharmacology Review (#001) by Ke Zhang, Ph.D. dated 6/6/2006
2. Pharmacology Review (#000) by Ke Zhang, Ph.D. dated 10/25/2006
3. Pharmacology Review (#004) by Ke Zhang, Ph.D. dated 10/26/2006
4. Pharmacology Review (#005) by Ke Zhang, Ph.D. dated 12/13/2006
5. Pharmacology Reviews (#005 and #006) by Ke Zhang, Ph.D. dated 12/18/2007
6. Pharmacology Reviews (SX #037 and SX#038, #040 and #041) by Ke Zhang, Ph.D. dated 8/13/2008

7. Pharmacology Review (#047) by Ke Zhang, Ph.D. dated 02/02/2009
8. Pharmacology Review (#076) by Ke Zhang, Ph.D. dated 05/13/2010
9. Pharmacology Review (#021) by Ke Zhang, Ph.D. dated 02/17/2011
10. Pharmacology Review (#061) by Ke Zhang, Ph.D. dated 09/28/2011
11. Pharmacology Review (#099) by Ke Zhang, Ph.D. dated 07/31/2012
12. Executive CAC meeting minutes dated 8/14/2008 and 2/18/2010 under IND 73,480 and 7/23/2012 under NDA 203,284

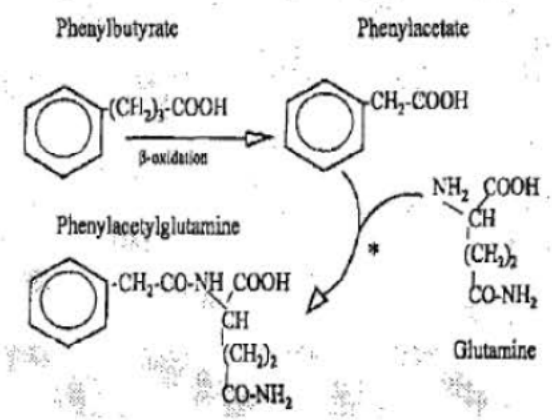
4 Pharmacology

4.1 Primary Pharmacology

Mechanism of action:

GT4P consists of three molecules of 4-phenylbutyric acid (PBA) on a triglyceride backbone. The results of the pharmacokinetic studies have demonstrated that following oral dosing of GT4P in rats or primates substantial levels of PBA were detected in plasma. However, neither GT4P nor its [redacted] (b) (4) degradants were detected in the plasma. The results suggest that PBA is released from the molecule following absorption of GT4P. There are also substantial levels of phenylacetic acid (PAA) detected in the plasma and urine of both rats and monkeys, indicating that PBA released from GT4P is further converted through ß-oxidation to PAA. The later is the substrate for metabolic processes that conjugate glutamine in the liver and kidney through the enzyme phenylacetyl-CoA: L-glutamine-N-acetyltransferase to form phenylacetylglutamine (PAGN). The biochemical formation of phenylacetylglutamine is depicted in the following table.

Biochemical Formation of Phenylacetylglutamine

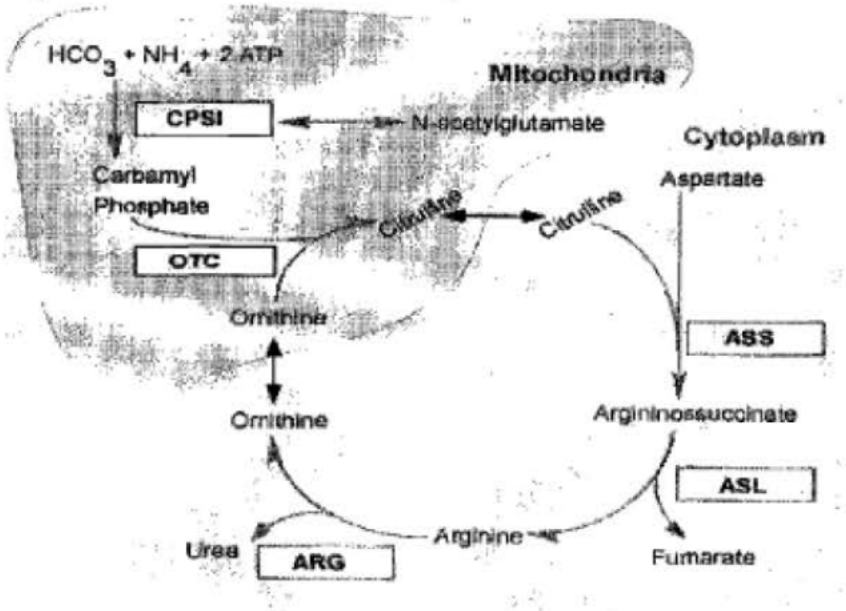


PAA may conjugate with glycine instead of glutamine to form phenylacetylglycine (PAG) instead of PAGN. PAGN and PAG are eliminated in the urine.

The urea cycle is a major route for metabolism of waste nitrogen in the body. The urea cycle normally is very efficient in removal of waste nitrogen in the form of ammonia and other nitrogenous products. Ammonia is a

normal metabolic product of amino acid catabolism and is converted to urea by a number of enzymes including enzymes: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), or arginase (ARG) in the liver. Urea is then eliminated via urinary excretion which removes 2 moles of waste nitrogen from ammonia per mole of urea generated. The urea cycle pathway is depicted in the following figure.

Figure 1. Urea Cycle Pathway



CPS = carbamyl phosphate synthetase
OTC = ornithine transcarbamylase
ASS = argininosuccinate synthetase
ASL = argininosuccinate lyase
ARG = arginase

Urea cycle disorders (UCDs) are inborn errors of metabolism which result from decreased or absent activity of any of the following enzymes: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), or arginase (ARG). In the patients with UCDs, the waste nitrogen cannot be converted into urea and toxic levels of ammonia were accumulated in the blood and brain. The therapeutic or pharmacological action of PBA in urea cycle disorders is to bind waste nitrogen in the form of PAGN or PAG and to eliminate it in the urine.

4.2 Secondary Pharmacology

4.3 Safety Pharmacology

Neurological effects: The results of a modified Irwn's test indicated that a single oral (gavage) dose of GT4P had no effects on neurobehavioral measures or core body temperature at 1 g/kg in cynomolgus monkeys (n=4). However, a higher oral dose of 4 g/kg reduced locomotor activity, impaired balance and co-ordination, and produced abnormal posture in 3 of the 4 monkeys.

Cardiovascular effects:

4-Phenylbutyric acid (PBA) and phenylacetic acid (PAA) are two active metabolites of GT4P. PBA at 894 µg/ml and PAA at 988 µg/ml inhibited hERG current by ~36% or 54%, respectively, as compared to the vehicle control in the HEK 293 cell transfected with hERG channels. PBA had no effects on the delayed rectifier (IKr) potassium current in the isolated rabbit cardiac myocytes at concentrations up to 1591.8 µg/ml.

A single oral dose of GT4P at 1 g/kg or 4 g/kg had no effects on blood pressure and heart rate in conscious cynomolgus monkeys. The results were presented in the following tables (taken from the sponsor).

Table 8.3-3: Blood Pressure Changes in Cynomolgus Monkeys after Oral Dosing of GT4P (0 – 6 hours after administration)

Treatment and dose	Maximum Increase (+ mmHg) and Decrease (- mmHg) in Blood Pressure (0 – 6 h post dose)					
	Systolic BP (mmHg)		Diastolic BP (mmHg)		Mean BP (mmHg)	
	Pre [1]	Change	Pre [1]	Change	Pre [1]	Change
Vehicle	97	+24 (5.75) [2] -5 (0.83)	61	+19 (5.75) -5 (0.83)	73	+20 (5.75) -5 (0.83)
GT4P 1 g/kg	102	+36 (5.75) -3 (0.67)	61	+28 (5.75) -2 (1.33)	75	+30 (5.75) -2 (0.67)
GT4P 4 g/kg	106	+28 (5.50) -2 (4.75)	62	+18 (5.50) 0	77	+21 (5.50) -1 (4.75)

[1] Pre-dose = mean values -30 to -10 minutes prior to dosing
[2] Number in parenthesis is the time (hours after dosing) of the maximum increase or decrease

Table 8.3-4: Heart Rate Changes in Cynomolgus Monkeys after Oral Dosing of GT4P (0 – 24 hours after administration)

Observation Period	Mean Change in HR (relative to pre-dose) b/min		
	Vehicle	GT4P 1 g/kg	GT4P 4 g/kg
0 – 6 h post-dosing	-3	-33	-29
6 – 18 h post-dosing	-19	-38	-30
18 – 24 h post-dosing	-17	-33	-35

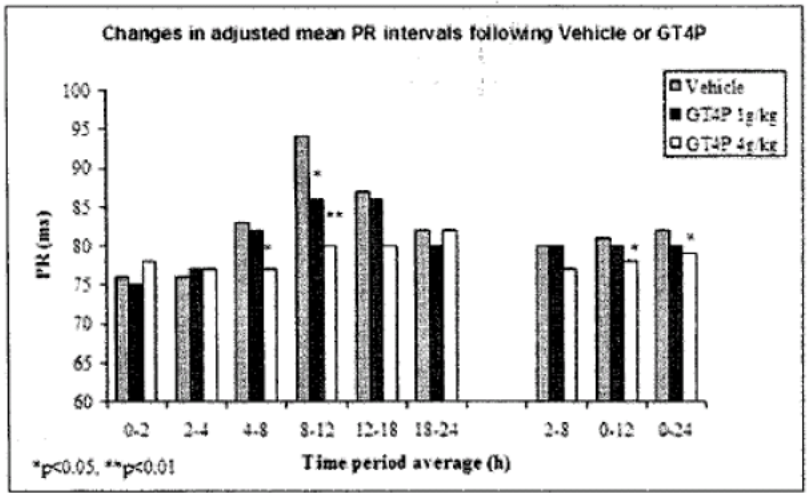
A single oral dose of GT4P significantly prolonged QTc interval by up to 25 ms at dose of 4 g/kg but not at 1 g/kg in the conscious, unrestrained cynomolgus monkeys by telemetry monitoring. The results were summarized in the following table.

Table 8.3-5: QTc Changes in Male and Female Cynomolgus Monkeys after Oral Administration of 4 g/kg GT4P

Time period (h)	Mean increase in QTc with 4 g/kg GT4P relative to the vehicle value	Prolongation (%)	P-value
0 – 2	+25 ms	10.5%	<0.01
4 – 8	+23 ms	9.1%	<0.05
2 – 8	+22 ms	8.8%	<0.05
0 – 12	+21 ms	8.4%	<0.05

Slightly shortening of the PR interval (8-14 ms) was also observed at 4 g/kg of GT4P in this study. The results were summarized in the following figure (taken from the sponsor).

Figure 3: PR Intervals in Cynomolgus Monkeys following a Single Oral Dose of Vehicle or GT4P



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GT4P at 4 g/kg prolonged QRS interval by 6 ms at 2-4 hours after dosing as compared to the vehicle groups. However, the effect of GT4P on the QRS interval was not observed at any other times. Hyppoactivity, hunched posture, unsteady gait, piloerection, vomiting and loose feces were also observed at 4 g/kg in this study.

Single oral doses of HPN-100 at 100 or 300 mg/kg/day had no clear treatment effects on ECGs including PR, QT_c, JT_c intervals (JT_c = QT_c-QRS), and QRS duration in anesthetized rabbits. HPN-100 did not induce any arrhythmia in this study. However, HPN-100 potentiated the pressor effect of methoxamine. For example, in the treatment groups with 100 or 300 mg/kg/day HPN-100, methoxamine increased the mean arterial pressure (MAP) by 72% and 104%, respectively, as compared to the baseline values. The systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) were increased similarly. However, the pressor effects of methoxamine were not seen in the control group. Slightly decreased heart rates were observed following the pressor effects. The clinical significance of these effects is not clear.

Pulmonary effects: A single oral dose of GT4P at 1 or 4 g/kg did not affect respiratory function, blood pH, pO_2, pCO_2, oxygen saturation, bicarbonate, or actual base excess values in conscious adult cynomolgus monkeys.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

A comparative pharmacokinetic study in monkeys
(UCY-002)

Methods: To assess the relative systemic exposure and excretion of GT4P and PBA, adult male monkeys (n=3) were given a single oral dose of 0.6 g PBA mole equivalents/kg (7.2 g/m2) as GT4P 80%, GT4P 95%, GT4P API, and PBA. There was a washout period of at least 14 days between each dose. Following each dose, blood samples were collected before dosing and at 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, and 24 hours after dosing. Urine samples were collected from 0-12 hours and 12-24 hours after dosing. Concentrations of GT4P and its degradants ([redacted] (b) (4)), and GT4P Phase I (PBA and PAA) and Phase II ((PAG, PAGN, PBG, and PBGN) metabolites were measured in plasma and urine using validated LC-MS/MS methods (see table below).

Table 8.4-1: GT4P and Degradants, and Phase I and Phase II GT4P Metabolites Analyzed in Biological Fluids

GT4P and degradants	GT4P, (b) (4) [redacted]
Phase I Metabolites	4-phenylbutyric acid (4-PBA), phenylacetic acid (PAA)
Phase II Metabolites	Phenylacetylglycine (PAG), phenylacetylglutamine (PAGN), phenylbutyrylglycine (PBG), phenylbutyrylglutamine (PBGN)

Results: GT4P (LOQ = 10 ng/mL) was quantifiable (13 µg/ml) only in one plasma sample from a monkey at 1 h after dosing the GT4P 80% formulation.

The plasma concentrations of the GT4P degradants [redacted] (b) (4) and the [redacted] (b) (4) were below the limits of quantification in all samples analyzed.

The plasma concentrations of PAG (LOQ = 1 µg/ml) and PBG (LOQ = 0.998 µg/ml) were also below the limits of quantification at all time points.

Total exposure (AUC24) and maximum plasma concentrations (Cmax) of PBA (LOQ = 1 µg/ml) and PAA (LOQ = 0.993 µg/ml) were lower with either oral administration of the GT4P formulation or the GT4P API than after oral administration of PBA. However, AUC24 for PAGN (LOQ = 0.961 µg/ml) was similar or greater after administration of GT4P (except for the 95% formulation) as compared with PBA.

The results were summarized in Table 8.4-2 and this table is attached below.

Table 8.4-2: Pharmacokinetic Metrics PBA, PAA and PAGN following a Single Oral Dose of GT4P or PB in Cynomolgus Monkeys

Treatment	Analyte	C_{max} (µg/mL)		T_{max} (hr)	AUC_{24} (µg·h/mL)	
		Mean	(SD)		Mean	(SD)
GT4P 80%	PBA	27.5	(3.9)	1	118	(29)
	PAA	15.2	(4.5)	2	55.4	(12.4)
	PAGN	10.5	(0.8)	4	72.7	(17.5)
GT4P 95%	PBA	1.04	-	2	-	-
	PAA	8.94	(2.45)	2	70.2	(35.4)
	PAGN	3.78	(1.35)	1.5	35.6	(19.2)
GT4P API	PBA	23.3	(7.4)	2	210	(54)
	PAA	38.5	(8.5)	8	483	(51)
	PAGN	10.6	(3.8)	12	161	(70)
PBA	PBA	269	(18)	0.5	259	(135)
	PAA	60	(24.9)	8	629	(460)
	PAGN	7.63	(1.17)	8	78.7	(35.6)
	PBG	3.67	(1.83)	0.5	3.84	(3.39)

The major metabolite excreted into urine 0-12 hours after oral dosing of PBA and GT4P (all formulations) was phenylacetylglutamine (PAGN). The mean cumulative amount of this metabolite in urine collected over 24 hours after dosing were: >130,000 µg, >114,000 µg, >69,000 µg, and 54,500 µg from animals dosed with GT4P 80%, PBA, GT4P API, and GT4P 95%, respectively.

Substantial amounts of PBA were excreted in the urine following PBA administration but very little of this metabolite was excreted after any of the GT4P administrations. PAA and PBG were also identified in the urine following PBA administration.

GT4P was not detected in the plasma following a single oral dose of GT4P in rats and in primates in the toxicity studies. However, measurable levels of PBA and PAA were found in both the plasma and urine of these species.

GT4P is hydrolyzed to glycerol and PBA. The later is ther hydrolyzed to PAA by ß-oxidation. The known metabolites of PBA are PAA, PAG, PAGN, PBGN and PBG.

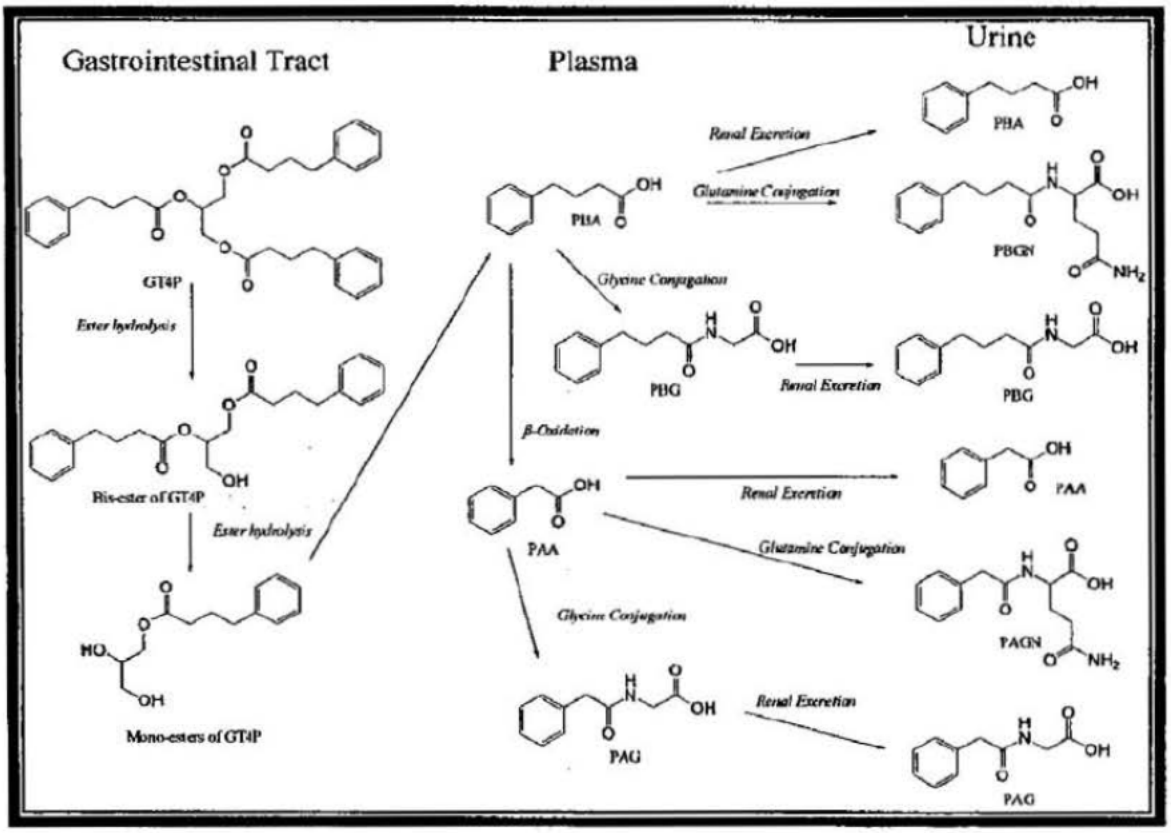
PAA is conjugated with glutamine to form PAGN. PAA may conjugate with glycine instead of glutamine to form phenylacetylglycine (PAG). PAGN and PAG are eliminated in the urine. The results were presented in the following table.

Table 8.4-4: Metabolites of PBA following In Vitro Incubation with Hepatocytes from Various Species

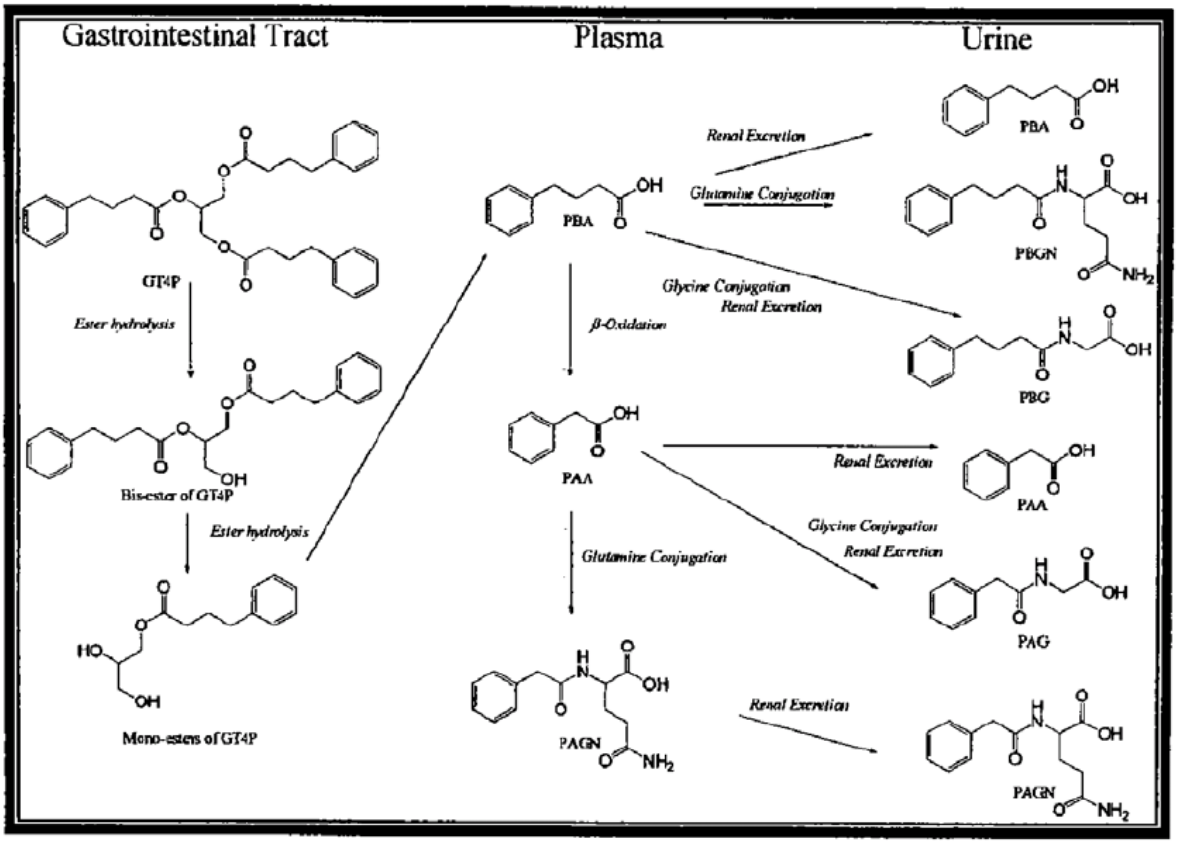
Species	Metabolites Produced	
	0.1 mM PBA	10 mM PBA
Human	PAGN > PAA, GU conjugate	PBGN≈MF-10
Monkey	PAA, GU conjugate	PAGN, PBGN
Dog	PAG > PAA	-
Rabbit	PAA	-
Mouse	PAA	PBGN
Rat	PAA	PAGN

-: Not Detected

The metabolic pathway in rats is depicted in the following figure.



The metabolic pathway in monkeys is depicted in the following figure.



A pharmacokinetic study was conducted in three male cynomolgus monkeys following a single oral dose (600 mg PBA equivalents/kg) of ^{14}C-HPN-100 (^{14}C-GT4P) and an intravenous dose (150 mg/kg) of ^{14}C-PBA (Study UCY0008). The oral bioavailability of PBA following oral administration of HPN-100 was 51–80% in monkeys. The results were presented in the sponsor's tables below.

Mean pharmacokinetic parameters for PBA, PAA, PAGN and total radioactivity following oral administration of HPN-100 are summarised below:

Administration	Dose route	Analyte	C_{max} (µg/mL)[a]	T_{max} (h)	AUC_t (µg.h/mL)	AUC_{168} (µg.h/mL)
HPN-100	oral	PBA	52.2	1.5	588	733
HPN-100	oral	PAA	114	8.0	1360	1520
HPN-100	oral	PAGN	31.6	8.0	930	940
HPN-100	oral	Radioactivity	883	8.0	11700	11800

[a] Results expressed as µg/mL or µg equivalents PBA/mL

Mean pharmacokinetic parameters for PBA, PAA, PAGN, PBG and total radioactivity following intravenous administration of PBA are summarised below:

Administration	Dose route	Analyte	C_{max} (µg/mL)[a]	T_{max} (h)	AUC_t (µg.h/mL)	AUC_{168} (µg.h/mL)
PBA	iv	PBA	706[b]	0	295	297
PBA	iv	PAA	175	2.0	1020	1090
PBA	iv	PAGN	34.3	2.0	553	564
PBA	iv	PBG	4.23	0.5	2.11	2.87
PBA	iv	Radioactivity	787[b]	0	2870	2870

[a] Results expressed as µg/mL or µg equivalents PBA/mL
[b] Extrapolated concentration at time zero

The radioactivity was widely distributed throughout the body with highest concentration in the large intestine followed by bile, plasma, kidney, liver, urinary bladder, and whole blood at 8 hours after a single oral dose of ^{14}C-HPN-100 in male monkeys.

The majority of the radioactivity was recovered in the urine and feces at 168 hours after dosing and the results were summarized in the sponsor's table below.

	PBA (intravenous) (% dose)	PBA (oral) (% dose)	HPN-100 (oral) (% dose)
Urine	79.41% ± 4.05%	79.38% ± 7.12%	44.57% ± 4.29%
Faeces	2.58% ± 0.39%	0.87% ± 0.41%	24.61% ± 4.94%
Overall total*	94.62% ± 0.89%	88.11% ± 5.16%	91.73% ± 2.56%

* Including cage debris and cage washes

Protein Binding:

Plasma protein binding of ^{14}C-PBA and ^{14}C-PAA was studied using *in vitro* ultra-filtration methods. The protein binding of PBA was 57-88% in mice, 34-94% in rats, 96-98% in rabbits, 75-98% in monkeys, and 81-98% in humans. The protein binding was decreased as PBA concentration increased in mice, rats, monkeys, and humans. Plasma protein binding of PAA was 6.6–15% in mice, 11-27% in rats, 27-76% in rabbits, 18-46% in monkeys, and 37-66% in humans, and was also concentration dependent.

Enzyme Induction/Inhibition:

Both PBA and PAA produced moderate *in vitro* induction of the human hepatic P450 enzymes CYP1A2 and CYP3A4/5 (up to ~31%, relative potency).

PBA inhibited human hepatic P450 enzymes CYP2C9, CYP2D6, and CYP3A4/5 activities by > 60% at 5 mM (0.82 mg/mL). The inhibition constants (K_i) for PBA were

1.29 mM or 0.212 mg/mL for CYP2C9, and 1.48 mM or 0.243 mg/mL for CYP2D6. The PBA IC50 for CYP3A4/5 was calculated and was 1.79–3.26 mM or 0.294–0.535 mg/mL.

PAA inhibited the human hepatic P450 enzymes CYP1A2, CYP2C8, and CYP2C9 (K_i = 15.1 mM or 2.056 mg/mL). PAA also inhibited CYP2C19, CYP2D6, and CYP3A4/5 by ≥ 37% at 20.7 mM.

5.2 Toxicokinetics

TK data were included in the reviews of the toxicity studies.

6 General Toxicology

6.1 Single-Dose Toxicity

Methods: Acute oral dose toxicity studies were conducted with GT4P in rats ([(b) (4)]510001) and monkeys ([(b) (4)]510003). The dosing information was summarized in a table along with the results in the result section. Animals were observed for mortality and clinical signs of toxicity daily for 14 days. Body weights and food consumption were recorded. Necropsy was performed and gross pathological examinations were conducted. Plasma and urine samples were analyzed for determination of PBA, PAA, PAGN, PBGN, GT4P, and [(b) (4)] and [(b) (4)] of GT4P using LC-MS/MS methods.

Results: The results are summarized in the following table.

Study #/Animal	Dosage (g/kg)	Mortality	Clinical Signs of Toxicity
(b) (4) 510001 Rats 3/sex/group	Oral gavage 0, 0.45, 0.65, 0.9, 1.2, 1.5, 2.3, 4.5 in corn oil	1.2 g/kg: 1 male 1.5 g/kg: 1 male and 1 female 2.3 g/kg: 3 males and 3 females 4.5 g/kg: 3 Males and 3 Females	Clinical signs were noted at 0.9 g/kg or higher and included hypoactivity, prostration, rigid muscle tone, impaired equilibrium and muscle coordination and/or signs of respiratory distress (gasping and labored and shallow respiration)
(b) (4) 510003 monkeys 1 male 1 female Dose escalating	Oral gavage 0, 0.45, 0.65, 0.9, 1.2, 1.8, 2.4, 3.5, 4.5, and 6.5 in corn oil	No deaths.	Abnormal excreta (mucoid feces, soft feces or diarrhea) after each dose. Emesis, hypoactivity and sleeping at 6.5 g/kg GT4P. A single incidence of tremors in 1 female at 6.5 g/kg.

GT4P and its (b) (4) were not detected in the plasma from rats and monkeys.

Plasma levels of PBA, PAA, and PAG in rats were summarized in the following table.

Table 8.5-4: Mean Peak (Cmax) and Total (AUC0-τ) following a Single Oral Dose of 0.9, 1.2 or 2.3 g/kg GT4P

Gender	Dose (g/kg)	PBA		PAA		PAG	
		C_{max} (µg/mL)	AUC_{last} (µg·h/mL)	C_{max} (µg/mL)	AUC_{last} (µg·h/mL)	C_{max} (µg/mL)	AUC_{last} (µg·h/mL)
Female	0.9	616.0	1333.0	718.0	4150.7	16.8	179
	1.2	400.0	1419.3	684.0	8211.9	30.3	288
	2.3	932.7	6887.5	1530.0	20560.0	305.0	3054
Male	0.9	470.7	1490.5	300.6	3214.6	18.0	324
	1.2	295.7	1429.9	454.1	6842.0	24.9	382
	2.3	1387	17352.0	688.5	9666.9	185.2	2298

Plasma levels of PBA, PAA, and PAG in monkeys were summarized in the following table.

Table 8.5-6: Mean Peak (Cmax) and Total (AUC0-τ) following a Single Oral Dose of 4.5 or 6.5 g/kg GT4P

Gender	Dose	PBA		PAA		PAGN	
	(g/kg)	C_{max} (µg/mL)	AUC_{last} (µg·h/mL)	C_{max} (µg/mL)	AUC_{last} (µg·h/mL)	C_{max} (µg/mL)	AUC_{last} (µg·h/mL)
Female	4.5	57.1	884.5	292.0	3810.4	89.5	949.4
Female	6.5	31.2	533.5	409.0	3171.7	161.0	1379.0
Male	4.5	96.8	638.4	527.0	6245.2	82.5	750.6
Male	6.5	108.0	1133.7	538.0	1723.0	69.6	1390.4

In summary, the major clinical signs of toxicity were hypoactivity, prostration, rigid muscle tone, impaired equilibrium and muscle coordination and/or signs of respiratory distress (gasping and labored and shallow respiration) observed at 0.9 g/kg or higher in rats. Emesis, hypoactivity, sleeping and tremors were observed at 6.5 g/kg in monkeys. The minimal lethal oral dose of GT4P was 1.2 g/kg for males and 1.5 g/kg for females in rats. The minimal lethal oral dose of GT4P was not identified in monkeys.

Repeat-Dose Toxicity

MOUSE

Study title: 14-day oral gavage dose ranging toxicity study with GT4P in mice

Key study findings: In the 14-day dose ranging toxicity study in mice, GT4P was given to mice (5/sex/group) by oral gavage at 0, 0.65, 0.9, 1.2, and 2.0 g/kg/day for 14 days. High dose was lethal (4 males and 4 females died). The central nervous system was the target organ of toxicity based on the clinical signs of toxicity including hypoactivity, impaired equilibrium, ptosis, and shallow or labored respiration. No effect dose was not identified. The dose of 0.65 g/kg/day was tolerated.

Study no.: (b) (4) 510007
Volume #, and page #: 4.8 and 382
Conducting laboratory and location:
(b) (4)

Date of study initiation: June 15, 2005
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: MPR-UXW-M0003.00.01

Species/strain: Crl:CD1(ICR) mice
Males: 10-12 weeks old, 29.1-27.8 g
Females: 10-12 week old, 23.4-29.8 g

Methods: To determine dose levels for a 90-day oral (gavage) toxicity study with GT4P in mice, GT4P was given by oral gavage to mice (10/sex/group) for 14 days at 0, 0.65, 0.9, 1.2 and 2.0 g/kg/day. Following parameters were monitored: mortality, clinical signs of toxicity, body weight, food consumption, and macroscopic examination. Blood samples were collected on Days 1 and 14 prior to dosing and at 1, 2, and 6 hours postdose for toxicokinetic evaluations. The toxicokinetic results were not submitted in this report.

Results:

Mortality: Four males and 4 females were found dead in the high dose group. One male in the 0.65 g/kg/day group, 2 males and 1 female in the 0.90 g/kg/day group and 1 female in the 1.2 g/kg/day group died due to intubation errors.

Clinical signs: Clinical signs of toxicity prior to death in the high dose animals were hypothermia (body and extremities cool to touch), decreased defecation, dermal atonia, hypoactivity, impaired equilibrium, ptosis (parial closure of the left or right eye), shallow or labored respiration, and yellow material on various body surfaces including the urogenital and anogenita1 areas, ventral trunk and hind1imbs. These clinical signs of toxicity were also observed in the surviving animals sporadically.

Body weights: The initial and final body weights in the control group were 33.6 g and 33.2 g for males and 25 g and 25.9 g for females. The high dose males had body weight loss (3.1 g). The females in the 1.2 g/kg (0.0 g) and 2.0 g/kg (0.4 g) had less terminal body weight gain as compared to the control (0.9 g).

Food Consumption: The mean food consumption was 5.2-5.4 g/animal/day in males and 5.3-5.7 g/animal/day in females.

The animals in the 2.0 g/kg/day consumed less food during the first week of the treatment (2.9-3.5 g/animal/day).

Gross pathology: There were no treatment related changes.

28-day oral dose ranging toxicity study in CByB6F1 mice

Study No: (b) (4)
Conducting Laboratory and Location:
(b) (4)
Date of study initiation: September 16, 2009
Report date: January 6, 2010
GLP compliance: This study was conducted in accordance with Good Laboratory Practice Regulations of the United States Food and Drug Administration (21 CFR Part 58).
QA-Report Yes (x) No ().

Animals: CByB6F1 mice
Weight: male: 23.9-31.8 g, 8 weeks old
female: 18.3-22.4 g, 8 weeks old
Drug lot#: XA210B

Methods: GT4P was given to mice (10/sex/group) by oral gavage at 0 (corn oil), 600, 900, and 1200 mg/kg/day in males or 900, 1500, and 2000 mg/kg/day in females for 28 days. The test article is undiluted colorless oil (neat). There were two 5-day dose ranging studies in CByB6F1 mice and the dose of 2000 mg/kg/day or higher was lethal for both males and females.

Animals in the 28-day study were observed for mortality, clinical signs of toxicity, body weights, food consumption, hematology, clinical chemistry, organs weights, gross pathology, and histopathology. The following tissues or organs were examined microscopically in the control and high-dose males and females, as well as mid-dose females.

Adrenal glands
Aorta
Bone (femur and sternum)
Bone marrow (femur and sternum)
Brain
Epididymides
Esophagus
Eyes
Gall bladder
Gross lesions
Harderian glands
Heart
Kidneys
Large intestine (cecum, colon, and rectum)
Liver
Lungs and bronchi
Lymph nodes (mesenteric and mandibular)
Mammary gland with adjacent skin
Nasal cavity
Ovaries
Pancreas
Parathyroid glands
Pituitary gland
Prostate gland
Salivary gland
Sciatic nerve
Seminal vesicles
Skeletal muscle (thigh)
Small intestine (duodenum, jejunum, and ileum)
Spinal cord (cervical, thoracic, and lumbar)
Spleen
Stomach
Testes
Thymus
Thyroid glands
Trachea
Urinary bladder
Uterus
Vagina

Toxicokinetic parameters were determined on day 25.

Results:

Mortality: High dose females (2000 mg/kg/day) were sacrificed on treatment day 2 due to clinical signs of toxicity.

Clinical Signs: Decreased motor activity (high dose males and females), prostration and labored breathing (high dose females) were observed.

Body Weights: Final body weight gain was decreased by 4.5% in the mid-dose females (1500 mg/kg/day). High dose females were sacrificed on treatment day 2. Final body weight gain was increased in the high dose males as compared to the control.

Food Consumption: The food consumption was decreased in treated females as compared to the control.

Hematology: There were no clear treatment-related changes.

Clinical Chemistry: There were no clear treatment-related changes.

Organ Weights: There were no treatment-related changes.

Gross Pathology: There were no treatment related changes.

Histopathology: Minimal vacuolation of epithelial cells i: glandular portion of the stomach was noted in 5 of the 1 terminated high-dose females.

Toxicokinetics: The results indicated that phenylbutyri acid (PBA), phenylacetic acid (PAA), and N-phenylacetyl glycine (PAG) were detected in plasma, suggesting that GT4: was rapidly degraded to PBA. The plasma levels of PBA PAA, and PAG were increased with the dose in females. Th data from males suggest that saturation of absorptio occurred at 900 mg/kg/day. The results were presented o Text Tables 1, 2, 3, 4, 5, and 6 on pages 270, 271, an 272. These tables are attached below.

Text Table 1: Average C_{max} and AUC_{last} for PBA in Male Mice on Study Day 27

Dose mg/kg	C_{max} µg/mL	AUC_{last} hr*µg/mL
	Male	Male
600	14.34	58.10
900	21.97	113.47
1200	12.49	110.23

Text Table 2: Average C_{max} and AUC_{last} for PBA in Female Mice on Study Day 27

Dose mg/kg	C_{max} µg/mL	AUC_{last} hr*µg/mL
	Female	Female
900	17.34	122.60
1500	33.40	236.04

Text Table 3: Average C_{max} and AUC_{last} for PAA in Male Mice on Study Day 27

Dose mg/kg	C_{max} µg/mL	AUC_{last} hr*µg/mL
	Male	Male
600	65.10	120.70
900	339.64	1354.10
1200	261.92	1317.32

Text Table 4: Average C_{max} and AUC_{last} for PAA in Female Mice on Study Day 27

Dose mg/kg	C_{max} µg/mL	AUC_{last} hr*µg/mL
	Female	Female
900	341.82	1923.07
1500	385.90	2727.27

Text Table 5: Average C_{max} and AUC_{last} for PAG in Male Mice on Study Day 27

Dose mg/kg	C_{max} µg/mL	AUC_{last} hr*µg/mL
	Male	Male
600	12.56	92.96
900	25.13	197.02
1200	20.15	188.60

Text Table 6: Average C_{max} and AUC_{last} for PAG in Female Mice on Study Day 27

Dose mg/kg	C_{max} µg/mL	AUC_{last} hr*µg/mL
	Female	Female
900	19.64	188.33
1500	23.15	222.25

In summary, GT4P was given by oral gavage to CByB6F1 mice at 0, 600, 900, and 1200 mg/kg/day in males or 900, 1500, and 2000 mg/kg/day in females for 28 days. Decreased motor activity was observed in high dose males (1200 mg/kg/day) and high dose females (2000 mg/kg/day). In addition, prostration and labored breathing were observed in high dose females. Based on the results of the dose ranging studies, which included two 5-day studies and the 28-day study, the dose of 2000 mg/kg/day was lethal in both males and females. Therefore, the maximum tolerated dose is estimated to be 1000 mg/kg/day, since it is half of the lethal dose of 2000 mg/kg/day.

13-week oral toxicity study in mice
(b) (4) 510008)

Study No: (b) (4) 510009
Conducting Laboratory and Location:
(b) (4)

Date of study initiation: September 1, 2005
Report date: September 22, 2006
GLP compliance: This study was conducted in accordance with Good Laboratory Practice Regulations of the United States Food and Drug Administration (21 CFR Part 58).
QA-Report Yes (x) No ().

Animals: Crl:CD®(ICR) mice
weight: male: 27.5-35.4 g, 8 week old
female: 21.4-25.4 g, 8 weeks old
Drug lot#: 6561C

Observations and times:

- **Clinical signs:** Clinical signs of toxicity were observed daily.
- **Body weights:** Body weights were determined weekly.
- **Food consumption:** Food consumption was determined weekly.
- **Hematology:** During week 13.
- **Clinical chemistry:** at termination.
- **Ophthalmologic Examination:** Before treatment and during week 11.
- **Functional observational battery:** The functional observation battery test was conducted before dosing and during weeks 0, 3, and 12. Following parameters were tested:

Arousal	Mobility
Backing	Mucous membranes/eye/skin color
Bizarre/stereotypic behavior	Muscle tone
Body temperature	Palpebral (eyelid) closure
Convulsions/tremors	Piloerection
Ease of handling animal in hand	Red/crusty deposits
Ease of removal from cage	Respiratory rate/character
Eye prominence	Rearing
Forelimb grip strength	Righting reflex
Fur appearance	Salivation
Gait	Startle response
Grooming	Tail pinch response
Lacrimation/chromodacryorrhea	Urination/defecation

-
- **Gross pathology**: Animals were necropsied at termination.
- **Organ weighed**: Organs were weighed at termination.
- **Histopathology**: Following organs or tissues were examined histopathologically from all animals from control and high groups:

Adrenal glands (2)	Liver
Aorta	Lungs (including bronchi, fixed by inflation with fixative)
Bone with marrow	Lymph nodes
Femur with articular surface	Mandibular
Sternum	Mesenteric
Bone marrow smear (from femur)[a]	Mammary gland (females only)
Brain	Ovaries with oviducts (2)
Cerebrum level 1	Pancreas
Cerebrum level 2	Peripheral nerve (sciatic)
Cerebellum with medulla/pons	Pituitary
Epididymides (2)[b]	Prostate
Eyes with optic nerve (2)[c]	Salivary glands [mandibular (2)]
Gallbladder	Seminal vesicles (2)
Gastrointestinal tract	Skeletal muscle (rectus femoris)
Esophagus	Skin
Stomach	Spinal cord (cervical, midthoracic, lumbar)
Duodenum	Spleen
Jejunum	Testes (2)[b]
Ileum	Thymus
Cecum	Thyroid [with parathyroids (2)]
Colon	Trachea
Rectum	Urinary bladder
Harderian glands (2)	Uterus with vagina
Heart	Zymbal's glands
Kidneys (2)	Gross lesions (when possible)
Lacrimal gland [exorbital (2)]	

[a] - Bone marrow smears were obtained at necropsy but not placed in formalin; slides were examined only if scientifically warranted.
[b] - Fixed in Bouin's solution
[c] - Fixed in Davidson's solution

The liver, kidney, and gross lesions were examined from all animals in the low and mid dose groups.

- **Toxicokinetics**: Toxicokinetic parameters were determined on days 0 and 90 before dosing and at 1, 2, 4, 6, 8, and 24 hours after dosing.

Methods: GT4P was given to mice (10/sex/group) by oral gavage at 0, 0.65, 0.90 and 1.20 g/kg/day for 90 consecutive days. The dose selection was based on the results of the 14-day oral dose ranging study in mice. In this study, the dose of 2 g/kg/day was lethal. The dose of 1.2 g/kg/day was selected as high dose.

For toxicology assessment, all animals were observed twice daily for mortality and clinical signs of toxicity. Body weights and food consumption were recorded weekly. A modified functional observational battery was conducted for all animals prior to the initiation of dose administration and for 5 animals/sex during study weeks 0, 3 and 12. Ophthalmic examinations were performed during study weeks -1 and 11. Hematology and clinical chemistry were performed on all animals at the scheduled necropsy (study week 13). Complete necropsies were conducted on all animals, and selected organs were weighed at the scheduled necropsy. Histopathological examination was conducted from the animal found dead and from all animals in the control and the high dose groups. The liver, kidney, and gross lesions were examined from all animals in the low and mid dose groups.

Results:

Clinical Signs: There were no treatment related clinical signs of toxicity.

Mortality: There were no test article-related deaths. One female and one male in the 0.65 g/kg/day group were found dead or sacrificed on study days 1 and 89. The death of the male was due to gavage error and the cause of death of the female was not known. One female in the 0.9 g/kg/day group died due to a mechanical injury. Hypoactivity, impaired equilibrium, cool to touch, labored respiration, dermal atonia, and decreased defecation were noted prior to death. These clinical signs of toxicity are not considered treatment related.

Body Weights: The initial and final body weights in the control group were 31.1 and 37 g for males and 23.8 and 29 g for females. There were no clear treatment related changes.

Food Consumption: Average food consumption in the control group was 5.1-6.5 g/animal/day for males and 5.8-7 g/animal/day for females. The food consumption was not clearly affected by the treatment.

Hematology: There were no clear treatment related changes.

Clinical Chemistry: There were no clear treatment related changes.

Ophthalmologic Examination: There were no treatment related changes.

Organ Weights: Higher liver weights (relative to final body weight) were noted in the treatment groups as compared to the control group. The results were summarized in Text Table 1 on page 34 of this report. This table is attached below.

Text Table 1
Test Article-Related Liver Weight Alterations (% ↑)

	Males			Females		
Dosage (g/kg/day)	**0.65**	**0.90**	**1.20**	**0.65**	**0.90**	**1.20**
Absolute	3	16*	15*	2	3	15
Relative to final body weight	5	10*	13*	4	6	12*
Relative to brain weight	<1	17*	15*	1	7	18*
Histologic correlation	Centrilobular hepatocellular hypertrophy (males)					

* = statistically significantly ($p<0.05$ or 0.01 using Dunnett's test) different from control group

Functional Observational Battery: There were no treatment related changes.

Gross Pathology: There were no treatment related changes.

Histopathology:

Minimal centrilobular hepatocellular hypertrophy was observed in one, six, and four males in the groups of 0.65, 0.90 and 1.20 g/kg/day, respectively (none in the control males and none in females). The lesions were concentrated in the central region of the classical hepatic lobule and consisted of slightly swollen hepatocytes.

Toxicokinetics: The results indicated that phenylbutyric acid (PBA), phenylacetic acid (PAA), and N-phenylacetyl-glycine (PAG) were detected in the plasma, suggesting that GT4P was rapidly degraded to PBA. The plasma levels of PBA, PAA, and PAG were increased with the dose. The results were presented on Text Tables 2, 3, 4, 5, 6, and 7. These tables are attached below.

Text Table 2 C_{max} and AUC_{∞} for PBA on Study Day 0		
Dose g/kg	C_{max} (µg/mL)	AUC_{∞} hr•µg/mL
0.65	102.2 - 142.6	120.8 - 301.0
0.9	66.0 - 124.5	211.0 - 233.7
1.2	103.9 - 189.2	457.7 - 519.0

Text Table 3 C_{max} and AUC_{∞} for PBA on Study Day 90		
Dose g/kg	C_{max} (µg/mL)	AUC_{∞} hr•µg/mL
0.65	31.2 - 60.1	112.0 - 141.2
0.9	61.0 - 123.1	164.5 - 186.4
1.2	48.1 - 135.5	137.0 - 212.5

Text Table 4 C_{max} and AUC_{∞} for PAA on Study Day 0		
Dose g/kg	C_{max} (µg/mL)	AUC_{∞} hr•µg/mL
0.65	180.3 - 417.5	430.7 - 1836.9
0.9	275.3 - 552.1	1595.2 - 2006.0
1.2	503.9 - 789.6	9998.6 - 11292.6

Text Table 5 C_{max} and AUC_{∞} for PAA on Study Day 90		
Dose g/kg	C_{max} (µg/mL)	AUC_{∞} hr•µg/mL
0.65	211.6 - 327.2	828.2 - 1086.2
0.9	338.9 - 388.1	1186.9 - 1756.1
1.2	546.3 - 640.9	2339.5 - 2473.2

Text Table 6 C_{max} and AUC_{∞} for PAG on Study Day 0		
Dose g/kg	C_{max} (µg/mL)	AUC_{∞} hr•µg/mL
0.65	36.0 - 162.6	255.5 - 606.3
0.9	30.7 - 239.2	235.4
1.2	50.4 - 208.6	549.0

Text Table 7 C_{max} and AUC_{∞} for PAG on Study Day 90		
Dose g/kg	C_{max} (µg/mL)	AUC_{∞} hr•µg/mL
0.65	29.3 - 63.0	238.0 - 352.2
0.9	33.2 - 60.5	279.6 - 460.9
1.2	41.8 - 82.6	337.4 - 789.1

Key study findings:

In summary, GT4P was give by oral gavage to mice at 0, 0.65, 0.90 and 1.20 g/kg/day for 90 days. The results indicated that there were no treatment-related deaths and clinical signs of toxicity. Treatment increased the liver weight and produced hepatocellular hypertrophy. The high dose of 1.20 g/kg/day is no-observed-adverse-effect level (NOAEL).

RAT

Study title: 14-day oral gavage toxicity study with GT4P in rats

Key study findings: GT4P was administered by oral gavage for 14 days to rats (10/sex/group) at 0, 0.65, 0.9 and 1.2 g/kg/day. There were no deaths. The central nervous system was the target organ of toxicity based on the clinical signs of toxicity. No effect dose was not identified. The dose of 0.65 g/kg/day was tolerated.

Study no.: (b) (4)-510002
Volume #, and page #: 4.7 and 001
Conducting laboratory and location:
(b) (4)

Date of study initiation: June 7, 2004
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: MPR-UXW-M0003.00.01

Species/strain: Crl:CD(SD)IGS BR rat
Males: 7 weeks old, 213-268 g
Females: 7 week old, 156-203 g

Methods: To determine the toxic effects of GT4P, GT4P was given by oral gavage to Crl:CDCB(SD)IGS BR rats (10/sex/group) for 14 days at 0, 0.65, 0.9 and 1.2 g/kg/day. Following parameters were monitored: mortality, clinical signs of toxicity, body weight, food consumption, ophthalmic examinations, clinical pathology, and gross and histopathology. For toxicokinetic study, rats (9/sex/group) were also treated with GT4P for 14 days. Blood samples were collected on Days 1 and 14 prior to dosing and at 1, 2, 4, 8, 12, and 24 hours postdose for toxicokinetic evaluations. The results of toxicokinetics were not provided in this report.

Results:

Mortality: There were no deaths.

Clinical signs: Clinical signs of toxicity were noted in 0.9 and 1.2 g/kg/day groups and these included hypoactivity, impaired equilibrium, impaired muscle coordination and rigid muscle tone.

Body weights: The initial and final body weights in the control group were 236 g and 310 g for males and 178 g and 204 g for females. The high dose males had less terminal body weight gain (26%) as compared to the control. No treatment related body weight changes in females were seen.

Food Consumption: There were no treatment related changes.

Ophthalmoscopy: There were no treatment related changes.

Hematology: Lower platelet counts were observed in the 0.9 and 1.2 g/kg/day group males and 0.65, 0.9 and 1.2 g/kg/day group females. Lower red blood cell counts and hematocrit levels were observed in the 1.2 g/kg/day group females. The results were summarized in the following table.

Parameter	Males (g/kg/day)				Females (g/kg/day)			
	0	0.65	0.90	1.2	0	0.65	0.90	1.2
Platelets (10^3/μL)	1197	1105	910*	948*	1233	933**	1047	907**
RBC (10^6/μL)	6.91	6.83	6.94	6.92	7.07	6.84	6.80	6.43**
Hematocrit (%)	40.3	39.5	40.7	40.7	40.5	39.6	39.1	36.9*

*p<0.05, **p<0.01, compared to the control group (Dunnett's test)

Clinical chemistry: There were no treatment related changes.

Urine analysis: Dose-related higher urine volume and lower pH levels were observed in all treatment groups. The results were summarized in the following table.

Urine Parameter	Males (g/kg/day)				Females (g/kg/day)			
	0	0.65	0.90	1.2	0	0.65	0.90	1.2
pH	6.1	5.3**	5.3**	5.5**	5.4	5.1	5.2	5.1
Volume (mL)	5.3	10.4	10.5	10.0	2.1	2.5	5.7	7.8**

**p<0.01, compared to the control group (Dunnett's test)

Organ weights: Slight higher liver weights and lower thymus weights were observed in the 0.9 and 1.2 g/kg/day

group males and 1.2 g/kg/day group females. The results were summarized in the following table.

Organ Weight		Males (g/kg/day)				Females (g/kg/day)			
		0	0.65	0.9	1.2	0	0.65	0.9	1.2
Liver	g	9.35	9.97	10.64	10.10	6.35	6.45	7.0	6.98
	%	3.23	3.42	3.71**	3.82**	3.37	3.41	3.61	3.70**
Thymus	g	0.50	0.50	0.46	0.37**	0.42	0.44	0.44	0.34
	%	0.174	0.175	0.158	0.142	0.224	0.236	0.224	0.180
Adrenal	g	0.056	0.053	0.050	0.046**	0.069	0.067	0.063	0.064
	%	0.020	0.018	0.017	0.017	0.037	0.036	0.032	0.034

**p<0.01, compared to the control group (Dunnett's test)
% = relative organ weight to body weight

Gross pathology: There were no treatment related changes.

Histopathology: There were no treatment related changes.

Following information was provide in the final report of this study submitted in Amendments #021 on December 3, 2007.

Table 3. Summary of Toxicokinetic Parameters of 4-Phenylbutyric Acid in Male and Female Rats Following Oral Administration of Glyceryl Tri-(4-Phenylbutyrate) (GT4P) at Dose Levels of 650, 900 and 1200 mg/kg/day for 14 Days

4-Phenylbutyric Acid

Day	Sex	Group	Dose (mg/kg)	C_{max} (μg/mL)	T_{max} (h)	C_{last} (μg/mL)	T_{last} (h)	$t_{1/2}$ (h)	$AUC_{(0-t)}$ (μg·h/mL)	$AUC_{(0-\infty)}$ (μg·h/mL)	$AUC_{(0-t)}$ /Dose	$AUC_{(0-\infty)}$ /Dose
0	M	2A	650	245	1.0	7.89	8.0	1.6	507	526	0.8	0.8
		3A	900	289	1.0	16.0	8.0	1.7	794	832	0.9	0.9
		4A	1200	351	2.0	3.59	24.0	3.9	1719	1739	1.4	1.4
	F	2A	650	254	1.0	32.5	8.0	ND	567	ND	0.9	NA
		3A	900	360	1.0	0.599	24.0	3.5	784	787	0.9	0.9
		4A	1200	353	2.0	3.53	24.0	ND	1607	ND	1.3	NA
13	M	2A	650	74.2	1.0	8.94	8.0	ND	124	ND	0.2	NA
		3A	900	42.1	1.0	10.4	8.0	ND	143	ND	0.2	NA
		4A	1200	48.3	2.0	16.2	8.0	ND	178	ND	0.1	NA
	F	2A	650	30.7	1.0	20.2	8.0	ND	141	ND	0.2	NA
		3A	900	70.8	4.0	24.1	8.0	ND	329	ND	0.4	NA
		4A	1200	64.6	1.0	2.26	8.0	1.6	175	180	0.1	0.2

NA: Not Applicable
ND: Not Determined. Insufficient data to determine TK parameters.
Note: Toxicokinetics for GT4P, phenylbutyrylglycine and phenylbutyrylglutamine were not analyzed or reported, since most of the plasma concentrations for GT4P, phenylbutyrylglycine and phenylbutyrylglutamine were BQL.

Table 4. Summary of Toxicokinetic Parameters of Phenylacetic Acid, N-Phenylacetylglycine and Phenylacetylglutamine in Male and Female Rats Following Oral Administration of Glyceryl Tri-(4-Phenylbutyrate) (GT4P) at Dose Levels of 650, 900 and 1200 mg/kg/day for 14 Days

Phenylacetic Acid

Day	Sex	Group	Dose (mg/kg)	C_{max} (μg/mL)	T_{max} (h)	C_{last} (μg/mL)	T_{last} (h)	$t_{1/2}$ (h)	$AUC_{(0-t)}$ (μg·h/mL)	$AUC_{(0-\infty)}$ (μg·h/mL)	$AUC_{(0-t)}$ /Dose	$AUC_{(0-\infty)}$ /Dose
0	M	2A	650	147	8.0	147	8.0	ND	966	ND	1.5	NA
		3A	900	450	8.0	450	8.0	ND	2036	ND	2.3	NA
		4A	1200	406	4.0	397	8.0	ND	2530	ND	2.1	NA
	F	2A	650	209	2.0	30.2	8.0	2.1	891	982	1.4	1.5
		3A	900	217	4.0	189	8.0	ND	1355	ND	1.5	NA
		4A	1200	382	4.0	104	24.0	10.6	5346	6942	4.5	5.8
13	M	2A	650	116	1.0	114	8.0	ND	751	ND	1.2	NA
		3A	900	419	8.0	419	8.0	ND	1987	ND	2.2	NA
		4A	1200	458	8.0	458	8.0	ND	2668	ND	2.2	NA
	F	2A	650	83.8	1.0	67.9	8.0	ND	507	ND	0.8	NA
		3A	900	273	2.0	178	8.0	ND	1355	ND	1.5	NA
		4A	1200	541	8.0	541	8.0	ND	2734	ND	2.3	NA

N-Phenylacetylglycine

Day	Sex	Group	Dose (mg/kg)	C_{max} (μg/mL)	T_{max} (h)	C_{last} (μg/mL)	T_{last} (h)	$t_{1/2}$ (h)	$AUC_{(0-t)}$ (μg·h/mL)	$AUC_{(0-\infty)}$ (μg·h/mL)	$AUC_{(0-t)}$ /Dose	$AUC_{(0-\infty)}$ /Dose
0	M	2A	650	34.5	2.0	26.7	8.0	15.6	237	838	0.4	1.3
		3A	900	35.8	4.0	0.749	24.0	3.4	529	533	0.6	0.6
		4A	1200	40.3	8.0	7.18	24.0	ND	630	ND	0.5	NA
	F	2A	650	35.8	4.0	24.6	8.0	ND	236	ND	0.4	NA
		3A	900	44.4	4.0	1.98	24.0	4.4	512	524	0.6	0.6
		4A	1200	37.9	4.0	12.0	24.0	13.0	516	740	0.4	0.6
13	M	2A	650	41.2	1.0	0.495	24.0	ND	524	ND	0.8	NA
		3A	900	54.9	8.0	0.659	24.0	ND	808	ND	0.9	NA
		4A	1200	77.9	4.0	1.28	24.0	3.2	1061	1067	0.9	0.9
	F	2A	650	42.3	8.0	42.3	8.0	ND	282	ND	0.4	NA
		3A	900	64.9	4.0	0.373	24.0	2.5	894	895	1.0	1.0
		4A	1200	72.2	4.0	1.73	24.0	3.5	1041	1049	0.9	0.9

Phenylacetylglutamine

Day	Sex	Group	Dose (mg/kg)	C_{max} (μg/mL)	T_{max} (h)	C_{last} (μg/mL)	T_{last} (h)	$t_{1/2}$ (h)	$AUC_{(0-t)}$ (μg·h/mL)	$AUC_{(0-\infty)}$ (μg·h/mL)	$AUC_{(0-t)}$ /Dose	$AUC_{(0-\infty)}$ /Dose
13	M	2A	650	0.497	4.0	0.430	8.0	ND	2.35	ND	0.0	NA
		3A	900	1.59	4.0	1.35	8.0	ND	8.66	ND	0.0	NA
		4A	1200	1.89	4.0	1.26	8.0	ND	11.1	ND	0.0	NA
	F	2A	650	0.000	ND	ND	ND	ND	0.000	ND	0.0	NA
		3A	900	0.407	1.0	0.392	4.0	ND	0.799	ND	0.0	NA
		4A	1200	1.18	1.0	1.12	8.0	ND	6.75	ND	0.0	NA

NA: Not Applicable

ND: Not Determined. Insufficient data to determine TK parameters.

Note: Toxicokinetics for phenylacetylglutamine at Day 0 were not analyzed or reported, since most of the plasma concentrations for phenylacetylglutamine were BQL.

The plasma levels of GT4P were not quantifiable in most of the samples (<5 ng/ml). The main plasma metabolites detected were 4-phenylbutyric acid, phenylacetic acid, phenylacetylglutamine, and N-phenylacetylglycine following oral administration of GT4P.

13-week oral toxicity study in rats
(b) (4) 510009)

Study No: (b) (4)-510009
Conducting Laboratory and Location:
(b) (4)

Date of study initiation: July 26, 2005
Report date: April 24, 2006 (draft report date)

GLP compliance: This study was conducted in accordance with Good Laboratory Practice Regulations of the United States Food and Drug Administration (21 CFR Part 58).
QA-Report Yes () No (x). This is draft report.

Animals: Crl:CD®(SD) rats
weight: male: 252-324 g, 8 week old
female: 159-218 g, 8 weeks old
Drug lot#: 6561C

Observations and times:

- **Clinical signs**: Clinical signs of toxicity were observed daily.
- **Body weights**: Body weights were determined weekly.
- **Food consumption**: Food consumption was determined weekly.
- **Hematology:** During week 13.
- **and clinical chemistry**: at termination.
- **Urinalysis**: at termination.
- **Ophthalmologic Examination**: Before treatment and during week 13.
- **Functional observational battery**: The functional observation battery test was conducted before dosing and during weeks 0, 3, and 12. Following parameters were tested:

Arousal	Mobility
Backing	Mucous membranes/eye/skin color
Bizarre/stereotypic behavior	Muscle tone
Body temperature	Palpebral (eyelid) closure
Convulsions/tremors	Piloerection
Ease of handling animal in hand	Red/crusty deposits
Ease of removal from cage	Respiratory rate/character
Eye prominence	Rearing
Forelimb grip strength	Righting reflex
Fur appearance	Salivation
Gait	Startle response
Grooming	Tail pinch response
Lacrimation/chromodacryorrhea	Urination/defecation

-
- **Gross pathology**: Animals were necropsied at termination.
- **Organ weighed**: Organs were weighed at termination.
- **Histopathology**: Following organs or tissues were examined histopathologically from all animals from control and high groups:

Adrenal glands (2)
Aorta
Bone with marrow
  Femur
  Sternum
Bone marrow smear (femur)[a]
Brain
  Cerebrum level 1
  Cerebrum level 2
  Cerebellum with medulla/pons
Epididymides[b]
Eyes with optic nerve (2)[c]
Gastrointestinal tract
  Esophagus
  Stomach
  Duodenum
  Jejunum
  Ileum
  Cecum
  Colon
  Rectum
Harderian glands (2)
Heart
Kidneys (2)
Lacrimal glands [exorbital (2)]
Liver (sections of 2 lobes)
Lungs (including bronchi, fixed by inflation with fixative)
Lymph nodes
  Mandibular (2)
  Mesenteric
Mammary gland (females only)
Ovaries with oviducts (2)
Pancreas
Peripheral nerve (sciatic)
Pituitary
Prostate
Salivary glands
  [mandibular (2)]
Seminal vesicles (2)
Skeletal muscle (rectus femoris)
Skin
Spinal cord (cervical, midthoracic, lumbar)
Spleen
Testes (2)[b]
Thymus
Thyroid [with parathyroids, if present (2)][d]
Trachea
Urinary bladder
Uterus
Vagina
Zymbal's glands (2)
Gross lesions (when possible)

[a] - Bone marrow smears were obtained at scheduled necropsy but not placed in formalin; slides were examined only if scientifically warranted.
[b] - Fixed in Bouin's solution
[c] - Fixed in Davidson's solution
[d] - Parathyroids were examined microscopically if in the same plane of section and in all cases where a gross lesion of the parathyroid was present

-
- **Toxicokinetics**: Toxicokinetic parameters were determined on days 0 and 87 before dosing and at 1, 2, 4, 6, 8, 12, 24, and 28 hours after dosing.

Methods: GT4P was given to rats (9-10/sex/group) by oral gavage at 0, 0.65, 0.90 and 1.20 g/kg/day for 91 consecutive days. For toxicology assessment, all animals were observed twice daily for mortality and clinical signs of toxicity. Body weights and food consumption were recorded weekly. A modified functional observational battery was conducted for all animals prior to the initiation of dose administration and for 5 animals/sex during study weeks 0, 3 and 12 at 8 to 9 hours post-dosing. Ophthalmic examinations were performed during study weeks -1 and 12. Hematology, clinical chemistry, and urinalysis were performed on all animals at the scheduled necropsy (study week 13). Blood

samples for plasma amino acid profiles were collected from all animals at the scheduled necropsy. Complete necropsies were conducted on all animals, and selected organs were weighed at the scheduled necropsy. Histopathological examination was conducted from the animal found dead and from all animals in the control and the high dose groups.

Results:

Clinical Signs: Transient rigid muscle tone was noted in all test article-treated groups. Hypoactivity was also noted on the first study day in the 0.90 and 1.20 g/g/day groups. Clear material around the mouth or on the ventral trunk was noted 1 hour after dose administration in all test article-treated groups.

Mortality: There were no test article-related deaths. One control female was found dead on study day 91.

Body Weights: The initial and final body weights in the control group were 284 and 571 g for males and 187 and 290 g for females. Decreased terminal body weight gain was noted in the low (11%), mid (21%), and high (37%) dose males as compared to the control. The decreased body weight gains were noted throughout the study. Body weights for the female groups were unaffected.

Food Consumption: Average food consumption in control group was 22-29 g/rat/day for males and 17-29 g/rat/day for females. The food consumption was not clearly affected by the treatment.

Hematology: Slightly decreased red blood cell counts, hemoglobin, hematocrit, and platelet counts were noted in the treatment groups. The results are summarized in the following table.

The mean absolute values (% changes)

	control	0.65 g/kg	0.9 g/kg	1.2 g/kg
Red Blood Cell counts (mil/ul)				
Males	9.02	8.54	8.43(-7%)	8.56
Females	8.49	7.62(-10%)	7.9	7.72(-9%)
Hemoglobin (g/dl)				
Males	15.7	15.4	15.1	15.1
Females	15.8	13.9(-12%)	14.5(-8%)	14.3(-10%)
Hematocrit (%)				
Males	51.2	49.1	48.8	48.7(-5%)
females	50.3	43.5(-14%)	46.5(-8%)	45.4(-10%)
Platelet count (thous/ul)				
Males	1082	984(-9%)	924(-15%)	895(-17%)

females	994	945	1022	870(-12%)

Clinical Chemistry: Slightly higher alkaline phosphatase (ALP) values were noted in the 0.90/kg/day group females and the 0.90 and 1.20 g/kg/day group males. Lower total protein values and globulin values and higher A/G ratios were noted in the 0.65, 0.90 and 1.20 g/kg/day group males. The results are summarized in the following table.

The mean absolute values (% changes)

	control	0.65 g/kg	0.9 g/kg	1.2 g/kg
ALP (U/l)				
Males	84	110(31%)	134(60%)	163(94%)
Females	44	56	75	65
Total protein (g/dl)				
Males	7.4	6.8	6.7	6.6
Globulin (g/dl)				
Males	3.1	2.5(-19%)	2.5(-19%)	2.3(-26%)
A/G ratio				
Males	1.41	1.71(21%)	1.75(24%)	1.94(38%)

Ophthalmologic Examination: There were no treatment related changes.

Urinalysis: Higher total urine volume was observed in the 1.20 g/kg/day group females (11.8 ml) as compared to the control (6.1 ml). Lower urine pH was observed in the 0.65 g/kg/day (5.8), 0.90 g/kg/day (5.8) and 1.20 g/kg/day (5.8) groups in females as compared to the control (6.4).

Organ Weights: Higher liver weights (relative to final body weight) were noted in the 1.20 g/kg/day group in males (3.38g/100g) and in the 0.65 g/kg/day (3.44g/100g), 0.90 g/kg/day (3.49g/100g) and 1.20 g/kg/day (3.96g/100g) groups in females compared to the control group (2.99g/100g in males and 3.02g/100g in females). Liver weights (relative to brain weight) were also higher in the 1.20 g/kg/day group females (548 g/100g) as compared to the control group (418g/100g). There were no treatment related histopathologic changes in the liver.

Functional Observational Battery: There were no treatment related changes.

Gross Pathology: There were no treatment related changes.

Histopathology: There were no test article-related microscopic pathology findings.

Toxicokinetics: The results were presented in Table 7 in this report. This table is attached below.

Table 7: Pharmacokinetic Parameters: PBA

Analyte	Study Day	Sex	Dose g/kg	Half-Life hr	Tmax hr	Cmax µg/mL	Cmax/D kg*µg/mL/g	Tlast hr	Clast µg/mL	AUC Last hr*µg/mL	AUC∞ hr*µg/mL	AUC∞/D obs hr*kg*µg/mL/g	Cmax/Clast %
PBA	0	F	0.65	1.63	1	345	530	12	1.9	663	667	1026	0.5
PBA	0	F	0.9	3.30	1	387	430	24	0.3	907	909	1010	0.1
PBA	0	F	1.2	3.86	1	523	436	24	6.8	1561	1599	1332	1.3
PBA	0	M	0.65	2.68	1	410	631	24	0.7	814	817	1256	0.2
PBA	0	M	0.9	1.67	1	412	458	12	4.2	873	883	981	1.0
PBA	0	M	1.2	13.62	1	505	421	24	8.5	1831	1997	1665	1.7
PBA	87	F	0.65	4.83	1	107	164	24	0.6	193	198	304	0.6
PBA	87	F	0.9	5.12	1	110	122	24	0.4	159	162	180	0.4
PBA	87	F	1.2	4.15	1	125	104	12	8.6	246	297	248	6.9
PBA	87	M	0.65	3.71	1	47	72	24	0.3	133	135	208	0.7
PBA	87	M	0.9	4.50	1	25	28	12	4.0	105	130	145	15.7
PBA	87	M	1.2	4.45	1	64	54	24	1.1	160	167	139	1.8

Table 7 (cont).: Pharmacokinetic Parameters: PAA

Analyte	Study Day	Sex	Dose g/kg	Half-Life hr	Tmax hr	Cmax µg/mL	Cmax/D kg*µg/mL/g	Tlast hr	Clast µg/mL	AUC Last hr*µg/mL	AUC∞ hr*µg/mL	AUC∞/D obs hr*kg*µg/mL/g	Cmax/Clast %
PAA	0	F	0.65	9.05	8	478	735	12	157	3627	5672	8726	32.8
PAA	0	F	0.9	7.68	12	462	513	12	462	3939	9058	10064	100.0
PAA	0	F	1.2	3.04	6	622	519	24	19	9689	9772	8143	3.0
PAA	0	M	0.65	8.03	4	535	823	12	272	3621	6766	10410	50.8
PAA	0	M	0.9	8.04	8	538	598	12	413	4719	9513	10570	76.7
PAA	0	M	1.2	6.10	12	817	681	24	14	11420	11543	9619	1.7
PAA	87	F	0.65	5.24	4	491	756	12	160	3448	4656	7163	32.5
PAA	87	F	0.9	4.67	4	630	700	12	182	4579	5802	6447	28.8
PAA	87	F	1.2	7.37	4	734	611	12	354	5932	9698	8082	48.3
PAA	87	M	0.65	1.86	6	404	622	12	41	2651	2761	4248	10.1
PAA	87	M	0.9	6.94	8	351	390	12	143	3371	4800	5333	40.6
PAA	87	M	1.2	4.38	6	720	600	12	279	5442	7206	6005	38.7

Table 7 (cont). Pharmacokinetic Parameters: PAG

Analyte	Study Day	Sex	Dose g/kg	Half-Life hr	Tmax hr	Cmax µg/mL	Cmax/D kg*µg/mL/g	Tlast hr	Clast µg/mL	AUC Last hr*µg/mL	AUC∞ hr*µg/mL	AUC∞/D obs hr*kg*µg/mL/g	Cmax/Clast %
PAG	0	F	0.65	20.99	1	31	48	12	16.6	232	734	1128	53.7
PAG	0	F	0.9	4.69	2	33	37	24	1.1	409	416	463	3.2
PAG	0	F	1.2	12.98	2	31	26	24	9.0	463	631	526	29.2
PAG	0	M	0.65	3.70	2	40	62	24	1.6	471	480	738	3.9
PAG	0	M	0.9	2.32	1	42	47	24	0.4	559	561	623	0.9
PAG	0	M	1.2	9.51	4	37	31	24	8.8	660	780	650	23.4
PAG	87	F	0.65	2.51	6	44	67	24	0.3	548	549	845	0.8
PAG	87	F	0.9	5.61	4	57	63	48	0.3	848	851	945	0.6
PAG	87	F	1.2	5.20	4	68	57	48	0.3	1107	1109	924	0.5
PAG	87	M	0.65	3.00	4	50	77	12	10.1	395	438	675	20.1
PAG	87	M	0.9	21.22	6	48	53	12	38.2	495	1664	1849	80.1
PAG	87	M	1.2	3.83	2	83	70	24	4.0	1044	1066	889	4.8

The results indicated that phenylbutyric acid (PBA), phenylacetic acid (PAA), and N-phenylacetyl-glycine (PAG) were

detected in the plasma, suggesting that GT4P was rapidly degraded to PBA. The plasma levels of PBA, PAA, and PAG were increased with the dose. The plasma levels of PBA and PAA were lower on day 87 than those on the first day.

Key study findings:

In summary, GT4P was give by oral gavage to Crl:CD(SD) rats at 0, 0.65, 0.90 and 1.20 g/kg/day for 91 days. The results indicated that there were no treatment-related deaths. Rigid muscle tone (all treatment groups) and hypoactivity (mid and high dose groups) were observed during first few days of treatment. Decreased terminal body weight gain was noted in the low (11%), mid (21%), and high (37%) dose males as compared to the control. Body weight gain was not affected in the female groups. There were no treatment-related histopathologic findings. In conclusion, no effect dose was not identified. The dose of 0.65 g/kg/day was the maximum tolerated dose for males based on the decrease of body weight gain. The dose of 1.20 g/kg/day was tolerated in females. The central nervous system was the target organ of toxicity based on the clinical signs of toxicity.

6-Month Oral Toxicity Study in Rats

Study No: (b) (4) 671001
Conducting Laboratory and Location:
(b) (4)

Date of study initiation: February 20, 2008
Report date: March 25, 2009
GLP compliance: This study was conducted in accordance with Good Laboratory Practice Regulations of the United States Food and Drug Administration (21 CFR Part 58).
QA-Report Yes (x) No ()

Animals: Crl:CD(SD) rats
Weight: male: 233-319 g, 8 weeks old
female: 176-228 g, 8 weeks old
Drug lot#: XA171

Methods: GT4P was given to rats (15/sex/group) by oral gavage at 0 (corn oil), 650, 900, and 1200 mg/kg/day for 6 months. The test article is an undiluted colorless oil (neat). The dose selection was based on the results of the 90-day toxicity study in rats. Animals were observed for

mortality, clinical signs of toxicity, body weights, food consumption, hematology, clinical chemistry, urinalysis, organs weights, ophthalmology, gross pathology, and histopathology. The following tissues or organs were collected for histopathological examination.

Adrenals (2)
Animal ID*
Aorta
Bone with marrow
  Femur with joint
  Sternum
Bone marrow smear (from femur) [a]
Brain
  Cerebrum 2 levels
  Cerebellum with medulla/pons
Cervix
Epididymides (2) [b]
Eyes with optic nerve (2) [c]
Gastrointestinal tract
  Esophagus
  Stomach
  Duodenum
  Jejunum
  Ileum
  Cecum
  Colon
  Rectum
Harderian glands
Heart
Kidneys (2)
Lacrimal gland (exorbital [2])
Liver (sections of 2 lobes)
Lungs (including bronchi, fixed by inflation with fixative)
Lymph nodes
  Mandibular (2)
  Mesenteric
Ovaries with oviducts (2)[d]
Pancreas
Peyer's patches
Pituitary
Prostate
Salivary glands [mandibular (2)]
Sciatic Nerve
Seminal vesicles (2)
Skeletal muscle (rectus femoris)
Skin (with mammary gland)[e]
Spinal cord (cervical, thoracic, lumbar)
Spleen
Testes (2) [b]
Thymus
Thyroid [with parathyroids, if present (2)][d]
Tongue
Trachea
Urinary bladder
Uterus
Vagina
All Gross lesions (when possible)

[a] - Bone marrow smears were obtained at the scheduled necropsy and from animals euthanized in extremis, but not placed in formalin; slides were not examined.
[b] - Fixed in Bouin's solution
[c] - Fixed in Davidson's solution
[d] - Parathyroids and oviducts were examined if in the plane of section and in all cases where a gross lesion of the organ was present.
[e] - For females, a corresponding section of skin was taken from the same anatomic area for males.
* - Not examined macroscopically

Toxicokinetic parameters were determined on days 0 and 177.

Results:

Mortality: Two control males were found dead. These deaths were due to gavage-related injury. A control female was sacrificed due to moribund condition (this female had a urinary tract infection).

One high dose male was found dead on day 145 with the following histopathological changes: dilation of the right heart ventricle, congestion of the kidneys, white area/irregular shape/hepatocellular infiltration of the liver, edema of the lungs, and reddening of the thymus. The relationship of this death to treatment with the test article is uncertain, but cannot be ruled out.

Clinical Signs: Hypoactivity and rigid muscle tone were observed in the middle- and high-dose groups. Wet or dried material on the mouth, ventral neck, forelimbs, and urogenital areas and reddened ears, face, and forelimbs were noted in the treatment groups.

Body Weights: The mean body weights for control, low-, middle-, and high-dose males were 281, 283, 280, and 282 g at study initiation, and 638, 606, 558, and 538 g at termination, respectively. The mean body weights for control, low, middle-, and high-dose females were 197, 199, 199, and 198 g at study initiation, and 350, 332, 321, and 316 g at termination, respectively. The terminal body weight gain was reduced by 10%, 22%, and 28% in the low-, middle-, and high-dose males, respectively, and by 13%, 20%, and 23% in low-, middle-, and high-dose females, respectively, as compared to the control values.

Food Consumption: There were no treatment-related changes.

Ophthalmology: There were no treatment-related changes.

Hematology: Minor changes occurred in some of these parameters. These changes are not considered to be clinically significant.

Clinical Chemistry: Slight alterations of the clinical chemistry values are summarized in the following table (taken from the study report).

Text Table 1: Serum Chemistry Values Attributed to Non-Adverse Adaptive Test Article Effects Primarily on Protein Metabolism at Study Weeks 12 and 26

Dosage:	Males				Females			
HPN-100 (g/kg/day)	**0**	**0.65**	**0.90**	**1.20**	**0**	**0.65**	**0.90**	**1.20**
Alkaline Phosphatase (U/L)								
Week 12 Mean	95	**119**	**139****	**156****	61	**84**	**85***	**87***
% Difference		25.3	46.3	64.2		37.7	39.3	42.6
Week 26 Mean	69	**98***	**112****	**138****	42	60	65	61
% Difference		42.2	62.3	100.0		42.9	54.8	45.2
Alanine Aminotransferase (U/L)								
Week 12 Mean	40	**86**	73	42	45	44	**89**	**56**
% Difference		115.0	82.5	5.0		-2.2	97.8	24.4
Week 26 Mean	41	**209**	**91**	69	51	51	**127****	39
% Difference		409.8	122.0	68.3		0.0	149.0	23.5
Aspartate Aminotransferase (U/L)								
Week 12 Mean	80	152	109	82	86	78	**129**	92
% Difference		90	36.3	2.5		-9.3	50.0	7.0
Week 26 Mean	78	302	143	109	97	86	**163***	75
% Difference		287.2	83.3	39.7		-11.3	68.0	-22.7
Gamma Glutamyltansferase (U/L)								
Week 12 Mean	0.7	0.8	0.8	0.7	1.1	1.1	**1.5**	**1.5**
% Difference		14.3	14.3	0.0		0.0	36.4	36.4
Week 26 Mean	0.3	**0.9**	0.7	0.6	0.5	0.5	**1.2**	0.6
%Difference		200	133.3	100.0		0.0	140.0	20.0
Urea Nitrogen (mg/dL)								
Week 12 Mean	14.4	13.3	15.8	**16.9***	17.0	14.2*	16.2	17.4
% Difference		-7.6	9.7	17.4		-16.5	-4.7	2.4
Week 26 Mean	13.6	12.4	14.2	14.9	15.5	14.1	16.1	**18.3**
% Difference		-8.8	4.4	9.6		-9.0	3.9	18.1

* = Significantly different from the control group at 0.05 using Dunnett's test
** = Significantly different from the control group at 0.01 using Dunnett's test

Text Table 1 (continued): Serum Chemistry Values Attributed to Non-Adverse Adaptive Test Article Effects Primarily on Protein Metabolism at Study Weeks 12 and 26

Dosage:	Males				Females			
HPN-100 (g/kg/day)	0	0.65	0.90	1.20	0	0.65	0.90	1.20
Serum Total Protein (g/dL)								
Week 12 Mean	6.8	**6.5****	**6.4****	**6.3****	7.4	7.2	7.4	7.3
% Difference		-4.4	-5.9	-7.4		-2.7	0.0	-1.4
Week 26 Mean	6.9	**6.6***	**6.5****	**6.4****	7.9	7.6	7.5	7.5
% Difference		-4.3	-5.8	-7.2		-3.8	-5.1	-5.1
Globulin (g/dL)								
Week 12 Mean	2.5	**2.1****	**1.9****	**1.9****	2.4	2.2	2.3	**2.2**
% Difference		-16.0	-24.0	-24.0		-8.3	-4.2	-8.3
Week 26 Mean	2.7	2.4**	**2.1****	**2.1****	2.6	2.4	2.4	**2.3**
% Difference		-11.1	-22.2	-22.2		-7.7	-7.7	-11.5
A/G ratio								
Week 12 Mean	1.7	**2.06***	**2.34****	**2.42****	2.14	2.25	2.29	**2.34**
% Difference		21.2	37.6	42.4		5.1	7.0	9.3
Week 26 Mean	1.58	**1.84**	**2.04***	**2.17****	2.08	2.20	2.19	**2.30**
% Difference		16.5	29.1	37.3		5.8	5.3	10.6
Phosphorus (mg/dL)								
Week 12 Mean	7.1	7.4	7.5	**8.2****	6.4	6.9	6.6	**7.1**
% Difference		4.2	5.6	15.5		7.8	3.1	10.9
Week 26 Mean	6.0	6.1	6.2	6.3	5.6	5.7	5.4	**6.3***
% Difference		1.7	3.3	5.0		1.8	-3.6	12.5
Glucose (mg/dL)								
Week 12 Mean	116	**102****	**100****	**110***	118	**104****	**103****	**106***
% Difference		-12.1	-13.8	-5.2		-11.9	-12.7	-10.2
Week 26 Mean	115	**105***	**107***	**111**	110	**103**	**99***	**105**
% Difference		-8.7	-7.0	-3.5		-6.4	-10.0	-4.5
Cholesterol (mg/dL)								
Week 12 Mean	69	62	**53****	**45****	92	95	102	99
% Difference		-10.1	-23.2	-34.8		3.3	10.9	7.6
Week 26 Mean	79	70	**58****	**49****	105	99	100	**88**
% Difference		-11.4	-26.6	-38.0		-5.7	-4.8	-16.2

* = Significantly different from the control group at 0.05 using Dunnett's test
** = Significantly different from the control group at 0.01 using Dunnett's test

Text Table 3: Alterations in Serum Chemistry Values Considered Secondary Test Article Effects at Study Weeks 12 and 26

Dosage:	Males				Females			
HPN-100 (g/kg/day)	0	0.65	0.90	1.20	0	0.65	0.90	1.20
Calcium (mg/dL)								
Week 12 Mean	11.0	**10.6****	**10.7***	**10.5****	11.2	10.9	11.0	11.0
% Difference		-3.6	-2.7	-4.5		-2.7	-1.8	-1.8
Week 26 Mean	10.9	**10.4****	**10.5****	**10.3****	11.5	**10.9****	**10.8****	**10.8****
% Difference		-4.6	-3.7	-5.5		-5.2	-6.1	-6.1
Potassium (mEq/dL)								
Week 12 Mean	4.75	4.60	4.63	4.55	4.33	4.36	**3.95***	**3.95***
% Difference		-3.2	-2.5	-4.2		0.7	-8.8	-8.8
Week 26 Mean	4.60	4.63	4.76	4.63	3.97	3.96	**3.84**	**3.71**
% Difference		0.7	3.5	0.7		-0.3	-3.3	-6.5
Sodium (mEq/L)								
Week 12 Mean	144	145	144	144	144	144	143	143
% Difference		0.7	0.0	0.0		0.0	-0.7	-0.7
Week 26 Mean	145	145	144	144	144	143	143	**142****
% Difference		0.0	-0.7	-0.7		-0.7	-0.7	-1.4

* = Significantly different from the control group at 0.05 using Dunnett's test
** = Significantly different from the control group at 0.01 using Dunnett's test

Urinalysis: Lower pH was noted in the treatment groups (5.9, 5.6, and 5.6 for low-, middle-, and high-dose males, respectively) during week 12 as compared to the control males (6.3). Higher total urine volume during week 12 was noted in the treatment groups (13.7, 10.7, and 14.7 ml for low-, middle-, and high-males, respectively) as compared to the control males (5.7 ml).

Organ Weights: Minor changes in some organ weights were noted.

Gross Pathology: There were no treatment-related changes.

Histopathology: Positive staining for hemosiderin (brown pigment) in Kupffer cells (high-dose group) and in the spleen (all treatment groups) was observed. The incidence and severity of these changes were summarized in the following sponsor's table.

Text Table 5. Incidence and Grade Of Non-Adverse Hepatocellular Cytoplasmic Staining Alterations Associated with Test Article Administration. Histologic Evaluation at the Scheduled Necropsy (Study Week 26)

Dosage:	Males				Females			
HPN-100 (g/kg/day):	0	0.65	0.90	1.20	0	0.65	0.90	1.20
Liver [a]	**13**	**15**	**15**	**14**	**14**	**15**	**15**	**15**
Alteration, cytoplasmic	0	11	12	13	0	8	12	14
Minimal	0	9	5	3	0	8	11	9
Mild	0	2	7	10	0	0	1	5

[a] = Number of tissues examined from each group. Animals excluded were 2 rats found dead (control group male no. 1203; and 1.2 g/kg/day group male no. 1137) and 2 rats euthanized in extremis (control group male no. 1125; and control group female no. 1316).

Text Table 6. Incidence and Grade Of Hemosiderin (Brown Pigment) in the Spleen Associated with Test Article Administration of glyceryl tri-(4-phenylbutyrate) by Histologic Evaluation at the Scheduled Necropsy (Study Week 26)

Dosage:	Males				Females			
HPN-100 (g/kg/day):	0	0.65	0.90	1.20	0	0.65	0.90	1.20
Spleen[a]	**13**	**15**	**15**	**14**	**14**	**15**	**15**	**15**
Brown Pigment	1	3	9	13	1	6	7	10
Minimal	1	2	4	4	1	6	5	5
Mild	1	1	4	5	0	0	2	5
Moderate	0	0	1	4	0	0	0	0

[a] = Number of tissues examined from each group. Animals excluded were 2 rats found dead (control group male no. 1203; and 1.2 g/kg/day group male no. 1137) and 2 rats euthanized in extremis (control group male no. 1125; and control group female no. 1316).

Minimal to mild lymphoid depletion in the spleen (middle- and high-dose groups) was also noted.

Toxicokinetics: GT4P is quickly hydrolyzed to glycerol and phenylbutyric acid (PBA) following oral administration and has not been detected in rat plasma. Therefore, the sponsor did not measure the plasma level of GT4P in this study. The results indicated that phenylbutyric acid (PBA), phenylacetic acid (PAA), and N-phenylacetyl-glycine (PAG) were detected in plasma. The results are summarized in the following table (taken from the study report).

Text Table 7. Summary of Toxicokinetic Parameter Ranges			
Study Day	Group (mg/kg/day)	C_{max} (ng/mL)	AUC_{all} (ng·h/mL)
PBA (T_{max} = 1 hr, $t_{1/2}$ = 1.6 - 6.2 hrs)			
0	0.65	286.7 - 289.2	477.4 - 609.5
	0.90	346.8 - 387.2	799.4 - 897.2
	1.20	396.7 - 435.1	1234.5 - 1325.8
177	0.65	35.9 - 94.6	198.6 - 257.2
	0.90	40.8 - 202.2	239.1 - 370.1
	1.20	44.7 - 60.4	107.4 - 193.9
PAA (T_{max} = 2 - 6 hrs, $t_{1/2}$ = 0.8 - 11 hrs)			
0	0.65	339.2 - 419.1	3448.5 - 3673.3
	0.90	499.7 - 564.9	5070.9 -5740.4
	1.20	629.7 - 701.7	8633.6 - 9894.5
177	0.65	415.9 - 425.9	2586.8 - 2847.8
	0.90	540.8 - 623.5	4590.9 - 4974.2
	1.20	740.6 - 756.8	8597.2 - 10186.1
PAG (T_{max} = 1 - 4 hrs, $t_{1/2}$ = 2.3 – 44.5 hrs)			
0	0.65	30.2 - 32.3	276.8 - 277.2
	0.90	34.6 - 37.1	396.7 - 423.7
	1.20	29.4 - 31.8	476.3 - 480.8
177	0.65	40.1 - 45.7	403.1 - 562.4
	0.90	58.6 - 82.4	713.0 - 719.8
	1.20	71.1 - 79.5	985.2 - 1128.5

Note: The doses are incorrectly shown as 0.65, 0.9, and 1.2 mg/kg/day. The actual dose levels were 0.65, 0.9, and 1.2 g/kg/day.

In summary, GT4P was given by oral gavage to rats at 0, 650, 900, and 1200 mg/kg/day for 6 months. Treatment with GT4P reduced the terminal body weight gain by at least 10% or more in all treatment groups. Therefore, a NOAEL (no observed adverse effect level) was not established. Central nervous system was a target organ of toxicity based on the observed clinical signs of toxicity (hypoactivity and rigid muscle tone in the 900 and 1200 mg/kg/day groups). One high-dose male was found dead. This death was possibly treatment-related.

MONKEY

Study title: 14-day nasogastric intubation toxicity study with GT4P in monkeys

Key study findings: In the 14-day oral toxicity study in monkeys, cynomolgus monkeys (three/sex/group) were given GT4P at 0 (corn oil), 1, 5, and 10 g/kg/day via nasogastric intubation for the dose ranging phase. One mid dose male and one high dose female were sacrificed after the first dose due to clinical signs of toxicity including hunched posture, hypoactivity, recumbancy, labored respiration, vomitus containing food and red discharge, discharge of bright yellow fluid from the anus, and cold to the touch. On Day 2, the high and mid doses were decreased to 5 g/kg/day and 2.5 g/kg/day, respectively. The two remaining high dose females were sacrifice due to the clinical signs of toxicity. The dosing was discontinued on Day 3. Based on these results, the sponsor selected doses for GT4P at 0, 1, 2.5, and 3.5 g/kg/day for the main study. The dosing in the mid and high dose groups (2.5 and 3.5 g/kg/day) was terminated on day 9 due to clinical signs of toxicity observed in these groups. The doses for the control and low dose group (1 g/kg/day) were continued for 14 days. The doses of 2.5 g/kg/day or higher were highly toxic and the dose of 1 g/kg/day was tolerated. No effect dose was not identified. The central nervous system was the target organ of toxicity based on the clinical signs of toxicity.

Study no.: 7602-105
Volume #, and page #: 4.4 and 195
Conducting laboratory and location:
(b) (4)

Date of study initiation: February 3, 2005
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: UXW-M0001-SD-5-13-27

Species/strain: Cynomolgus monkeys (Macaca fascicularis)
Males: 2.5 - 5 years old, 2.8-4.3 kg
Females: 2.5 - 5 years old, 2.6-3.1 kg

Methods: There were two phases in this study (phase 1 and phase 2). In phase 1 (dose ranging), male and female cynomolgus monkeys (3/sex/group) were given GT4P neat at 0, 1, 5, and 10 g/kg/day via nasogastric intubation. One mid dose male and one high dose female were sacrificed after the first dose due to clinical signs of toxicity including hunched posture, hypoactivity, recumbancy, labored respiration, vomitus containing food and red discharge, discharge of bright yellow fluid from the anus, and cold to the touch. On Day 2, the high and mid doses were decreased to 5 g/kg/day and 2.5 g/kg/day, respectively. The two remaining high dose females were sacrifice due to the clinical signs of toxicity. The dosing was discontinued on Day 3. This concluded Phase 1 of the study. Surviving animals were reevaluated and assigned to Phase 2.

In Phase 2 (main study), to evaluate the toxicity of GT4P, animals were administered GT4P at doses of 0, 1, 2.5, and 3.5 g/kg/day for 14 consecutive days. The doses of 1, 2.5, and 3.5 g/kg/day were selected based on the results of phase 1 in this study. The dosing in the mid and high dose groups (2.5 and 3.5 g/kg/day) was terminated on day 9 due to clinical signs of toxicity observed in these groups (see below). The doses for the control and low dose group (1 g/kg/day) were continued for 14 days.

Following parameters were monitored: mortality, clinical observations, body weight, electrocardiographic and ophthalmic examinations, clinical pathology, and gross and histopathology. Blood samples were collected on Days 1 (Phases 1 and 2) and 14 (Phase 2) prior to dosing and at 0.5, 1, 2, 4, 8, 12, and 24 hours postdose for

toxicokinetic evaluations. An additional blood sample was collected from all animals approximately 3 hours post dose on Day 9 of Phase 2.

Results:

Mortality: Phase 1: One mid dose male and one high dose female were sacrificed after the first dose due to clinical signs of toxicity including hunched posture, hypoactivity, recumbancy, labored respiration, vomitus containing food and red discharge, discharge of bright yellow fluid from the anus, and cold to the touch. On Day 2, the high and mid doses were decreased to 5 g/kg/day and 2.5 g/kg/day, respectively. The two remaining high dose females were also sacrifice due to the clinical signs of toxicity.

Phase 2: One male and one female at 2.5 g/kg/day and one female at 3.5 g/kg/day were sacrificed on day 2 due to clinical signs of toxicity (see below). Due to clinical signs of toxicity observed in these groups (2.5 and 3.5 g/kg/day), the remaining animals were sacrificed on day 9.

Clinical signs: Phase 1: Clinical signs of toxicity prior to sacrifice included hunched posture, hypoactivity, recumbancy, labored respiration, vomitus containing food and red discharge, discharge of bright yellow fluid from the anus and cold to the touch. Hypoactivity was also observed in low dose animals.

Phase 2: Clinical signs prior to sacrifice included thin appearance, oily haircoat, oily anal discharge, hunched posture, hypoactivity, tremors, ataxia, recumbency, vomitus, red discharge of unknown source, black feces, no feces, labored and/or audible respiration, low or no food consumption, and decreased body temperature observed in the mid and high dose groups. Hunched posture, hypoactivity, vomitus containing food, low food consumption, and black feces were also observed in the low-dose (1 g/kg/day) animals.

Hypoactivity, vomitus containing food, yellow-colored feces or non-formed feces, and low food consumption were also observed in the control animals

Body weights: For phase 2 study, the initial and final body weights in the control group were 3.9 kg and 3.9 kg for males and 3.1 kg and 3.1 kg for females (from days 1 to

15). The body weight was reduced by 0.2-0.4 kg in males and 0.1-0.3 kg in females in the treatment groups (from days 1 to 8).

Ophthalmoscopy: There were no treatment related changes.

ECG: There were no treatment related changes.

Hematology: There were no treatment related changes.

Clinical chemistry: There were no treatment related changes.

Gross pathology: There were no treatment related changes.

Organ weights: There were no treatment related changes.

Histopathology: There were no treatment related changes.

Toxicokinetics: The toxicokinetic results were summarized in the following table.

Table 19: Summary of Preliminary Toxicokinetic Metrics in Monkeys that Received 1 g/kg/day of GT4P for 14 Days

Analyte	Sex	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (µg/mL)	AUC_{24} (µg·h/mL)	AUC_{∞} (µg·h/mL)
PBA	M	19.6	2.7	79.8	707	1434
PBA	F	24.6	2.7	94.9	702	1229
PAA	M	4.0	5.3	235.7	2634	2646
PAA	F	4.2	6.0	393.6	4278	4298
PAGN	M	19.9	5.3	50.4	674	1227
PAGN	F	10.3	4.7	83.6	1058	1281

Following information was provide in the final report of this study submitted in Amendments #005 and #006 on December 1, 2006 and March 9, 2007, respectively.

Text Table 1: C_{max} and AUC_{∞} for PBA on Study Day 0

Dose (g/kg)	C_{max} (µg/mL)	AUC_{∞} (hr*µg/mL)
0.65	345-410	667-817
0.9	387-412	883-909
1.2	505-523	1599-1997

Text Table 2: C_{max} and AUC_{∞} for PBA on Study Day 87

Dose (g/kg)	C_{max} (µg/mL)	AUC_{∞} (hr*µg/mL)
0.65	47-107	135-198
0.9	25-110	130-162
1.2	64-125	167-297

Text Table 3: C_{max} and AUC_{∞} for PAA on Study Day 0

Dose (g/kg)	C_{max} (µg/mL)	AUC_{∞} (hr*µg/mL)
0.65	478-535	5672-6766
0.9	462-538	9058-9513
1.2	622-817	9772-11543

Text Table 4: C_{max} and AUC_{∞} for PAA on Study Day 87

Dose (g/kg)	C_{max} (µg/mL)	AUC_{∞} (hr*µg/mL)
0.65	404-491	2761-4656
0.9	351-630	4800-5802
1.2	720-734	7206-9698

Text Table 5: C_{max} and AUC_{∞} for PAG on Study Day 0

Dose (g/kg)	C_{max} (µg/mL)	AUC_{∞} (hr*µg/mL)
0.65	31-40	480-734
0.9	33-42	416-561
1.2	31-37	631-780

13-week oral toxicity study in monkeys
((b) (4)510010)

Study No: (b) (4)510010
Conducting Laboratory and Location:
(b) (4)

Date of study initiation: August 25, 2005
Report date: April 24, 2006 (draft report date)
GLP compliance: This study was conducted in accordance with Good Laboratory Practice Regulations of the United States Food and Drug Administration (21 CFR Part 58).
QA-Report Yes () No (x). This is draft report.

Animals: Cynomolgus monkeys, 2-2.5 years old
weight: male: 1.9-2.2 kg
female: 1.8-2.1 kg
Drug lot#: 6561C

Observations and times:
- **Clinical signs:** Clinical signs of toxicity were observed daily.

- **Body weights**: Body weights were determined weekly.
- **Food consumption**: Not determined.
- **Hematology**: at termination.
- **Clinical chemistry**: at termination.
- **Urinalysis**: at termination.
- **Ophthalmologic Examination**: Before treatment and during week 13.
- **Functional observational battery**: The functional observation battery test was conducted before dosing and on days 4, 32, and 82. Following parameters were tested:

5.3.1. HOME CAGE OBSERVATIONS

General posture	Grooming/bug-picking
Head posture	Facial coloring
Gait	Abnormal behavior
Tremors	General demeanor
Scratching	Excreta
Biting	Visual tracking
Digit sucking	Retrieval of reinforcement (food/fruit)
Arousal	Response to handling
Fur appearance	

5.3.2. RESTRAINT OBSERVATIONS

Clonic convulsions	Vocalization
Tonic convulsions	Buccal movements
Pupillary reflex	Palpebral (eyelid) closure
Pupillary size	Lacrimation
Respiratory rate	Salivation
Facial coloring	Piloerection
Rectal temperature	

-
- **ECG**: ECG was determined before dosing and on study day 85.
- **Gross pathology**: Animals were necropsied at termination.
- **Organ weighed**: Organs were weighed at termination.
- **Histopathology**: Following organs or tissues were examined histopathologically from all animals from control and high groups:

Adrenal glands (2)	Lymph nodes
Aorta	Mandibular
Bone with marrow	Mesenteric
Sternum	Ovaries (2)
Bone marrow smear[a]	Oviducts (2)
Brain	Pancreas
Cerebrum level 1	Peripheral nerve (sciatic)
Cerebrum level 2	Pituitary
Cerebellum with medulla/pons	Prostate
Epididymides (2)[b]	Salivary glands [mandibular (2)]
Eyes with optic nerve (2)[c]	Seminal vesicles
Gallbladder	Skeletal muscle (rectus femoris)
Gastrointestinal tract	Skin with mammary gland
Esophagus	Spinal cord (cervical, midthoracic,
Stomach	lumbar)
Duodenum	Spleen
Jejunum	Testes (2)[b]
Ileum	Thymus
Cecum	Thyroid [with parathyroids (2)]
Colon	Trachea
Rectum	Urinary bladder
Heart	Uterus with cervix
Kidneys (2)	Vagina
Larynx	Gross lesions (when possible)
Liver (sections of 2 lobes)	
Lungs [including bronchi, fixed by inflation with fixative (2)]	

[a] - Bone marrow smears were obtained at scheduled necropsy but not placed in formalin; slides were examined only if scientifically warranted.
[b] - Fixed in Bouin's solution
[c] - Fixed in Davidson's solution

-
- **Toxicokinetics**: Toxicokinetic parameters were determined on days 0 and 87 before dosing and at 0, 1, 2, 4, 6, 8, 12, 24, and 28 hours after dosing.

Methods: GT4P was given to monkeys (4/sex/group) by nasogastric intubation at 0, 0.75, 1.25, and 1.75 g/kg/day for 91 days. The animals were observed twice daily for mortality and clinical signs of toxicity. Body weights were recorded weekly. Food consumption was not determined. Hematology, clinical chemistry, and urinalysis were performed prior to the initiation of dose administration and during study week 13. Blood samples for toxicokietic evaluation were collected from all animals on study days 0 and 87 at 0, 1, 2, 4, 8, 12, and 24 hours after dose administration. Blood samples for plasma amino acid profiles were collected from all animals on the day of the scheduled necropsy. A modified functional observational battery was conducted for all animals prior to the initiation of dose administration and on days 4, 32, and 82. Ophthalmic examinations were performed before dosing and during study week 12. Electrocardiograms were recorded before dosing and during

study week 12. Complete necropsies were performed on all animals, and selected organs were weighed at the scheduled necropsy. Histopathological examination was conducted from all animals in control and high groups.

Results:

Clinical Signs: "Inappetence" was noted in the mid and high dose males and low, mid, and high dose females mainly during the first study week.

Tremors (continuous or intermittent) were observed in 1 mid dose female and 2 high dose females. The tremor was noted approximately 1 hour after dosing and sometimes it was accompanied by hypoactivity, impaired muscle coordination, twitching, body pallor, and labored respiration.

Mortality: All animals survived to the scheduled necropsy.

Body Weights: The initial and final body weights in the control group were 1988 and 2263 g for males and 1802 and 1994 g for females. Decreased terminal body weight gain was noted in the mid (19%) and high (24%) dose males or in the mid (13%) and high dose (20%) females as compared to the control group.

Hematology: Slight lower hemoglobin, hematocrit, red blood cell, platelet and/or reticulocyte counts were noted in all treatment groups as compared to the control group. The results at week 13 are summarized in the following table.

The mean absolute values (% changes)

	control	0.75 g/kg	1.25 g/kg	1.75 g/kg
Red Blood Cell counts (mil/ul)				
Males	5.19	5.09	4.48(-14%)	4.86(-6%)
Females	5.01	4.65	4.70	4.28(-15%)
Hemoglobin (g/dl)				
Males	12.1	11.4	10.4(-14%)	11.4
Females	11.8	11.1	11.1	10.5(-11%)
Hematocrit (%)				
Males	37.3	36.6	31.8(-15%)	35.6
females	37.5	35.8	35.0	32.9(-12%)
Platelet count (thous/ul)				
Males	384	432	354	302(-21%)
females	415	317(-24%)	370(-11%)	332(-20%)
Reticulocyte counts (thous/ul)				
Males	45.6	43.9	41.5	21.2(-54%)
females	40.4	67.1	41.2	33.9(-16%)

Clinical Chemistry: There were no treatment related changes.

Ophthalmologic Examination: There were no treatment related changes.

Urinalysis: Slight lower urine pH was noted in the 1.25 g/kg/day (7.1) and 1.75 g/kg/day (5.9) groups in males or in the 0.75 g/kg/day (6.5), 1.25 g/kg/day (5.4) and 1.75 (5.4) g/kg/day groups in females as compared to the control (8.0 in males and 7.3 in females).

Organ Weights: Increase in the liver weight and decrease in thymus weight were noted. The results were presented in Text Tables 2 and 3. These tables are attached below.

Text Table 2: Test Article-Related Liver Weight Alterations
(% increase from control group values)

	Males			Females		
Dosage (g/kg/day)	0.75	1.25	1.75	0.75	1.25	1.75
Absolute	7	12	22	24	16	21
Relative to final body weight	11	25	36*	25*	19	25*
Relative to brain weight	12	16	23	32*	25	36*
Histologic correlation	Centrilobular hepatocellular hypertrophy					

*- significantly ($p < 0.05$ or 0.01, Dunnett's test) different from control group values

Text Table 3: Test Article-related Thymus Weight Alterations in Males
(% decrease from control group values)

Dosage (g/kg/day)	0.75	1.25	1.75
Absolute	38	35	36
Relative to final body weight	36	30	31
Relative to brain weight	37	36	39
Histologic correlation	Lymphoid depletion		

Functional Observational Battery: There were no treatment related changes.

Gross Pathology: Small thymus was noted in the high dose group.

Histopathology: Centrilobular hepatocellular hypertrophy (minimal to mild) was noted in all treatment groups. Mild fatty infiltrate was identified in the sternal bone marrow of males in all treatment groups and in the mid and high dose female groups. Minimal to mild lymphoid depletion was noted in all treatment male groups and the high dose females. The lymphoid depletion was characterized by a uniform diminution of size of both cortex and medulla in the thymus.

Toxicokinetics: The results were presented in Tables 7, 8, and 9 in this report. These tables are attached below.

Table 7: Pharmacokinetic Parameters: PBA Study Day 0

Dose g/kg	Sex	Animal No.	No_points Lambda z	HalfLife hr	T_{max} Hr	C_{max} ug/ml	T_{last} ug/ml	C_{last} ug/ml	AUC_{last} ug/ml*ug/ml	AUC_{∞} ug/ml*ug/ml	AUC_{∞}/D ug/ml*kg*ug/ml/mg
0.75	Female	1806	4	5.79	4	84.92	24	6.2	612.8	664.7	886.2
0.75	Female	1807	5	2.25	1	76.53	12	2.9	298.5	308.0	410.7
0.75	Female	1813	3	1.69	4	77.65	12	2.9	489.2	496.2	661.7
0.75	Female	1819	3	10.42	1	63.06	12	18.2	372.7	646.6	862.2
			Average	5.04	2.50	75.54	15.00	7.57	443.29	528.89	705.19
			St.Dev	4.02	1.73	9.11	6.00	7.27	137.57	165.48	220.65
0.75	Male	1787	5	4.77	1	117.78	12	20.2	558.8	697.7	930.2
0.75	Male	1794	4	2.54	2	119.94	12	5.9	501.8	523.3	697.8
0.75	Male	1799	3	5.73	2	89.25	12	14.7	449.8	571.2	761.6
0.75	Male	1803	3	2.87	2	57.33	24	1.1	689.4	693.9	925.2
			Average	3.98	1.75	96.08	15.00	10.45	549.97	621.52	828.70
			St.Dev	1.53	0.50	29.37	6.00	8.58	103.08	87.97	117.29
1.25	Female	1808	3	7.27	1	81.00	24	6.8	759.7	830.6	664.5
1.25	Female	1812	4	7.85	2	148.83	24	10.5	996.9	1115.3	892.2
1.25	Female	1820	3	7.00	1	37.61	24	7.3	576.8	650.6	520.5
1.25	Female	1822	3	3.99	1	58.18	24	1.5	365.8	374.5	299.6
			Average	6.53	1.25	81.40	24.00	6.51	674.78	742.72	594.18
			St.Dev	1.73	0.50	48.32	0.00	3.71	268.35	311.24	248.99
1.25	Male	1791	4	11.73	1	166.43	24	14.5	930.8	1176.2	941.0
1.25	Male	1798	5	5.13	1	84.50	12	15.7	512.3	628.8	503.0
1.25	Male	1801	5	3.93	2	195.29	24	4.1	1370.9	1394.1	1115.3
1.25	Male	1802	3	15.65	1	152.94	24	22.7	1069.8	1583.4	1266.7
			Average	9.11	1.25	149.79	21.00	14.26	970.96	1195.62	956.50
			St.Dev	5.55	0.50	46.98	6.00	7.70	356.72	412.87	330.30
1.75	Female	1811	3	6.15	2	135.97	24	6.3	917.1	972.9	555.9
1.75	Female	1814	3	9.95	1	149.62	24	11.2	895.9	1056.4	603.7
1.75	Female	1817	4	12.91	2	90.53	24	22.3	1084.4	1500.4	857.4
1.75	Female	1821	3	7.89	1	58.21	24	10.8	783.5	906.4	517.9
			Average	9.22	1.50	108.58	24.00	12.65	920.23	1109.02	633.73
			St.Dev	2.90	0.58	42.02	0.00	6.83	124.18	268.06	153.18
1.75	Male	1789	5	10.92	2	111.24	24	21.3	1078.1	1413.9	808.0
1.75	Male	1790	4	15.93	1	179.20	24	33.0	1444.9	2202.9	1258.8
1.75	Male	1793	3	8.78	1	79.18	24	13.1	878.5	1044.2	596.7
1.75	Male	1795	3	32.43	2	189.60	24	20.4	1150.3	2104.2	1202.4
			Average	17.01	1.50	139.81	24.00	21.95	1137.93	1691.31	966.46
			St.Dev	10.71	0.58	53.30	0.00	8.23	234.68	556.14	317.79

Table 7 (cont).: Pharmacokinetic Parameters: PBA Study Day 87

Dose g/kg	Sex	Animal No.	No_points Lambda z	HalfLife hr	T_{max} Hr	C_{max} ug/ml	T_{last} ug/ml	C_{last} ug/ml	AUC_{last} ug/ml*ug/ml	AUC_{∞} ug/ml*ug/ml	AUC_{∞}/D ug/ml*kg*ug/ml/mg
0.75	Female	1806	3	4.33	1	61.88	24	1.8	454.0	465.1	620.1
0.75	Female	1807	3	2.17	1	56.26	12	2.7	270.7	279.0	372.0
0.75	Female	1813	6	3.87	1	81.38	24	1.4	545.4	553.4	737.8
0.75	Female	1819	3	3.76	2	44.98	24	1.1	345.6	351.7	468.9
			Average	3.53	1.25	61.12	21.00	1.75	403.90	412.28	549.71
			St.Dev	0.94	0.50	15.22	6.00	0.67	120.65	121.29	161.72
0.75	Male	1787	3	6.23	1	111.61	24	11.0	983.9	1083.1	1444.2
0.75	Male	1794	4	7.51	2	53.19	12	19.0	378.3	584.4	779.2
0.75	Male	1799	6	5.17	1	75.73	24	2.6	579.9	599.2	798.9
0.75	Male	1803	6	6.19	1	58.48	24	3.2	604.6	633.4	844.6
			Average	6.28	1.25	74.75	21.00	8.97	636.69	725.03	966.70
			St.Dev	0.96	0.50	26.39	6.00	7.72	252.72	239.63	319.50
1.25	Female	1808	4	13.15	4	65.41	24	17.9	653.0	992.1	793.7
1.25	Female	1812	4	16.58	2	96.01	24	11.9	724.2	1008.1	806.5
1.25	Female	1820	4	17.22	2	67.09	24	14.8	704.4	1071.0	856.8
1.25	Female	1822	3	3.91	2	41.17	24	1.1	344.9	351.3	281.1
			Average	12.71	2.50	67.42	24.00	11.41	606.62	855.64	684.51
			St.Dev	6.14	1.00	22.44	0.00	7.27	177.06	337.92	270.34
1.25	Male	1791	3	63.06	8	20.10	24	16.6	381.2	1887.7	1510.2
1.25	Male	1798	6	4.39	1	78.01	24	1.9	500.4	512.7	410.2
1.25	Male	1801	3	6.39	1	90.64	24	6.5	700.7	760.6	608.4
1.25	Male	1802	6	22.68	1	44.66	24	16.2	516.4	1044.9	835.9
			Average	24.13	2.75	58.35	24.00	10.29	524.70	1051.48	841.18
			St.Dev	27.22	3.50	32.04	0.00	7.25	131.93	598.40	478.72
1.75	Female	1811	4	8.61	1	158.78	24	8.3	865.4	968.2	553.3
1.75	Female	1814	4	6.97	2	81.82	24	5.7	582.8	640.5	366.0
1.75	Female	1817	3	52.82	1	61.78	24	29.1	809.7	3029.7	1731.2
1.75	Female	1821	4	79.70	2	37.51	24	15.4	449.6	2217.2	1267.0
			Average	37.03	1.50	84.97	24.00	14.63	676.87	1713.89	979.36
			St.Dev	35.50	0.58	52.43	0.00	10.49	194.64	1109.48	633.99
1.75	Male	1789	4	4.78	4	128.20	24	6.3	1192.0	1235.3	705.9
1.75	Male	1790	4	12.50	2	79.13	24	16.9	832.2	1137.5	650.0
1.75	Male	1793	3	11.93	1	132.63	24	8.3	812.9	955.5	546.0
1.75	Male	1795	6	6.79	1	122.48	24	13.4	867.1	998.7	570.7
			Average	9.00	2.00	115.61	24.00	11.23	926.03	1081.75	618.14
			St.Dev	3.81	1.41	24.67	0.00	4.85	178.70	128.50	73.43

Table 8 Pharmacokinetic Parameters: PAA Study Day 0

Dose g/kg	Sex	Animal No.	No_points Lambda z	HalfLife hr	T_{max} hr	C_{max} ug/ml	T_{last} hr	C_{last} ug/ml	AUC_{last} hr*ug/ml	AUC_{∞} hr*ug/ml	AUC_{∞}/D hr*kg*ug/ml/mg
0.75	Female	1806	3.0	2.04	8	381.09	24	2.14	4421.26	4427.54	5903.39
0.75	Female	1807	3.0	1.15	4	288.55	12	2.33	1808.91	1812.77	2417.03
0.75	Female	1813	3.0	3.72	4	293.14	12	65.96	2277.99	2631.73	3508.97
0.75	Female	1819	3.0	1.95	4	172.57	12	10.08	1266.54	1294.91	1726.55
			Average	2.21	5	283.84	15	20.12	2443.68	2541.74	3388.98
			St. Dev.	1.08	2	85.53	6	30.78	1381.65	1372.38	1829.84
0.75	Male	1787	3.0	1.80	4	321.90	12	14.78	2144.24	2182.62	2910.17
0.75	Male	1794	3.0	1.10	4	298.28	12	1.89	1897.12	1900.10	2533.47
0.75	Male	1799	3.0	3.21	4	440.22	12	78.12	3021.12	3382.57	4510.09
0.75	Male	1803	3.0	3.89	4	88.01	24	1.11	521.94	528.14	704.18
			Average	2.50	4	287.10	15	23.97	1896.10	1998.36	2664.48
			St. Dev.	1.28	0	146.53	6	36.64	1035.30	1172.06	1562.75
1.25	Female	1808	3.0	2.34	4	499.55	24	5.14	6377.34	6394.72	5115.77
1.25	Female	1812	3.0	9.38	8	654.65	24	212.03	10746.83	13615.74	10892.59
1.25	Female	1820	3.0	1.93	8	244.61	24	1.08	3051.52	3054.53	2443.62
1.25	Female	1822	3.0	1.61	2	92.12	12	2.82	565.51	572.07	457.66
			Average	3.82	6	372.73	21	55.27	5185.30	5909.26	4727.41
			St. Dev.	3.72	3	252.14	6	104.52	4406.32	5664.52	4531.62
1.25	Male	1791	3.0	13.00	4	550.77	24	236.86	9729.14	14172.28	11337.83
1.25	Male	1798	3.0	4.67	4	227.64	12	69.51	1946.22	2414.96	1931.97
1.25	Male	1801	3.0	16.45	4	663.10	12	473.35	5922.15	17155.88	13724.71
1.25	Male	1802	3.0	42.89	8	569.83	24	415.13	10331.69	36018.73	28814.99
			Average	19.25	5	502.84	18	298.71	6982.30	17440.47	13952.37
			St. Dev.	16.51	2	189.91	7	182.95	3883.71	13924.56	11139.64
1.75	Female	1811	3.0	6.50	8	766.12	24	152.82	11836.58	13270.47	7583.12
1.75	Female	1814	3.0	7.36	8	686.41	24	157.67	10079.42	11752.58	6715.76
1.75	Female	1817	3.0	21.65	8	395.70	24	242.37	7580.72	15149.65	8656.94
1.75	Female	1821	0.0	N/A	12	324.48	24	159.71	5542.77	N/A	N/A
			Average	11.84	9	543.18	24	178.14	8759.87	13390.90	7651.94
			St. Dev.	8.51	2	215.87	0	42.91	2765.71	1701.73	972.42
1.75	Male	1789	3.0	5.46	8	683.70	24	90.08	8990.32	9699.29	5542.45
1.75	Male	1790	3.0	20.67	8	607.98	24	353.57	10531.54	21075.25	12043.00
1.75	Male	1793	3.0	4.34	8	269.11	24	24.85	4270.26	4425.80	2529.03
1.75	Male	1795	3.0	31.08	8	880.11	24	616.48	16754.64	44396.33	25369.33
			Average	15.39	8	610.22	24	271.25	10136.69	19899.17	11370.95
			St. Dev.	12.84	0	254.69	0	270.49	5153.71	17747.84	10141.62

Table 8 (cont). Pharmacokinetic Parameters: PAA Study Day 87

Dose g/kg	Sex	Animal No.	No_points Lambda z	HalfLife hr	T_{max} hr	C_{max} ug/ml	T_{last} hr	C_{last} ug/ml	AUC_{last} hr*ug/ml	AUC_{∞} hr*ug/ml	AUC_{∞}/D hr*kg*ug/ml/mg
0.75	Female	1806	3.0	2.46	4	377.84	12	39.79	2421.61	2563.05	3417.40
0.75	Female	1807	3.0	1.03	2	64.88	8	1.24	191.92	193.78	258.37
0.75	Female	1813	3.0	1.79	4	494.21	24	1.07	5084.28	5087.05	6782.74
0.75	Female	1819	4.0	1.63	2	54.68	12	1.21	253.64	256.48	341.97
			Average	1.73	3	247.90	14	10.83	1987.86	2025.09	2700.12
			St. Dev.	0.59	1	222.40	7	19.31	2310.04	2319.97	3093.29
0.75	Male	1787	3.0	4.53	2	136.94	24	1.41	720.48	729.69	972.92
0.75	Male	1794	3.0	1.95	2	30.97	8	3.07	83.37	92.00	122.67
0.75	Male	1799	4.0	1.59	2	167.67	12	2.99	758.02	764.88	1019.84
0.75	Male	1803	3.0	7.24	2	66.35	24	1.34	299.56	313.53	418.04
			Average	3.83	2	100.48	17	2.20	465.36	475.02	633.37
			St. Dev.	2.62	0	62.83	8	0.96	328.71	327.44	436.59
1.25	Female	1808	3.0	6.51	8	597.12	24	114.39	8340.25	9414.72	7531.78
1.25	Female	1812	4.0	2.59	4	361.54	24	1.86	2407.49	2414.42	1931.54
1.25	Female	1820	3.0	4.74	4	191.34	24	1.29	902.54	911.33	729.06
1.25	Female	1822	4.0	1.73	2	87.06	12	2.28	277.20	282.89	226.31
			Average	3.89	5	309.27	21	29.95	2981.87	3255.84	2604.67
			St. Dev.	2.16	3	222.76	6	56.29	3682.44	4202.18	3361.75
1.25	Male	1791	7.0	3.41	0	406.15	24	6.80	2000.02	2033.50	1626.80
1.25	Male	1798	3.0	1.28	2	179.11	12	2.02	1041.84	1045.57	836.46
1.25	Male	1801	4.0	1.54	2	174.73	12	2.44	597.47	602.91	482.33
1.25	Male	1802	4.0	2.79	4	664.19	24	4.92	6328.49	6348.31	5078.64
			Average	2.26	2	356.04	18	4.04	2491.96	2507.57	2006.06
			St. Dev.	1.01	2	232.12	7	2.24	2623.79	2629.40	2103.52
1.75	Female	1811	3.0	6.82	8	989.95	24	205.42	15954.29	17976.33	10272.19
1.75	Female	1814	3.0	1.83	8	569.11	24	1.95	7979.12	7984.27	4562.44
1.75	Female	1817	3.0	48.22	2	93.87	24	7.85	454.70	1000.71	571.83
1.75	Female	1821	3.0	2.52	4	286.96	24	3.69	3934.97	3948.41	2256.23
			Average	14.85	6	484.97	24	54.73	7080.77	7727.43	4415.67
			St. Dev.	22.36	3	389.12	0	100.49	6667.01	7408.00	4233.15
1.75	Male	1789	3.0	1.94	4	492.36	24	1.59	4948.87	4953.33	2830.47
1.75	Male	1790	3.0	2.40	4	265.74	24	1.51	2213.28	2218.49	1267.71
1.75	Male	1793	3.0	4.83	8	805.41	24	87.11	11529.22	12135.74	6934.71
1.75	Male	1795	3.0	8.47	8	796.56	24	220.20	12249.60	14939.99	8537.14
			Average	4.41	6	590.01	24	77.60	7735.24	8561.89	4892.51
			St. Dev.	2.99	2	260.61	0	103.27	4933.88	5964.14	3408.08

Table 9 Pharmacokinetic Parameters: PAGN Study Day 0

Dose g/kg	Sex	Animal No.	No_points Lambda z	HalfLife hr	T_{max} hr	C_{max} ug/ml	T_{last} hr	C_{last} ug/ml	AUC_{last} hr*ug/ml	AUC_{∞} hr*ug/ml	AUC_{∞}/D hr*kg*ug/ml/mg
0.75	Female	1806	0	N/A	12	50.5	24	9.3	837.3	N/A	N/A
0.75	Female	1807	4	4.84	4	48.9	24	3.2	497.2	519.3	692.3
0.75	Female	1813	3	5.72	4	34.7	24	5.0	556.0	597.5	796.7
0.75	Female	1819	3	3.93	8	41.8	24	2.6	554.1	568.7	758.2
			Average	4.8	7.0	43.9	24.0	5.0	611.2	561.8	749.1
			St. Dev.	0.9	3.8	7.2	0.0	3.1	153.2	39.6	52.8
0.75	Male	1787	3	5.04	4	81.4	24	7.9	1052.9	1110.4	1480.5
0.75	Male	1794	5	4.71	2	46.9	24	2.5	464.5	481.7	642.3
0.75	Male	1799	3	3.34	4	58.1	24	2.3	819.7	830.5	1107.4
0.75	Male	1803	3	5.45	4	53.2	24	5.3	645.4	686.8	915.7
			Average	4.6	3.5	59.9	24.0	4.5	745.6	777.4	1036.5
			St. Dev.	0.9	1.0	15.1	0.0	2.7	251.0	264.2	352.2
1.25	Female	1808	3	8.89	8	46.5	24	14.6	828.5	1015.5	812.4
1.25	Female	1812	4	15.12	4	71.5	24	28.1	1181.0	1793.7	1434.9
1.25	Female	1820	3	5.01	8	41.2	24	5.3	685.4	723.5	578.8
1.25	Female	1822	4	5.87	4	33.9	24	3.4	379.2	408.4	326.7
			Average	8.7	6.0	48.3	24.0	12.8	768.5	985.2	788.2
			St. Dev.	4.6	2.3	16.3	0.0	11.3	332.8	593.2	474.6
1.25	Male	1791	4	31.18	4	35.5	24	23.0	652.2	1686.3	1349.1
1.25	Male	1798	3	3.31	4	56.3	24	2.2	828.5	839.0	671.2
1.25	Male	1801	3	3.01	8	99.7	24	3.1	1496.6	1509.9	1207.9
1.25	Male	1802	0	N/A	12	61.2	24	55.2	1324.6	N/A	N/A
			Average	12.5	7.0	63.2	24.0	20.9	1075.5	1345.1	1076.1
			St. Dev.	16.2	3.8	26.8	0.0	24.8	399.8	447.1	357.7
1.75	Female	1811	0	N/A	12	55.1	24	25.1	989.4	N/A	N/A
1.75	Female	1814	0	N/A	12	65.7	24	36.1	1274.5	N/A	N/A
1.75	Female	1817	3	14.74	8	50.0	24	23.9	886.5	1394.3	796.8
1.75	Female	1821	3	17.25	8	34.6	24	18.6	635.0	1097.0	626.9
			Average	16.0	10.0	51.4	24.0	25.9	946.4	1245.7	711.8
			St. Dev.	1.8	2.3	13.0	0.0	7.4	264.6	210.2	120.1
1.75	Male	1789	0	N/A	12	90.2	24	37.2	1607.0	N/A	N/A
1.75	Male	1790	3	33.84	8	74.1	24	53.7	1489.5	4112.7	2350.1
1.75	Male	1793	0	N/A	12	47.7	24	29.1	941.2	N/A	N/A
1.75	Male	1795	0	N/A	12	79.3	24	48.2	1420.6	N/A	N/A
			Average	33.8	11.0	72.8	24.0	42.1	1364.6	4112.7	2350.1
			St. Dev.	N/A	2.0	18.1	0.0	11.0	292.5	N/A	N/A

Table 9 (cont). Pharmacokinetic Parameters: PAGN Study Day 87

Dose g/kg	Sex	Animal No.	No_points Lambda z	HalfLife hr	T_{max} hr	C_{max} ug/ml	T_{last} hr	C_{last} ug/ml	AUC_{last} hr*ug/ml	AUC_{∞} hr*ug/ml	AUC_{∞}/D hr*kg*ug/ml/mg
0.75	Female	1806	3	3.69	8	77.2	24	4.4	1073.5	1096.7	1462.3
0.75	Female	1807	3	20.49	2	43.1	24	3.4	291.5	393.4	524.6
0.75	Female	1813	3	4.57	4	67.7	24	5.2	877.2	911.3	1215.0
0.75	Female	1819	5	5.20	2	42.4	24	2.3	317.5	334.8	446.3
			Average	8.5	4.0	57.6	24.0	3.8	639.9	684.0	912.1
			St. Dev.	8.0	2.8	17.6	0.0	1.2	395.7	377.9	503.8
0.75	Male	1787	4	6.98	4	93.6	24	13.1	1157.1	1289.2	1719.0
0.75	Male	1794	3	6.39	2	34.7	24	2.5	302.3	325.8	434.4
0.75	Male	1799	4	4.60	4	60.3	24	2.9	616.8	636.2	848.3
0.75	Male	1803	4	7.68	4	62.3	24	9.2	799.9	901.4	1201.9
			Average	6.4	3.5	62.7	24.0	6.9	719.0	788.2	1050.9
			St. Dev.	1.3	1.0	24.1	0.0	5.1	357.1	408.6	544.7
1.25	Female	1808	3	22.65	8	95.5	24	55.8	1667.3	3492.0	2793.6
1.25	Female	1812	4	6.31	4	119.4	24	13.6	1346.8	1470.2	1176.2
1.25	Female	1820	4	7.00	4	68.3	24	8.9	852.7	942.8	754.3
1.25	Female	1822	5	6.51	2	48.2	24	4.5	431.6	474.0	379.2
			Average	10.6	4.5	82.8	24.0	20.7	1074.6	1594.7	1275.8
			St. Dev.	8.0	2.5	31.2	0.0	23.7	544.1	1328.7	1062.9
1.25	Male	1791	4	14.98	4	62.8	24	23.6	774.5	1285.0	1028.0
1.25	Male	1798	4	4.48	4	95.0	24	4.8	878.7	909.7	727.8
1.25	Male	1801	6	5.73	1	75.3	24	4.6	640.6	678.3	542.7
1.25	Male	1802	3	7.08	4	137.4	24	31.2	2423.1	2742.5	2194.0
			Average	8.1	3.3	92.6	24.0	16.1	1179.2	1403.9	1123.1
			St. Dev.	4.7	1.5	32.6	0.0	13.5	835.0	926.7	741.4
1.75	Female	1811	3	10.62	8	153.0	24	56.2	2733.0	3594.4	2054.0
1.75	Female	1814	3	3.54	4	123.0	24	5.4	1848.1	1875.5	1071.7
1.75	Female	1817	3	66.44	2	49.2	24	27.7	797.4	3451.8	1972.5
1.75	Female	1821	5	11.34	2	146.9	24	36.8	2011.9	2613.7	1493.6
			Average	23.0	4.0	118.1	24.0	31.5	1847.6	2883.9	1647.9
			St. Dev.	29.2	2.8	47.7	0.0	21.1	798.7	799.4	456.8
1.75	Male	1789	3	3.56	4	199.4	24	8.6	2818.5	2862.8	1635.9
1.75	Male	1790	4	6.83	4	132.9	24	17.7	1770.7	1945.4	1111.7
1.75	Male	1793	4	17.84	4	136.6	24	53.9	2249.0	3636.1	2077.8
1.75	Male	1795	0	N/A	12	169.5	24	75.4	3200.3	N/A	N/A
			Average	9.4	6.0	159.6	24.0	38.9	2509.6	2814.8	1608.4
			St. Dev.	7.5	4.0	31.2	0.0	31.2	628.8	846.4	483.6

The results indicated that phenylbutyric acid (PBA), phenylacetic acid (PAA), and phenylacetylglutamine (PAGN) were detected in the plasma, suggesting that GT4P was rapidly degraded to PBA. The plasma levels of PBA, PAA, and PAGN were increased with the dose. There was no drug accumulation over time. The maximum plasma level of PBA on the first day of dosing at 1.25 g/kg/day was 81 µg/ml in females or 150 µg/ml in males. In the phase I clinical trial in healthy volunteers with GT4P, the maximum plasma level of PBA following a single dose of GT4P at 78.9 mg/kg was 37 µg/ml.

In summary, GT4P was given by nasogastric intubation to cynomolgus monkeys at 0, 0.75, 1.25 and 1.75 g/kg/day for 91 days. All animals survived to the scheduled termination. Tremors (continuous or intermittent) were observed in 1 mid dose

female and 2 high dose females. The tremor was sometimes accompanied by hypoactivity, impaired muscle coordination, twitching, body pallor, and labored respiration. Decreased terminal body weight gain was noted in the mid (19%) and high (24%) dose males or in the mid (13%) and high dose (20%) females as compared to the control group. Pathological examination revealed small thymus (high dose males) and minimal to mild lymphoid depletion (all treatment male groups and the high dose females). Histopathological examination also revealed centrilobular hepatocellular hypertrophy (all treatment groups) and mild fatty infiltration in the sternal bone marrow (all treatment male groups and the mid and high dose female groups). No effect dose was not identified. The dose of 1.25 g/kg/day was close to or slightly higher than the maximum tolerated dose based on the reduction of body weight gain and clinical signs of toxicity. The central nervous system was the target organ of toxicity based on the clinical signs of toxicity.

Following information was provide in the final report of this study submitted in Amendments #005 and #006 on December 1, 2006 and March 9, 2007, respectively.

Table 5: Average C_{max} and AUC_{∞} for PBA on Study Day 0

Dose g/kg	C_{max} (µg/mL)	AUC_{∞} hr*µg/mL
0.75	76-96	529-622
1.25	81-150	743-1196
1.75	109-140	1109-1677

Table 6: Average C_{max} and AUC_{∞} for PBA on Study Day 89

Dose g/kg	C_{max} µg/mL	AUC_{∞} hr*µg/mL
0.75	61-75	412-725
1.25	58-67	856-1051
1.75	85-116	1082-1714

Table 7: Average Cmax and AUC_∞ for PAA on Study Day 0

Dose g/kg	C_{max} (µg/mL)	AUC_∞ hr*µg/mL
0.75	284-287	1998-2542
1.25	373-503	5909-17440
1.75	543-610	13391-19862

Table 8: Average Cmax and AUC_∞ for PAA on Study Day 89

Dose g/kg	C_{max} µg/mL	AUC_∞ hr*µg/mL
0.75	101-248	475-2025
1.25	309-356	2508-3256
1.75	485-590	7727-8562

Table 9: Average Cmax and AUC_∞ for PAGN on Study Day 0

Dose g/kg	C_{max} (µg/mL)	AUC_∞ hr*µg/mL
0.75	44-60	562-777
1.25	48-63	985-1345
1.75	51-73	1246-4113

Table 10: Average Cmax and AUC_∞ for PAGN on Study Day 89

Dose g/kg	C_{max} µg/mL	AUC_∞ hr*µg/mL
0.65	58-63	684-788
0.9	83-93	1404-1595
1.2	118-160	2815-2884

A 12-month oral toxicity study in Monkeys

Study title: A 12-month oral toxicity study in Monkeys

Study no.:	(b) (4) 671002
Study report location:	N/A
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 27, 2008
GLP compliance:	YES
QA statement:	YES
Drug, lot #, and % purity:	Glyceryl Tri (4-Phenylbutyrate), Lot no. XA171 / 98.8-101.2%

Key Study Findings

Methods

Doses:	0.7, 1.1, and 1.5 g/kg/day (corn oil administered to control group)
Frequency of dosing:	daily
Route of administration:	Oral via nasogastric intubation
Dose volume:	0.64, 1.0, and 1.36 mL/kg for low, middle, and high dose groups
Formulation/Vehicle:	Neat liquid
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	8/sex/group 4/sex/group were necripsied at 26 weeks
Age:	2-4 years old at initiation
Weight:	1974 g to 3468 g for the males and 1912 g to 2705 g for the females at initiation
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	There were no deviations that affected the outcome of this study.

Hypoactivity, hunched posture, thinness, impaired equilibrium, increased respiration rate, pallor, and cool to touch were observed in the high dose group. Bodyweight at study termination was decreased in males in all drug-treated groups, compared to the control value. Reductions (~5-10%) in red blood cell count, hemoglobin, and hematocrit occurred in the middle and high dose groups. Liver weight (absolute and relative) was increased in all treatment groups at weeks 26 and 52, and this change was associated with hepatocellular hypertrophy. At the 26-week and 52-week sacrifice, most of the drug-treated animals exhibited hepatocellular hypertrophy, with dose-dependent severity.

Observations and Results

Mortality: All animal survived to termination.

Clinical Signs:

Hypoactivity, hunched posture, thinness and body pale and/or cool to touch, impaired equilibrium, and increased respiration rate were observed in several animals in the high dose group.

Body Weights: The initial body weights were 2591, 2657, 2551, and 2542 g in males and 2220, 2223, 2181, and 2201 g in females in the control, low, middle, and high dose groups, respectively. **.** The mean body weight of the control males and females at study termination was 3861 g and 2885 g, respectively.

At termination, the mean body weights were ~14%, 8% and 22% lower than the control group values for the low, mid, and high dose groups in males, respectively, and 10% lower than the control group values for the high dose females.

Feed Consumption: Not determined.

Ophthalmoscopy: There were no treatment related changes.

ECG: There were no treatment related changes.

Hematology:

Decreased red blood cell counts, hemoglobin, and hematocrit and increased reticulocyte counts were noted mainly in the middle and high dose groups at study weeks 12 and 25. The results were summarized in the sponsor's table below.

Text Table 2: Test Article-Related Alterations in Red Blood Cell Hematologic Parameters

Dosage	Males				Females			
HPN-100 (g/kg/day)	0	0.70	1.1	1.5	0	0.70	1.1	1.5
Red Blood Cells (mil/µL)								
Week -2 Mean	5.37	5.58	5.66	5.49	5.38	5.69	5.29	5.45
% Difference		3.9	5.4	2.2		5.8	-1.7	1.3
Week 12 Mean	5.69	5.81	5.56	**5.13****	5.77	5.73	**5.28**	**5.33**
% Difference		2.1	-2.3	-9.8		-0.7	-8.5	-7.6
Week 25 Mean	5.47	5.60	5.36	**5.05***	5.60	5.61	**5.20**	**5.36**
% Difference		2.4	-2.0	-7.7		0.2	-7.1	-4.3
Week 51 Mean	5.43	5.55	5.57	5.23	5.37	5.79	5.22	**4.87**
% Difference		2.2	2.6	-3.7		7.8	-2.8	-9.3
Hemoglobin (g/dL)								
Week -2 Mean	13.0	13.2	13.4	13.3	12.9	13.3	12.7	13.2
% Difference		1.5	3.1	2.3		3.1	-1.6	2.3
Week 12 Mean	13.6	13.6	13.2	**12.6***	13.6	13.3	**12.6**	**12.9**
% Difference		0.0	-2.9	-7.4		-2.2	-7.4	-5.1
Week 25 Mean	13.5	13.6	13.1	**12.6***	13.4	13.3	12.8	13.2
% Difference		0.7	-3.0	-6.7		-0.7	-4.5	-1.5
Week 51 Mean	13.7	13.2	14.1	13.6	13.4	14.1	12.9	12.5
% Difference		-3.6	2.9	-0.7		5.2	-3.7	-6.7
Hematocrit (%)								
Week -2 Mean	40.7	41.3	42.5	42.1	40.0	41.6	40.1	41.8
% Difference		1.5	4.4	3.4		4.0	0.3	4.5
Week 12 Mean	41.8	41.3	40.7	**38.6**	42.0	41.2	**38.8**	**39.7**
% Difference		-1.2	-2.6	-7.7		-1.9	-7.6	-5.5
Week 25 Mean	41.5	41.3	40.5	**39.3**	41.9	41.8	39.8	41.5
% Difference		-0.5	-2.4	-5.3		-0.2	-5.0	-1.0
Week 51 Mean	42.1	40.3	43.1	42.9	41.1	44.5	39.8	38.5
% Difference		-4.3	2.4	1.9		8.3	-3.2	-6.3
Reticulocyte (thous/µL)								
Week -2 Mean	58.7	57.5	63.6	62.9	71.7	59.1	62.1	65.1
% Difference		-2.0	8.3	7.2		-17.6	-13.4	-9.2
Week 12 Mean	50.0	45.8	45.9	**77.8**	62.1	63.9	43.3	53.5
% Difference		-8.4	-8.2	55.6		2.9	-30.3	-13.8
Week 25 Mean	45.7	48.0	61.9	**68.4***	55.1	65.7	54.6	68.3
% Difference		5.0	35.4	49.7		19.2	-0.9	24.0
Week 51 Mean	44.1	50.5	67.2*	66.2*	62.1	82.7	44.9	70.0
% Difference		14.5	52.4	50.1		33.2	-27.7	12.7

* = Significantly different from the control group at 0.05 using Dunnett's test
** = Significantly different from the control group at 0.01 using Dunnett's test

Clinical Chemistry: Marginal alterations were observed, but these were not treatment related.

Urinalysis: Slightly lowered pH and higher ketone level were noted in all treatment groups as compared to the control group.

Gross Pathology: There were no treatment related changes.

Organ Weights: Increased liver and kidney weights were noted in the treatment groups. The results were summarized in the sponsor's table below.

Text Table 3: Body and Organ Weight Changes Associated with Test Article Administration

Dosage	Males				Females			
HPN-100 (g/kg/day)	0	0.7	1.1	1.5	0	0.7	1.1	1.5
Final Body Weight (Kg)								
Week 26	3576	**3292**	**2919**	**2708**	2708	**2655**	**2523**	**2438**
% Difference		-7.9	-18.4	-24.3		-2.0	-6.8	-10.0
Week 52	3861	**3328**	**3535**	**3019**	2885	**2813**	**2586**	**2586**
% Difference		-13.8	-8.4	-21.8		-2.5	-10.4	-10.4
Liver Weight (g)								
Week 26								
Absolute weight	62.8	**76.0**	**73.8**	**79.6**	53.6	**63.6**	**64.1**	**77.2****
% Difference		21.0	17.4	26.6		18.8	19.6	44.2
Relative to Body	1.76	**2.32****	**2.54 ****	**2.96****	1.99	**2.39**	**2.54**	**3.21****
% Difference		31.9	44.6	68.8		20.2	27.7	61.3
Relative to Brain	86.89	**113.42**	**107.63**	**128.5****	83.09	**105.68**	**109.61**	**139.8****
% Difference		**30.5**	**23.9**	47.9		**27.2**	**31.9**	68.3
Week 52								
Absolute weight	67.95	**70.82**	**91.96**	90.39	54.65	**65.25**	**71.31**	73.64
% Difference		**4.2**	**35.3**	33.0		**19.4**	**30.5**	34.7
Relative to Body	1.74	**2.13**	**2.60****	2.98**	1.886	**2.324***	**2.750****	2.866**
% Difference		**22.0**	**49.3**	71.2		**23.2**	**45.8**	52.0
Relative to Brain	95.55	**101.87**	**143.93***	146.06**	85.64	**102.45**	**120.56***	130.67**
% Difference		**6.6**	**50.6**	52.9		**19.6**	**40.8**	52.6
Kidney Weight (g)								
Week 26								
Absolute weight	13.67	**16.05**	**13.84**	14.79	11.20	**11.91**	**12.77**	12.07
% Difference		**17.4**	**1.2**	8.2		**6.3**	**14.0**	7.8
Relative to Body	0.384	**0.492***	**0.476**	0.551**	0.422	**0.449**	**0.506**	0.503
% Difference		**28.1**	**24.0**	43.5		**6.4**	**19.9**	19.2
Relative to Brain	18.95	**24.02**	**20.22**	23.86	17.32	**19.79**	**21.86***	21.86*
% Difference		**26.7**	**6.7**	25.9		**14.3**	**26.2**	26.2
Week 52								
Absolute weight	15.60	**15.04**	**17.48**	16.61	11.15	**12.32**	**13.43**	14.15
% Difference		**-3.6**	**12.1**	6.5		**10.5**	**20.4**	26.9
Relative to Body	0.403	**0.455**	**0.498**	0.552*	0.388	**0.441**	**0.516**	0.557
% Difference		**12.9**	**23.6**	37.0		**13.7**	**33.0**	43.6
Relative to Brain	21.88	**21.63**	**27.48**	26.99	17.53	**19.41**	**22.63**	25.04*
% Difference		**-1.1**	**25.6**	23.3		**10.7**	**29.1**	42.8

* = Significantly different from the control group at 0.05 using Dunnett's test
** = Significantly different from the control group at 0.01 using Dunnett's test

Histopathology: The tissues listed in the table below from the study report were examined in all animals.

Adrenals (2)
Animal ID*
Aorta
Bone with marrow
  Sternum
  Femur with joint
Bone marrow smear (from rib)[a]
Brain
  Cerebrum level 1
  Cerebrum level 2
  Cerebellum with medulla/pons
Cervix
Epididymides (2)[b]
Eyes with optic nerves (2)[c]
Gallbladder
Gastrointestinal tract
  Esophagus
  Stomach
  Duodenum
  Jejunum
  Ileum
  Cecum
  Colon
  Rectum
Heart
Kidneys (2)
Larynx
Liver (sections of two lobes)
Lungs (including bronchi, fixed by inflation with fixative)
Lymph node
  Mesenteric
  Mandibular (2)
Ovaries (2)
Oviducts
Pancreas
Pituitary
Prostate
Salivary glands [mandibular (2)]
Sciatic nerve
Seminal vesicles (2)
Skeletal muscle (rectus femoris)
Skin with mammary gland
Spinal cord
  Cervical
  Thoracic
  Lumbar
Spleen
Testes (2)[b]
Thymus
Thyroid [with parathyroids (2)]
Trachea
Urinary bladder
Uterus
Vagina
All gross lesions (when possible)

a - Not taken from animals found dead; not placed in formalin; to be examined only if scientifically warranted (based on hematology and histopathologic findings).
b - To be placed in Bouin's solution.
c - To be placed in Davidson's solution.
* - Not to be examined macroscopically.

Liver hypertrophy was noted in all treatment groups. The hypertrophy was characterized by enlarged hepatocytes with stippled to granular eosinophilic cytoplasm that compressed and constricted sinusoidal spaces without evidence of passive congestion or ischemia. The incidence and severity of the liver hypertrophy are summarized in the following sponsor's table.

Text Table 4. Incidence and Severity of Test Article-Related Liver Changes at Study Weeks 26 and 51.

	Males				Females			
Dosage Level(g/kg/day):	**0**	**0.7**	**1.1**	**1.5**	**0**	**0.7**	**1.1**	**1.5**
Liver (week 26)[a]	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Hypertrophy, hepatocellular	0	3	4	4	0	4	4	4
Minimal	0	3	4	0	-	4	4	0
Mild	0	0	0	4	-	-	0	4
Apoptosis, hepatocellular	0	1	1	1	0	0	0	0
Minimal	-	1	1	1	-	-	-	-
Liver (week 52)[a]	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Hypertrophy, hepatocellular	0	4	3	4	1	3	4	4
Minimal	-	4	0	0	1	3	1	2
Mild	-	0	3	2	0	0	3	2
Moderate	-	0	0	2	0	0	0	0
Apoptosis, hepatocellular	0	0	0	1	0	0	2	0
Minimal	-	-	-	1	-	-	2	-

[a] = Number of tissues examined from each group.

Toxicokinetics: Plasma levels of the metabolites PBA, PAA, and PAGN were measured. The results are shown in the tables below (taken from the study report).

Text Table 5. Summary of Mean Toxicokinetic Parameters (Males)			
Study Day	Group (g/kg/day)	C_{max} (µg/mL)	AUC_{last} (µg*h/mL)
PBA (T_{max} = 1.5 – 3.4 hrs, $t_{1/2}$ = 6.8 – 23.27 hrs)			
0	0.7	69.14	420.27
	1.1	70.93	669.68
	1.5	114.77	974.03
180	0.7	64.58	533.85
	1.1	83.61	678.99
	1.5	77.96	662.98
358	0.7	67.43	622.40
	1.1	64.31	504.83
	1.5	68.54	609.43
PAA (T_{max} = 5.0 - 8.3 hrs, $t_{1/2}$ = 1.68 - 9.8 hrs)			
0	0.7	264.31	2592.9
	1.1	303.36	3699.4
	1.5	556.10	9397.3
180	0.7	219.02	1708.6
	1.1	331.02	3274.3
	1.5	506.52	6872.0
358	0.7	240.77	2398.15
	1.1	281.38	2204.09
	1.5	606.07	9910.14
PAGN (T_{max} = 4.0 - 8.3 hrs, $t_{1/2}$ = 4.7 - 17.0 hrs)			
0	0.7	36.49	535.46
	1.1	47.98	784.79
	1.5	71.75	1237.62
180	0.7	54.47	706.07
	1.1	85.39	1232.91
	1.5	113.13	1778.68
358	0.7	43.36	737.82
	1.1	77.82	1026.48
	1.5	136.64	1844.23

Text Table 5. Summary of Mean Toxicokinetic Parameters (Females)			
Study Day	Group (g/kg/day)	C_{max} (µg/mL)	AUC_{last} (µg*h/mL)
PBA (T_{max} = 1 – 2.3 hrs, $t_{1/2}$ = 5.1 – 35.2 hrs)			
0	0.7	58.18	458.19
	1.1	72.65	612.97
	1.5	128.32	757.72
180	0.7	92.67	506.86
	1.1	77.73	650.44
	1.5	95.36	711.73
358	0.7	49.39	370.02
	1.1	73.76	592.39
	1.5	59.66	529.26
PAA (T_{max} = 3.0 - 7.0 hrs, $t_{1/2}$ = 2.0 - 11.1 hrs)			
0	0.7	148.28	1454.0
	1.1	201.09	2708.7
	1.5	367.44	5254.3
180	0.7	338.13	2428.6
	1.1	339.30	3428.3
	1.5	592.59	6949.4
358	0.7	75.47	363.90
	1.1	309.48	2794.24
	1.5	405.63	4199.69
PAGN (T_{max} = 4.0 - 6.8 hrs, $t_{1/2}$ = 4.0 - 17.1 hrs)			
0	0.7	39.58	502.91
	1.1	41.82	649.78
	1.5	76.81	1140.47
180	0.7	85.07	979.84
	1.1	90.96	1289.29
	1.5	147.39	2074.35
358	0.7	59.74	437.54
	1.1	94.86	1400.51
	1.5	159.47	1396.38

7 Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Ames test
Study report No: 7602-100
Testing Laboratory: (b) (4)

Date of study initiation: December 3, 2004
Date of study report: November 29, 2005
GLP Compliance: This study was conducted in accordance with Good Laboratory Practice Regulations of the FDA and OECD.
QA-report: Yes (x) No ()
Drug lot No.: MPR-UXW-M0003.00.01

Study Endpoint: To determine the potential mutagenic effects of GT4P.

Methods: To examine the potential mutagenic effects of GT4P, the reverse mutation assay (Ames test) was conducted using plate incorporation method in four strains Salmonella typhimurium (TA 98, TA100, TA1535 and TA1537) and one strain E coli WP2 trp uvr in the presence and absence of metabolic activation, S-9 mix from rat liver. The following concentrations were tested: 10, 33.3, 100, 333, 1000, and 5000 µg/plate with and without S-9. Positive controls, benzo[a]pyrene, 2-nitrofluorane, 2-aminoanthracene, sodium azide, ICR-191, and 4-N-nitroquinoline-N-oxide, were tested. The results should be considered positive if the test substance induced a two fold increase in the mean revertant colonies as compared to the control and this increase should be a dose response to increasing concentrations of the test article.

- **Strain/species/cell line:** Four strains of Salmonella typhimurium (TA98, TA100, TA1535 and TA1537).
- **Dose selection criteria:**
  - **Basis of dose selection:** The high concentration of 5000 µg/plate was used.
- **Metabolic activation system:** Metabolic activation, S-9 mix, was from rat liver.
- **Control:**
  - **Negative control:** dimethyl sulfoxide.

Positive control: Positive controls, benzo[a]pyrene, 2-nitrofluorane, 2-aminoanthracene, sodium azide, ICR-191, and 4-N-nitroquinoline-N-oxide were tested.

- **Exposure conditions:** The reverse mutation assay (Ames test) was conducted using the plate incorporation method.
- **Dose used in defining study:** The following concentrations were tested: 10, 33.3, 100, 333, 1000, and 5000 µg/plate with and without S-9.
- **Analysis:**
- **Cytotoxic endpoints:** The condition of the bacterial backgound lawn was evaluated for evidence of cytotoxicity.
  - **Genetic toxicity endpoints/results:** Number of revertant colonies.
  - **Statistical methods:** Number of revertant colonies were averaged for each concentration.

Criteria for positive results: The results should be considered positive if the test substance induced a two fold increase in the mean revertant colonies as compared to

the control and this increase should be a dose response to increasing concentrations of the test article.

Results:

- **Study validation:** The positive controls significantly increased the colonies compared to the solvent controls.

- **Study outcome:** GT4P did not significantly increase the colonies as compared to the solvent control in the presence and absence of S-9 mix. The results were summarized in Tables 3 and 5 in this report. These tables are attached below.

Table 3 : Mutagenicity Assay Results – Summary

Test Article ID: GT4P

Assay No.: 26443-0-409OECD Trial No.: B1

Date Plated: 05-Jan-05 Vehicle: DMSO

Date Counted: 10-Jan-05 Plating Aliquot: 50 µL

		Mean Revertants Per Plate with Standard Deviation										Back-ground Lawn[a]
	Dose/Plate	TA98		TA100		TA1535		TA1537		WP2*uvr*A		
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Microsomes: Rat Liver												
Vehicle Control		18	2	129	22	11	2	9	2	17	6	N
Test Article	10.0 µg	28	6	118	16	8	2	6	1	18	6	N
	33.3 µg	23	5	114	8	11	6	4	2	16	2	N
	100 µg	21	2	113	6	12	6	6	2	15	4	N
	333 µg	19	0	122	2	12	4	6	3	13	4	N/NP*[d]
	1000 µg	23	6	135	11	11	3	5	3	9	1	N/NP*[e]
	5000 µg	15	6	156	9	14	5	8	2	17	4	NP*
Positive Control[b]		429	58	1130	137	150	24	251	77	546	56	N
Microsomes: None												
Vehicle Control		14	6	118	3	15	1	4	1	17	2	N
Test Article	10.0 µg	11	1	87	11	17	2	3	2	19	7	N
	33.3 µg	11	3	105	13	9	1	5	2	15	1	NP*
	100 µg	12	5	105	13	12	3	5	1	14	2	NP*
	333 µg	12	5	108	4	11	3	4	3	15	6	NP*
	1000 µg	11	2	120	9	12	5	2	2	10	2	NP*
	5000 µg	9	3	115	13	13	1	4	1	19	2	NP*
Positive Control[c]		397	31	1236	99	943	33	576	88	280	41	N

[a] Background Lawn Evaluation Codes:
N = normal R = reduced O = obscured A = absent P = precipitate

[b]

TA98	benzo[a]pyrene	2.5 µg/plate
TA100	2-aminoanthracene	2.5 µg/plate
TA1535	2-aminoanthracene	2.5 µg/plate
TA1537	2-aminoanthracene	2.5 µg/plate
WP2*uvr*A	2-aminoanthracene	25.0 µg/plate

[c]

TA98	2-nitrofluorene	1.0 µg/plate
TA100	sodium azide	2.0 µg/plate
TA1535	sodium azide	2.0 µg/plate
TA1537	ICR-191	2.0 µg/plate
WP2*uvr*A	4-nitroquinoline-N-oxide	1.0 µg/plate

[d] The first entry is the lawn evaluation for tester TA98, TA1537, and WP2*uvr*A.
The second entry is the lawn evaluation for tester strains TA100 and TA1535.

[e] The first entry is the lawn evaluation for tester strain TA98.
The second entry is the lawn evaluation for tester strains TA100, TA1535, TA1537, and WP2*uvr*A

* The test article precipitate did not interfere with scoring.

Table 5 : Mutagenicity Assay Results – Summary

Test Article ID: GT4P

Assay No.: 26443-0-409OECD Trial No.: C1

Date Plated: 20-Jan-05 Vehicle: DMSO

Date Counted: 26-Jan-05, 27-Jan-05 Plating Aliquot: 50 µL

	Dose/Plate	Mean Revertants Per Plate with Standard Deviation										Back-ground Lawn[a]
		TA98		TA100		TA1535		TA1537		WP2*uvrA*		
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Microsomes: Rat Liver												
Vehicle Control		21	5	118	14	15	2	10	1	21	6	N
Test Article	10.0 µg	17	7	118	11	18	2	9	1	13	2	N
	33.3 µg	20	8	120	26	13	3	11	6	17	2	N
	100 µg	19	10	120	19	11	3	11	2	12	2	N
	333 µg	19	3	125	11	10	5	10	1	14	4	NP*
	1000 µg	18	6	130	8	12	6	7	1	13	4	NP*
	5000 µg	19	4	106	8	16	2	8	3	11	2	NP*
Positive Control[b]		395	22	973	20	136	43	150	52	558	134	N
Microsomes: None												
Vehicle Control		20	4	74	10	11	3	4	2	16	2	N
Test Article	10.0 µg	17	8	70	9	11	1	7	2	16	4	N
	33.3 µg	14	3	79	1	12	5	4	1	18	3	N
	100 µg	19	6	83	3	11	4	9	1	13	4	NP*
	333 µg	18	1	73	10	14	0	8	2	17	2	NP*
	1000 µg	10	5	84	9	16	4	8	3	17	4	NP*
	5000 µg	7	3	83	17	11	1	5	3	13	1	NP*
Positive Control[c]		333	25	1445	195	1036	90	883	37	437	53	N

[a] Background Lawn Evaluation Codes:
N = normal R = reduced O = obscured A = absent P = precipitate

[b]
TA98	benzo[a]pyrene	2.5 µg/plate
TA100	2-aminoanthracene	2.5 µg/plate
TA1535	2-aminoanthracene	2.5 µg/plate
TA1537	2-aminoanthracene	2.5 µg/plate
WP2*uvr*A	2-aminoanthracene	25.0 µg/plate

[c]
TA98	2-nitrofluorene	1.0 µg/plate
TA100	sodium azide	2.0 µg/plate
TA1535	sodium azide	2.0 µg/plate
TA1537	ICR-191	2.0 µg/plate
WP2*uvr*A	4-nitroquinoline-N-oxide	1.0 µg/plate

* The test article precipitate did not interfere with scoring.

Conclusion: The results suggest that GT4P was not mutagenic in this test system.

In Vitro Assays in Mammalian Cells

Study title: In vitro chromosomal aberration test in Human peripheral blood lymphocytes
Study No: 7602-101
Testing Laboratory: (b) (4)

Date of study initiation: December 14, 2004
Date of study report: July 25, 2005

GLP Compliance: This study was conducted in accordance with Good Laboratory Practice Regulations of the FDA and OECD.
QA-report: Yes (x) No ()
Drug lot No.: MPR-UXW-M0003.00.01
Study Endpoint: To determine the potential clastogenic effects of GT4P.

Methods: To examine the potential induction of chromosomal aberrations by GT4P, the *in vitro* chromosomal aberration test was conducted using human lymphocytes in the presence and absence of metabolic activation, S-9 mix from rat liver.

In the initial assay, the treatment period was for 3 hours with and without metabolic activation, and cultures were harvested -22 hours from the initiation of treatment. Cultures were incubated with test article at 6.78, 9.69, 13.8, 19.8, 28.2, 40.4, 57.6, 82.4, 118, 168, 240, 343, 490, 700, and 1000 µg/ml with and without metabolic activation. Cultures treated with concentrations of 82.4, 168, 240, and 343 µg/ml without metabolic activation and 118, 168, 240, and 343 µg/ml with metabolic activation were analyzed for chromosomal aberrations. In the confirmatory chromosomal aberrations assay, the treatment period was -22 hours without metabolic activation and 3 hours with metabolic activation, and cultures were harvested -22 hour from the initiation of treatment. Cultures were incubated with test article at 3.13, 6.25, 12.5, 25.0, 50.0, 100, 200, 250, 300, 350, 425, and 500 µg/ml without metabolic activation and 50.0, 100, 200, 250, 300, 350, 425, and 500 µg/ml with metabolic activation. Cultures treated with concentrations of 250, 300, 350, and 425 µg/ml without metabolic activation and 300, 350, 425, and 500 µg/ml with metabolic activation were analyzed for chromosomal aberrations. Positive controls (chlorambucil and cyclophosphamide) were also tested. Cells were arrested in metaphase using colcemid ~3 hours before harvest.

- **Strain/species/cell line**: Human peripheral lymphocytes.
- **Metabolic activation system**: Metabolic activation, S-9 mix, was from rat liver.
- **Control**:
- **Negative control**: DMSO.

- **Positive control**: Two positive controls (mitomycin C and cyclophosphamide) were tested.
- **Exposure conditions**: Cells were exposed to the test drug for 3 or 22 hours and sampled 22 hours after exposure.

- **Analysis**:
  - **Counting method**: Slides were prepared and stained for analysis of chromosomal aberration.
  - **Cytotoxic endpoints**: Percentage of cell survival was used to measure the cytotoxicity.
- **Genetic toxicity endpoints/results**: percentage of cells with chromosomal aberration.
  - **Statistical methods**: Percent of aberrant cells is analyzed by one-tail binomial test and compared pairwisely to the control.
  - **Criteria for positive results**: The result is considered positive if a significant increase in the number of cells with chromosomal aberrations is observed at one or more concentrations.

Results:

- Study validation: The positive controls significantly increased the frequency of the chromosomal aberration.

- Study outcome: GT4P did not significantly increase the frequency of the chromosomal aberration.

The results were summarized in Tables 2, 4, 6, and 8 and these tables are attached below.

Table 4: Chromosomal Aberrations in Human Lymphocytes - With Metabolic Activation – 3-Hour Treatment, ~22-Hour Harvest

Assay No.: 26443-0-449OECD Trial No.: B1 Date: 12/15/04 Lab No.: CY121404 Test Article: GT4P

				# Cells Scored for Aberrations	% Mitotic Index Reduction[a]	# Cells Scored for pp and er	# of pp Cells	# of er Cells	Judgement (+/-)[b]	Numbers and Percentages of Cells Showing Structural Chromosome Aberrations							Judgement (+/-)[d]
										gaps	simple breaks	chte	chre	mab	Totals[c] g-	Totals[c] g+	
Controls																	
Negative.	RPMI 1640		A	100		100	0	0		5	3				3	8	
			B	100		100	0	0		2					0	2	
			Total	200		200				7	3				3	10	
			Average	%	--		0.0	0.0		3.5	1.5				1.5	5.0	
Vehicle:	DMSO	10.0 µL/mL	A	100		100	0	0		3	1				1	4	
			B	100		100	0	0		1	1				1	2	
			Total	200		200				4	2				2	6	
			Average	%	0		0.0	0.0		2.0	1.0				1.0	3.0	
Positive:	CP	25.0 µg/mL	A	50		100	0	0		7	12	2	1		14	19	
			B	50		100	0	0		5	15	1			15	18	
			Total	100		200				12	27	3	1		29	37	
			Average	%	--		0.0	0.0	-	12.0	27.0	3.0	1.0		29.0	37.0	
Test Article		118 µg/mL	A	100		100	0	0		2	1				1	3	
			B	100		100	0	0		1	1				1	1	
			Total	200		200				3	2				2	4	
			Average	%	22		0.0	0.0	-	1.5	1.0				1.0	2.0	-
		168 µg/mL	A	100		100	0	0		5					0	5	
			B	100		100	0	0		5	1				1	6	
			Total	200		200				10	1				1	11	
			Average	%	24		0.0	0.0	-	5.0	0.5				0.5	5.5	-
		240 µg/mL	A	100		100	0	0		4	3				3	6	
			B	100		100	0	0		2	2				2	4	
			Total	200		200				6	5				5	10	
			Average	%	32		0.0	0.0	-	3.0	2.5				2.5	5.0	-
		343 µg/mL	A	100		100	0	0		1	2				2	3	
			B	100		100	0	0		1	1				1	2	
			Total	200		200				2	3				3	5	
			Average	%	32		0.0	0.0	-	1.0	1.5				1.5	2.5	-

chte: chromatid exchange chre: chromosome exchange mab: multiple aberrations, greater than 4 aberrations pp: polyploidy er: endoreduplication

[a] % Mitotic index reduction as compared to the vehicle control.

[b] Significantly greater in % polyploidy and % endoreduplication than the vehicle control, $p \leq 0.01$.

[c] -g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.

[d] Significantly greater in -g than the vehicle control, $p \leq 0.01$. RPMI 1640 = culture medium DMSO = dimethylsulfoxide CP = Cyclophosphamide

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Table 6: Chromosomal Aberrations in Human Lymphocytes - Without Metabolic Activation - ~22-Hour Treatment, ~22-Hour Harvest

Assay No.: 26443-0-449OECD Trial No.: C1 Date: 01/20/05 Lab No.: CY011705 Test Article: GT4P

				# Cells Scored for Aberrations	% Mitotic Index Reduction[a]	# Cells Scored for pp and er	# of pp Cells	# of er Cells	Judgement (+/-)[b]	Numbers and Percentages of Cells Showing Structural Chromosome Aberrations: simple gaps	simple breaks	chte	chre	mab	Totals[c] g-	Totals[c] g+	Judgement (+/-)[d]
Controls																	
Negative:	RPMI 1640		A	100		100	0	0		1					0	1	
			B	100		100	0	0		1					0	1	
			Total	200		200				2					0	2	
			Average	%	--		0.0	0.0		1.0					0.0	1.0	
Vehicle:	DMSO	10.0 µL/mL	A	100		100	1	0		3	1				1	4	
			B	100		100	0	0			2				2	2	
			Total	200		200				3	3				3	6	
			Average	%	0		0.5	0.0		1.5	1.5				1.5	3.0	
Positive:	MMC	0.300 µg/mL	A	75		100	0	0		3	11	6			16	17	
			B	50		100	0	0		2	14	6			20	20	
			Total	125		200				5	25	12			36	37	
			Average	%	--		0.0	0.0	-	4.0	20.0	9.6			28.8	29.6	+
Test Article		250 µg/mL	A	100		100	0	0			1				1	1	
			B	100		100	0	0							0	0	
			Total	200		200					1				1	1	
			Average	%	17		0.0	0.0	-		0.5				0.5	0.5	-
		300 µg/mL	A	100		100	1	0			2				2	2	
			B	100		100	0	0			4	1			5	5	
			Total	200		200					6	1			7	7	
			Average	%	37		0.5	0.0	-		3.0	0.5			3.5	3.5	-
		350 µg/mL	A	100		100	0	0		1	2				2	3	
			B	100		100	1	0		1	2				2	3	
			Total	200		200				2	4				4	6	
			Average	%	66		0.5	0.0	-	1.0	2.0				2.0	3.0	-
		425 µg/mL	A	100		100	0	0		1	2				2	3	
			B	100		100	1	0			2				2	2	
			Total	200		200				1	4				4	5	
			Average	%	57		0.5	0.0	-	0.5	2.0				2.0	2.5	-

chte: chromatid exchange chre: chromosome exchange mab: multiple aberrations, greater than 4 aberrations pp: polyploidy er: endoreduplication

[a] % Mitotic index reduction as compared to the vehicle control.

[b] Significantly greater in % polyploidy and % endoreduplication than the vehicle control, $p \leq 0.01$.

[c] -g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.

[d] Significantly greater in -g than the vehicle control, $p \leq 0.01$. RPMI 1640 = culture medium DMSO = dimethylsulfoxide MMC = Mitomycin C

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Table 8: Chromosomal Aberrations in Human Lymphocytes - With Metabolic Activation - 3-Hour Treatment, ~22-Hour Harvest

Assay No.: 26443-0-449OECD Trial No.: C1 Date: 01/20/05 Lab No.: CY011705 Test Article: GT4P

				# Cells Scored for Aberrations	% Mitotic Index Reduction[a]	# Cells Scored for pp and er	# of pp Cells	# of er Cells	Judgement (+/-)[b]	Numbers and Percentages of Cells Showing Structural Chromosome Aberrations							Judgement (+/-)[d]
											simple				Totals[c]		
										gaps	breaks	chte	chre	mab	g-	g+	
Controls																	
Negative:	RPMI 1640		A	100		100	0	0		2					0	2	
			B	100		100	0	0			2		1		3	3	
			Total	200		200				2	2		1		3	5	
			Average	%	--		0.0	0.0		1.0	1.0		0.5		1.5	2.5	
Vehicle.	DMSO	10.0 µL/mL	A	100		100	0	0		1					0	1	
			B	100		100	0	0		1					0	1	
			Total	200		200				2					0	2	
			Average	%	0		0.0	0.0		1.0					0.0	1.0	
Positive:	CP	25.0 µg/mL	A	100		100	0	0		10	24	1			25	34	
			B	100		100	1	0		2	20	1			21	23	
			Total	200		200				12	44	2			46	57	
			Average	%	--		0.5	0.0	-	6.0	22.0	1.0			23.0	28.5	+
Test Article		300 µg/mL	A	100		100	0	0		1	1				1	2	
			B	100		100	0	0		1	1				1	2	
			Total	200		200				2	2				2	4	
			Average	%	--		0.0	0.0	-	1.0	1.0				1.0	2.0	-
		350 µg/mL	A	100		100	0	0			1				1	1	
			B	100		100	0	0		1	1				1	2	
			Total	200		200				1	2				2	3	
			Average	%	--		0.0	0.0	-	0.5	1.0				1.0	1.5	-
		425 µg/mL	A	100		100	1	1							0	0	
			B	100		100	0	0							0	0	
			Total	200		200									0	0	
			Average	%	--		0.5	0.5	-						0.0	0.0	-
		500 µg/mL	A	100		100	1	0			1	1			2	2	
			B	100		100	0	0		1	2				2	3	
			Total	200		200				1	3	1			4	5	
			Average	%	2		0.5	0.0	-	0.5	1.5	0.5			2.0	2.5	-

chte: chromatid exchange chre: chromosome exchange mab: multiple aberrations, greater than 4 aberrations pp: polyploidy er: endoreduplication

[a] % Mitotic index reduction as compared to the vehicle control.

[b] Significantly greater in % polyploidy and % endoreduplication than the vehicle control, $p \leq 0.01$.

[c] -g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.

[d] Significantly greater in -g than the vehicle control, $p \leq 0.01$. RPMI 1640 = culture medium DMSO = dimethylsulfoxide CP = Cyclophosphamide

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Conclusion: The results indicated that GT4P was not clastogenic in this test system.

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: In vivo rat micronucleus test
Study report No: 7602-102
Testing Laboratory: (b) (4) (b) (4)
Date of study initiation: January 4, 2005
Date of study report: December 2, 2005
GLP Compliance: The study report was conducted in accordance with GLP Regulations of the UK and OECD.
QA-report: Yes (x) No ()
Drug Batch No.: MPR-UXW-M0003000.01
Study Endpoint: Frequency of cells with micronucleated reticulocytes.

Methods: To examine the potential mutagenic effects of GT4P, micronucleus test was conducted using rat bone marrow cells. A single dose of GT4P was given to rats by oral gavage at 500, 1000, and 2000 mg/kg. In the current study, bone marrow was collected at termination. Vehicle and positive controls (cyclophosphamide) were also tested. The frequency of micronucleated reticulocyte was determined.

- **Strain/species/cell line**: CD(SD)BR rat.
- **Metabolic activation system**: None.
- **Control**:
  - **Vehicle**: corn oil.
  - **Positive control**: cyclophosphamide.
- **Exposure conditions**: rats were sacrificed 24 hours after dosing and bone marrow was collected.
- **Dose used in defining study**: 500, 1000, and 2000 mg/kg
- **Analysis**:
  - **Counting method**: Slides were prepared and examined for presence of micronucleated polychromatic erythrocytes.
  - **Cytotoxic endpoints**: Proportion of reticulocytes to total erythrocytes was determined as an indicator of bone marrow toxicity.
  - **Genetic toxicity endpoints/results**: Frequency of micronucleated reticulocytes.
  - **Statistical methods**: Frequency of micronucleated reticulocytes was analyzed.
  - **Criteria for positive results**: The result is considered positive if a significant increase in the micronucleated reticulocytes is observed dose-dependently.

Results:

- **Study validation**: The positive controls significantly increased the frequency of micronucleated reticulocytes.
- **Study outcome**: GT4P did not significantly increase the frequency of micronucleated reticulocytes as compared to the control. The results were summarized in Table 5 in this report and this table is attached below.

Table 5: Micronucleus Assay – Summary Table

Assay No.: 26443-0-454OECD
Test Article: GT4P: glyceryl tri(4-phenyl butyrate)
Initiation of Dosing: 21 Dec 2004

Treatment	Dose	Harvest Time	% Micronucleated PCEs Mean of 2000 per Animal ± S.E. Males	Ratio PCE:NCE Mean ± S.E. Males
Controls				
Vehicle	Corn Oil 10 mL/kg	24 hr	0.07 ± 0.02	0.93 ± 0.05
		48 hr	0.02 ± 0.01	0.71 ± 0.03
Positive	CP 60 mg/kg	24 hr	1.85 ± 0.31 *	0.66 ± 0.02 **
Test Article	500 mg/kg	24 hr	0.03 ± 0.01	0.87 ± 0.06
	1000 mg/kg	24 hr	0.03 ± 0.01	0.87 ± 0.06
	2000 mg/kg	24 hr	0.08 ± 0.03	0.94 ± 0.03
		48 hr	0.06 ± 0.02	0.73 ± 0.02

* Significantly greater than the corresponding vehicle control, $p \leq 0.01$.
** Significantly less than the corresponding vehicle control, $p \leq 0.05$.
CP = Cyclophosphamide
PCE = Polychromatic erythrocyte
NCE = Normochromatic erythrocyte

In conclusion, GT4P was not mutagenic under this testing condition.

7.4 Genetic Toxicity Studies with metabolites

1. Studies with 4-phenylbutyric Acid (PBA)

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Bacterial Reverse Mutation Assay

Study no.: (b) (4)
Study report location: N/A
Conducting laboratory and location: (b) (4)
Date of study initiation: 28 June 2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: 4-Phenylbutyric Acid, 06315BHV and 99.7%

Key Study Findings

Methods

Strains:	TA98, TA100, TA1535 and TA1537 and *Escherichia coli* WP2 *uvr*A
Concentrations in definitive study:	1.5, 5.0, 15, 50, 150, 500, 1500 and 5000 µg per plate
Basis of concentration selection:	the maximum dose of 5000 µg per plate was tested.
Negative control:	Dimethyl sulfoxide (DMSO)
Positive control:	See table below
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Incubated for 48-72 hours using the plate incorporation method

Strain	S9 Activation	Positive Control	Concentration (µg/plate)
TA98, TA1535 and TA1537	Rat	2-aminoanthracene (b) (4) Lot No. 03403ED Exp. Date 22-Jan-2012 CAS No. 613-13-8 Purity 99.8%	1.0
TA100			2.0
WP2 *uvr*A			15
TA98	None	2-nitrofluorene (b) (4) Lot No. S43858 Exp. Date 31-Jan-2014 CAS No. 607-57-8 Purity 97.9%	1.0
TA100, TA1535		sodium azide (b) (4) Lot No. A23U048 Exp. Date 04-Dec-2012 CAS No. 26628-22-8 Purity 100.0%	1.0
TA1537		9-aminoacridine (b) (4) Lot No. 106F06682 Exp. Date 28-Oct-2011 CAS No. 90-45-9 Purity >97%	75
WP2 *uvr*A		methyl methanesulfonate (b) (4) Lot No. 76296KJ Exp. Date 09-Jun-2012 CAS No. 66-27-3 Purity 99.8%	1,000

Study Validity

The positive controls significantly increased the colonies compared to the solvent controls.

Results

The results suggest that test article 4-phenylbutyric Acid was not mutagenic in this test system. The results were summarized in the sponsor's tables below.

Table 4
Confirmatory Mutagenicity Assay without S9 activation

Study Number: (b) (4) Study Code: (b) (4)
Experiment: B3 Date Plated: 7/15/2011
Exposure Method: Plate incorporation assay Evaluation Period: 7/25/2011 to 7/28/2011

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98	**4-Phenylbutyric Acid**	5000 µg	*19*	*2*	*1.2*	18^{A}, 18^{A}, 22^{A}
		1500 µg	*16*	*5*	*1.0*	10^{A}, 20^{A}, 17^{A}
		500 µg	*22*	*10*	*1.4*	32^{A}, 22^{A}, 13^{A}
		150 µg	*22*	*6*	*1.4*	17^{A}, 22^{A}, 28^{A}
		50 µg	*24*	*6*	*1.5*	26^{A}, 28^{A}, 17^{A}
	DMSO	50 µL	*16*	*7*		13^{A}, 10^{A}, 24^{A}
TA100	**4-Phenylbutyric Acid**	5000 µg	*102*	*5*	*1.0*	106^{A}, 96^{A}, 103^{A}
		1500 µg	*84*	*9*	*0.8*	93^{A}, 84^{A}, 75^{A}
		500 µg	*83*	*9*	*0.8*	93^{A}, 82^{A}, 75^{A}
		150 µg	*86*	*4*	*0.9*	82^{A}, 87^{A}, 89^{A}
		50 µg	*92*	*7*	*0.9*	97^{A}, 84^{A}, 96^{A}
	DMSO	50 µL	*100*	*24*		82^{A}, 91^{A}, 128^{A}
TA1535	**4-Phenylbutyric Acid**	5000 µg	*11*	*2*	*2.2*	10^{M}, 13^{M}, 9^{M}
		1500 µg	*10*	*3*	*2.0*	8^{M}, 14^{M}, 8^{M}
		500 µg	*10*	*1*	*2.0*	9^{M}, 11^{M}, 9^{M}
		150 µg	*10*	*4*	*2.0*	15^{M}, 9^{M}, 7^{M}
		50 µg	*8*	*1*	*1.6*	7^{M}, 8^{M}, 8^{M}
	DMSO	50 µL	*5*	*3*		5^{M}, 8^{M}, 3^{M}
TA1537	**4-Phenylbutyric Acid**	5000 µg	*13*	*2*	*1.3*	12^{M}, 15^{M}, 12^{M}
		1500 µg	*13*	*5*	*1.3*	9^{M}, 19^{M}, 12^{M}
		500 µg	*14*	*4*	*1.4*	19^{M}, 11^{M}, 12^{M}
		150 µg	*12*	*1*	*1.2*	13^{M}, 12^{M}, 11^{M}
		50 µg	*14*	*3*	*1.4*	13^{M}, 11^{M}, 17^{M}
	DMSO	50 µL	*10*	*1*		10^{M}, 11^{M}, 9^{M}

Key to Automatic & Manual Count Flags

^{M}: Manual count ^{A}: Automatic count

Table 4 cont.
Confirmatory Mutagenicity Assay without S9 activation

Study Number: (b) (4)
Experiment: B3
Exposure Method: Plate incorporation assay

Study Code: (b) (4)
Date Plated: 7/15/2011
Evaluation Period: 7/25/2011 to 7/28/2011

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
WP2*uvr*A	**4-Phenylbutyric Acid**	5000 µg	*22*	*4*	*1.1*	22^{A}, 18^{A}, 26^{A}
		1500 µg	*37*	*12*	*1.9*	51^{A}, 31^{A}, 29^{A}
		500 µg	*36*	*2*	*1.8*	36^{A}, 37^{A}, 34^{A}
		150 µg	*34*	*8*	*1.7*	27^{A}, 32^{A}, 42^{A}
		50 µg	*31*	*2*	*1.6*	29^{A}, 32^{A}, 32^{A}
	DMSO	50 µL	*20*	*4*		24^{A}, 18^{A}, 17^{A}
TA98	**2NF**	1.0 µg	*181*	*8*	*11.3*	187^{A}, 172^{A}, 184^{A}
TA100	**SA**	1.0 µg	*515*	*29*	*5.2*	518^{A}, 543^{A}, 485^{A}
TA1535	**SA**	1.0 µg	*531*	*30*	*106.2*	496^{A}, 545^{A}, 551^{A}
TA1537	**9AAD**	75 µg	*1237*	*127*	*123.7*	1353^{A}, 1256^{A}, 1102^{A}
WP2*uvr*A	**MMS**	1000 µg	*342*	*32*	*17.1*	337^{A}, 312^{A}, 376^{A}

Key to Positive Controls

2NF	2-nitrofluorene
SA	sodium azide
9AAD	9-Aminoacridine
MMS	methyl methanesulfonate

Key to Automatic & Manual Count Flags

^{M}: Manual count ^{A}: Automatic count

Table 5
Confirmatory Mutagenicity Assay with S9 activation

Study Number: (b) (4) Study Code: (b) (4)
Experiment: B3 Date Plated: 7/15/2011
Exposure Method: Plate incorporation assay Evaluation Period: 7/25/2011 to 7/28/2011

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98	**4-Phenylbutyric Acid**	5000 µg	*21*	*4*	*0.8*	24^{A}, 22^{A}, 17^{A}
		1500 µg	*28*	*7*	*1.1*	36^{A}, 22^{A}, 27^{A}
		500 µg	*32*	*4*	*1.2*	28^{A}, 32^{A}, 36^{A}
		150 µg	*28*	*4*	*1.1*	31^{A}, 29^{A}, 23^{A}
		50 µg	*22*	*8*	*0.8*	19^{A}, 15^{A}, 31^{A}
	DMSO	50 µL	*26*	*6*		28^{A}, 31^{A}, 19^{A}
TA100	**4-Phenylbutyric Acid**	5000 µg	*105*	*12*	*0.9*	112^{A}, 91^{A}, 113^{A}
		1500 µg	*114*	*16*	*1.0*	102^{A}, 133^{A}, 108^{A}
		500 µg	*110*	*18*	*1.0*	126^{A}, 113^{A}, 91^{A}
		150 µg	*120*	*3*	*1.1*	117^{A}, 120^{A}, 122^{A}
		50 µg	*97*	*16*	*0.9*	115^{A}, 83^{A}, 94^{A}
	DMSO	50 µL	*112*	*8*		108^{A}, 106^{A}, 121^{A}
TA1535	**4-Phenylbutyric Acid**	5000 µg	*7*	*3*	*0.8*	10^{A}, 6^{A}, 5^{A}
		1500 µg	*15*	*4*	*1.7*	19^{A}, 15^{A}, 11^{A}
		500 µg	*8*	*3*	*0.9*	9^{A}, 11^{A}, 5^{A}
		150 µg	*11*	*6*	*1.2*	15^{A}, 14^{A}, 4^{A}
		50 µg	*15*	*3*	*1.7*	14^{A}, 13^{A}, 18^{A}
	DMSO	50 µL	*9*	*2*		8^{A}, 11^{A}, 8^{A}
TA1537	**4-Phenylbutyric Acid**	5000 µg	*11*	*3*	*0.9*	13^{A}, 11^{A}, 8^{A}
		1500 µg	*10*	*4*	*0.8*	5^{A}, 13^{A}, 11^{A}
		500 µg	*15*	*3*	*1.3*	19^{A}, 13^{A}, 13^{A}
		150 µg	*16*	*4*	*1.3*	19^{A}, 11^{A}, 18^{A}
		50 µg	*14*	*4*	*1.2*	13^{A}, 18^{A}, 10^{A}
	DMSO	50 µL	*12*	*2*		11^{A}, 10^{A}, 14^{A}

Key to Automatic & Manual Count Flags

^{M}: Manual count ^{A}: Automatic count

Table 5 cont.
Confirmatory Mutagenicity Assay with S9 activation

Study Number: (b) (4)
Study Code: (b) (4)
Experiment: B3
Date Plated: 7/15/2011
Exposure Method: Plate incorporation assay
Evaluation Period: 7/25/2011 to 7/28/2011

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
WP2*uvrA*	**4-Phenylbutyric Acid**	5000 µg	*21*	*1*	*0.6*	22^{A}, 20^{A}, 22^{A}
		1500 µg	*30*	*11*	*0.8*	42^{A}, 20^{A}, 28^{A}
		500 µg	*36*	*6*	*1.0*	29^{A}, 38^{A}, 40^{A}
		150 µg	*32*	*5*	*0.9*	37^{A}, 31^{A}, 28^{A}
		50 µg	*27*	*3*	*0.7*	29^{A}, 23^{A}, 28^{A}
	DMSO	50 µL	*37*	*8*		40^{A}, 43^{A}, 28^{A}
TA98	**2AA**	1.0 µg	*235*	*45*	*9.0*	278^{A}, 238^{A}, 189^{A}
TA100	**2AA**	2.0 µg	*717*	*42*	*6.4*	728^{A}, 752^{A}, 671^{A}
TA1535	**2AA**	1.0 µg	*59*	*8*	*6.6*	66^{A}, 51^{A}, 61^{A}
TA1537	**2AA**	1.0 µg	*39*	*8*	*3.3*	46^{A}, 31^{A}, 40^{A}
WP2*uvrA*	**2AA**	15 µg	*197*	*16*	*5.3*	212^{A}, 181^{A}, 199^{A}

Key to Positive Controls
2AA 2-aminoanthracene
Key to Automatic & Manual Count Flags
^{M}: Manual count ^{A}: Automatic count

In Vitro Assays in Mammalian Cells

Study title: *In Vitro* Mammalian Chromosome Aberration Test

Study no.: (b) (4)
Study report location: N/A
Conducting laboratory and location: (b) (4)
Date of study initiation: June 16, 2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: 4-phenylbutyric Acid, 06315BHV and 99.7%

Key Study Findings

Methods

Cell line: Chinese hamster ovary (CHO) cells

Concentrations in definitive study:	See table below
Basis of concentration selection:	cell growth inhibition
Negative control:	DMSO
Positive control:	Mitomycin C 0.1-0.2 ug/ml and Cyclophosphamide 10-15 ug/ml
Formulation/Vehicle:	DMSO
Incubation & sampling time:	The cells were treated for 4 or 20 hours All cells were harvested 20 hours after treatment

Treatment Condition	Treatment Time	Recovery Time	Dose levels (µg/mL)
Non-activated	4 hr	16 hr	243, 486, 970, 1080, 1150, 1200, 1260
	20 hr	0 hr	12, 24, 48, 95, 190, 380, 430, 530, 760
S9-activated	4 hr	16 hr	243, 486, 970, 1080, 1150, 1200, 1260

Study Validity

The positive and solvent controls fulfilled the requirements for a valid test.

Results

The results were summarized in the following sponsor's table.

TABLE 10

SUMMARY

Treatment µg/mL	S9 Activation	Treatment Time	Mean Mitotic Index	Cells Scored		Aberrations Per Cell (Mean +/- SD)		Cells With Aberrations	
				Numerical	Structural			Numerical (%)	Structural (%)
DMSO	-S9	4	10.1	200	200	0.000	±0.000	1.5	0.0
4-Phenylbutyric Acid									
486	-S9	4	9.8	200	200	0.000	±0.000	2.5	0.0
1080	-S9	4	9.9	200	200	0.000	±0.000	1.0	0.0
1200	-S9	4	9.3	200	200	0.005	±0.071	0.5	0.5
MMC 0.2	-S9	4	8.0	200	100	0.130	±0.338	2.0	13.0**
DMSO	+S9	4	13.4	200	200	0.030	±0.198	1.5	2.5
4-Phenylbutyric Acid									
486	+S9	4	12.2	200	200	0.000	±0.000	1.5	0.0
970	+S9	4	11.6	200	200	0.010	±0.100	1.5	1.0
1080	+S9	4	11.6	200	200	0.085	±0.344	3.0	7.0*
CP 10	+S9	4	3.5	200	100	0.340	±0.623	1.5	26.0**
DMSO	-S9	20	14.1	200	200	0.020	±0.140	2.0	2.0
4-Phenylbutyric Acid									
95	-S9	20	13.9	200	200	0.005	±0.071	3.0	0.5
190	-S9	20	14.2	200	200	0.015	±0.122	2.0	1.5
380	-S9	20	14.6	200	200	0.005	±0.071	3.0	0.5
MMC 0.1	-S9	20	7.7	200	100	0.210	±0.456	2.0	19.0**

Treatment: Cells from all treatment conditions were harvested 20 hours after the initiation of the treatments.

Aberrations per Cell: Severely damaged cells were counted as 10 aberrations.

Percent Aberrant Cells: *, $p \leq 0.05$; **, $p \leq 0.01$; using Fisher's Exact test.

The results indicated that PBA significantly increased the proportion of cells with structural aberrations in the presence of S-9 after 4 hours treatment. In the absence of S-9, PBA did not significantly increase the proportion of cells with aberrations.

Repeated In Vitro Assays in Mammalian Cells

Study title: *In Vitro* Mammalian Chromosome Aberration Test

Study no.:	(b) (4)
Study report location:	N/A
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 14, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	4-phenylbutyric Acid, 06315BHV and 99.7%

Key Study Findings

Methods

Cell line:	Human peripheral lymphocytes
Concentrations in definitive study:	210, 419, 840, 1080, 1320 and 1640 µg/mL in 4-hour treatment groups with and without S-9, and 85, 165, 327, 419, 512, 650, 840, 1080, 1320 and 1640 µg/mL in 20-hour treatment group
Basis of concentration selection:	cell growth inhibition
Negative control:	DMSO
Positive control:	Mitomycin C 0.1-0.2 ug/ml and Cyclophosphamide 10-15 ug/ml
Formulation/Vehicle:	DMSO
Incubation & sampling time:	The cells were treated for 4 or 20 hours All cells were harvested 20 hours after treatment

Study Validity

The positive and solvent controls met the requirements for a valid test.

Results

The results were summarized in the following sponsor's table.

TABLE 4
SUMMARY

Treatment µg/mL	S9 Activation	Treatment Time	Mean Mitotic Index	Cells Scored Numerical	Cells Scored Structural	Aberrations Per Cell (Mean +/- SD)		Cells With Aberrations Numerical (%)	Cells With Aberrations Structural (%)
DMSO	-S9	4	9.4	200	200	0.000	±0.000	0.0	0.0
4-Phenylbutyric Acid									
1080	-S9	4	9.3	200	200	0.010	±0.100	0.0	1.0
1320	-S9	4	7.9	200	200	0.005	±0.071	0.0	0.5
1640	-S9	4	8.4	200	200	0.015	±0.158	0.0	1.0
MMC, 0.6	-S9	4	5.1	200	100	0.190	±0.419	0.0	18.0**
DMSO	+S9	4	11.0	200	200	0.000	±0.000	0.5	0.0
4-Phenylbutyric Acid									
1080	+S9	4	10.3	200	200	0.005	±0.071	0.5	0.5
1320	+S9	4	8.6	200	200	0.000	±0.000	0.0	0.0
1640	+S9	4	7.3	200	200	0.030	±0.299	0.0	1.5
CP, 5	+S9	4	3.6	200	100	0.100	±0.302	0.0	10.0**
DMSO	-S9	20	10.7	200	200	0.000	±0.000	0.0	0.0
4-Phenylbutyric Acid									
165	-S9	20	9.3	200	200	0.000	±0.000	0.0	0.0
419	-S9	20	8.3	200	200	0.000	±0.000	1.0	0.0
650	-S9	20	5.2	200	200	0.010	±0.100	0.0	1.0
MMC, 0.3	-S9	20	7.5	200	100	0.130	±0.367	0.0	12.0**

Treatment: Cells from all treatment conditions were harvested at 20 hours after the initiation of the treatments.

Aberrations per Cell: Severely damaged cells were counted as 10 aberrations.

Percent Aberrant Cells: *, $p \leq 0.05$; **, $p \leq 0.01$; using the Fisher's Exact test.

The results indicated that PBA did not significantly increase the proportion of cells with aberrations in the presence or absence of S-9.

2. Studies with Phenylacetic Acid (PAA)

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Bacterial Reverse Mutation Assay

Study no.:	(b) (4)
Study report location:	N/A
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 6, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Phenylacetic Acid STBB0962V and 99.6%

Key Study Findings

Methods

Strains:	TA98, TA100, TA1535 and TA1537 and *Escherichia coli* WP2 *uvr*A
Concentrations in definitive study:	1.5, 5.0, 15, 50, 150, 500, 1500 and 5000 µg per plate
Basis of concentration selection:	the maximum dose of 5000 µg per plate was tested.
Negative control:	Dimethyl sulfoxide (DMSO)
Positive control:	See table below
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Incubated for 48-72 hours using the plate incorporation method

Strain	S9 Activation	Positive Control	Concentration (µg/plate)
TA98, TA1535 and TA1537	Rat	2-aminoanthracene [redacted] (b) (4) Lot No. 03403ED Exp. Date 22-Jan-2012 CAS No. 613-13-8 Purity 99.8%	1.0
TA100			2.0
WP2 *uvr*A			15
TA98	None	2-nitrofluorene [redacted] (b) (4) Lot No. S43858 Exp. Date 31-Jan-2014 CAS No. 607-57-8 Purity 97.9%	1.0
TA100, TA1535		sodium azide [redacted] (b) (4) Lot No. A23U048 Exp. Date 04-Dec-2012 CAS No. 26628-22-8 Purity 100.0%	1.0
TA1537		9-aminoacridine [redacted] (b) (4) Lot No. 106F06682 Exp. Date 28-Oct-2011 CAS No. 90-45-9 Purity >97%	75
WP2 *uvr*A		methyl methanesulfonate [redacted] (b) (4) Lot No. 76296KJ Exp. Date 09-Jun-2012 CAS No. 66-27-3 Purity 99.8%	1,000

Study Validity

The positive controls significantly increased the colonies compared to the solvent controls.

Results

The results indicated that the test article, phenylacetic acid, did not significantly increase the colonies as compared to the solvent controls, indicating that phenylacetic acid was not mutagenic under the assay conditions. The results were summarized in the sponsor's tables below.

Table 4
Confirmatory Mutagenicity Assay without S9 activation

Study Number: (b) (4)
Experiment: B3
Exposure Method: Plate incorporation assay
Study Code: (b) (4),
Date Plated: 7/22/2011
Evaluation Period: 7/26/2011

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98	**Phenylacetic Acid**	5000 µg	*7*	*2*	*0.5*	5^{M}, 8^{M}, 9^{M}
		1500 µg	*10*	*4*	*0.7*	7^{M}, 10^{M}, 14^{M}
		500 µg	*11*	*2*	*0.8*	12^{M}, 9^{M}, 13^{M}
		150 µg	*16*	*6*	*1.1*	22^{M}, 11^{M}, 16^{M}
		50 µg	*10*	*3*	*0.7*	8^{M}, 14^{M}, 9^{M}
	DMSO	50 µL	*14*	*2*		12^{M}, 16^{M}, 15^{M}
TA100	**Phenylacetic Acid**	5000 µg	*97*	*5*	*1.1*	101^{A}, 91^{A}, 99^{A}
		1500 µg	*87*	*9*	*1.0*	78^{A}, 96^{A}, 87^{A}
		500 µg	*93*	*12*	*1.0*	80^{A}, 97^{A}, 103^{A}
		150 µg	*88*	*11*	*1.0*	77^{A}, 99^{A}, 89^{A}
		50 µg	*91*	*11*	*1.0*	84^{A}, 85^{A}, 103^{A}
	DMSO	50 µL	*91*	*2*		93^{A}, 92^{A}, 89^{A}
TA1535	**Phenylacetic Acid**	5000 µg	*11*	*3*	*1.6*	10^{A}, 9^{A}, 14^{A}
		1500 µg	*11*	*2*	*1.6*	13^{A}, 11^{A}, 10^{A}
		500 µg	*10*	*4*	*1.4*	6^{A}, 13^{A}, 11^{A}
		150 µg	*15*	*2*	*2.1*	13^{A}, 15^{A}, 17^{A}
		50 µg	*12*	*2*	*1.7*	14^{A}, 10^{A}, 11^{A}
	DMSO	50 µL	*7*	*2*		8^{A}, 8^{A}, 4^{A}
TA1537	**Phenylacetic Acid**	5000 µg	*2*	*2*	*0.4*	0^{A}, 3^{A}, 3^{A}
		1500 µg	*5*	*3*	*1.0*	5^{A}, 3^{A}, 8^{A}
		500 µg	*4*	*1*	*0.8*	5^{A}, 5^{A}, 3^{A}
		150 µg	*6*	*2*	*1.2*	8^{A}, 4^{A}, 6^{A}
		50 µg	*7*	*2*	*1.4*	9^{A}, 5^{A}, 6^{A}
	DMSO	50 µL	*5*	*1*		4^{A}, 5^{A}, 5^{A}

Table 4 cont.
Confirmatory Mutagenicity Assay without S9 activation

Study Number: (b) (4) Study Code: (b) (4)
Experiment: B3 Date Plated: 7/22/2011
Exposure Method: Plate incorporation assay Evaluation Period: 7/26/2011

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
WP2*uvrA*	**Phenylacetic Acid**	5000 µg	*9*	*2*	*0.3*	8^{A}, 8^{A}, 11^{A}
		1500 µg	*24*	*7*	*0.9*	19^{A}, 22^{A}, 32^{A}
		500 µg	*31*	*13*	*1.2*	24^{A}, 23^{A}, 46^{A}
		150 µg	*26*	*7*	*1.0*	20^{A}, 33^{A}, 24^{A}
		50 µg	*31*	*4*	*1.2*	27^{A}, 31^{A}, 34^{A}
	DMSO	50 µL	*26*	*3*		27^{A}, 22^{A}, 28^{A}
TA98	**2NF**	1.0 µg	*231*	*10*	*16.5*	240^{A}, 232^{A}, 221^{A}
TA100	**SA**	1.0 µg	*429*	*10*	*4.7*	435^{A}, 417^{A}, 435^{A}
TA1535	**SA**	1.0 µg	*519*	*115*	*74.1*	402^{A}, 524^{A}, 631^{A}
TA1537	**9AAD**	75 µg	*299*	*17*	*59.8*	307^{A}, 279^{A}, 311^{A}
WP2*uvrA*	**MMS**	1000 µg	*307*	*19*	*11.8*	328^{A}, 292^{A}, 301^{A}

Key to Positive Controls

2NF	2-nitrofluorene
SA	sodium azide
9AAD	9-Aminoacridine
MMS	methyl methanesulfonate

Key to Automatic & Manual Count Flags

^{M}: Manual count ^{A}: Automatic count

Table 5
Confirmatory Mutagenicity Assay with S9 activation

Study Number: (b) (4) Study Code: (b) (4)
Experiment: B3 Date Plated: 7/22/2011
Exposure Method: Plate incorporation assay Evaluation Period: 7/26/2011

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98	**Phenylacetic Acid**	5000 µg	*8*	*3*	*0.5*	9^{M}, 10^{M}, 5^{M}
		1500 µg	*9*	*4*	*0.6*	6^{M}, 13^{M}, 7^{M}
		500 µg	*16*	*3*	*1.1*	13^{M}, 18^{M}, 17^{M}
		150 µg	*21*	*3*	*1.4*	24^{M}, 21^{M}, 19^{M}
		50 µg	*19*	*8*	*1.3*	28^{M}, 16^{M}, 13^{M}
	DMSO	50 µL	*15*	*4*		14^{M}, 19^{M}, 11^{M}
TA100	**Phenylacetic Acid**	5000 µg	*91*	*15*	*0.9*	78^{A}, 108^{A}, 87^{A}
		1500 µg	*120*	*7*	*1.2*	126^{A}, 113^{A}, 120^{A}
		500 µg	*121*	*13*	*1.2*	128^{A}, 129^{A}, 106^{A}
		150 µg	*125*	*17*	*1.2*	105^{A}, 138^{A}, 131^{A}
		50 µg	*105*	*11*	*1.0*	117^{A}, 102^{A}, 96^{A}
	DMSO	50 µL	*103*	*16*		96^{A}, 91^{A}, 121^{A}
TA1535	**Phenylacetic Acid**	5000 µg	*10*	*3*	*0.8*	9^{A}, 8^{A}, 14^{A}
		1500 µg	*11*	*5*	*0.8*	14^{A}, 5^{A}, 13^{A}
		500 µg	*11*	*3*	*0.8*	9^{A}, 10^{A}, 14^{A}
		150 µg	*11*	*2*	*0.8*	13^{A}, 10^{A}, 9^{A}
		50 µg	*12*	*6*	*0.9*	8^{A}, 19^{A}, 8^{A}
	DMSO	50 µL	*13*	*2*		11^{A}, 15^{A}, 14^{A}
TA1537	**Phenylacetic Acid**	5000 µg	*2*	*2*	*0.3*	4^{A}, 0^{A}, 3^{A}
		1500 µg	*6*	*2*	*0.8*	5^{A}, 5^{A}, 9^{A}
		500 µg	*5*	*1*	*0.6*	5^{A}, 6^{A}, 4^{A}
		150 µg	*8*	*5*	*1.0*	5^{A}, 6^{A}, 14^{A}
		50 µg	*7*	*2*	*0.9*	9^{A}, 5^{A}, 6^{A}
	DMSO	50 µL	*8*	*3*		10^{A}, 5^{A}, 8^{A}

Table 5 cont.
Confirmatory Mutagenicity Assay with S9 activation

Study Number: (b) (4) Study Code: (b) (4)
Experiment: B3 Date Plated: 7/22/2011
Exposure Method: Plate incorporation assay Evaluation Period: 7/26/2011

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
WP2*uvr*A	**Phenylacetic Acid**	5000 µg	*17*	*6*	*0.5*	14^{A}, 23^{A}, 13^{A}
		1500 µg	*26*	*6*	*0.7*	20^{A}, 28^{A}, 31^{A}
		500 µg	*25*	*7*	*0.7*	20^{A}, 23^{A}, 33^{A}
		150 µg	*28*	*9*	*0.8*	29^{A}, 18^{A}, 36^{A}
		50 µg	*27*	*12*	*0.7*	20^{A}, 20^{A}, 41^{A}
	DMSO	50 µL	*37*	*10*		26^{A}, 41^{A}, 45^{A}
TA98	**2AA**	1.0 µg	*262*	*25*	*17.5*	240^{A}, 289^{A}, 256^{A}
TA100	**2AA**	2.0 µg	*823*	*147*	*8.0*	705^{A}, 777^{A}, 988^{A}
TA1535	**2AA**	1.0 µg	*58*	*3*	*4.5*	61^{A}, 55^{A}, 57^{A}
TA1537	**2AA**	1.0 µg	*31*	*14*	*3.9*	18^{A}, 28^{A}, 46^{A}
WP2*uvr*A	**2AA**	15 µg	*144*	*8*	*3.9*	149^{A}, 134^{A}, 148^{A}

Key to Positive Controls
2AA 2-aminoanthracene
Key to Automatic & Manual Count Flags
^{M}: Manual count ^{A}: Automatic count

In Vitro Assays in Mammalian Cells

Study title: *In Vitro* Mammalian Chromosome Aberration Test

Study no.: (b) (4)
Study report location: N/A
Conducting laboratory and location: (b) (4)
Date of study initiation: June 24, 2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Phenylacetic Acid, STBB0962V and 99.6%

Key Study Findings

Methods

Cell line:	Chinese hamster ovary (CHO) cells
Concentrations in definitive study:	116, 233, 466, 666, 950, and 1360 ug/ml
Basis of concentration selection:	cell growth inhibition
Negative control:	DMSO
Positive control:	Mitomycin C 0.1-0.2 ug/ml Cyclophosphamide 10-15 ug/ml
Formulation/Vehicle:	DMSO
Incubation & sampling time:	The cells were treated for 4 or 20 hours All cells were harvested 20 hours after treatment

Study Validity

The positive and solvent controls met the requirements for a valid test.

Results

The results indicated that phenylacetic acid did not significantly increase the proportion of cells with aberrations in the presence or absence of S-9.

3. Studies with Phenylacetylglutamine (PAGN)

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Bacterial Reverse Mutation Assay with

Study no.:	(b) (4)
Study report location:	N/A
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 6, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Phenylacetylglutamine (PAGN) UXW-M0053-SD2-1-6-41 and 90.98%

Key Study Findings

Methods

Strains:	TA98, TA100, TA1535 and TA1537 and *Escherichia coli* WP2 *uvr*A
Concentrations in definitive study:	1.5, 5.0, 15, 50, 150, 500, 1500 and 5000 µg per plate
Basis of concentration selection:	the maximum dose of 5000 µg per plate was tested.
Negative control:	Water
Positive control:	See table below
Formulation/Vehicle:	Water
Incubation & sampling time:	Incubated for 48-72 hours using the plate incorporation method

Strain	S9 Activation	Positive Control	Concentration (µg/plate)
TA98, TA1535 and TA1537	Rat	2-aminoanthracene (b) (4) Lot No. 03403ED Exp. Date 22-Jan-2012 CAS No. 613-13-8 Purity 99.8%	1.0
TA100			2.0
WP2 *uvr*A			15
TA98	None	2-nitrofluorene (b) (4) Lot No. S43858 Exp. Date 31-Jan-2014 CAS No. 607-57-8 Purity 97.9%	1.0
TA100, TA1535		sodium azide (b) (4) Lot No. A23U048 Exp. Date 04-Dec-2012 CAS No. 26628-22-8 Purity 100.0%	1.0
TA1537		9-aminoacridine (b) (4) Lot No. 106F06682 Exp. Date 28-Oct-2011 CAS No. 90-45-9 Purity >97%	75
WP2 *uvr*A		methyl methanesulfonate (b) (4) Lot No. 76296KJ Exp. Date 09-Jun-2012 CAS No. 66-27-3 Purity 99.8%	1,000

Study Validity

The positive controls significantly increased the colonies compared to the solvent controls.

Results

The results suggest that test article, phenylacetylglutamine (PAGN), was not mutagenic under the assay conditions. The results were summarized in the sponsor's tables below.

Table 3
Confirmatory Mutagenicity Assay without S9 activation

Study Number: (b) (4) Study Code: (b) (4)
Experiment: B2 Date Plated: 7/22/2011
Exposure Method: Plate incorporation assay Evaluation Period: 7/28/2011

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98	**PAGN**	5000 µg	*14*	*4*	*1.0*	18^{M}, 11^{M}, 13^{M}
		1500 µg	*11*	*2*	*0.8*	9^{M}, 13^{M}, 12^{M}
		500 µg	*14*	*4*	*1.0*	14^{M}, 10^{M}, 17^{M}
		150 µg	*15*	*5*	*1.1*	9^{M}, 16^{M}, 19^{M}
		50 µg	*12*	*4*	*0.9*	16^{M}, 8^{M}, 13^{M}
	Water	100 µL	*14*	*3*		11^{M}, 16^{M}, 14^{M}
TA100	**PAGN**	5000 µg	*111*	*6*	*1.4*	107^{A}, 118^{A}, 109^{A}
		1500 µg	*104*	*13*	*1.3*	118^{A}, 103^{A}, 92^{A}
		500 µg	*101*	*5*	*1.2*	97^{A}, 99^{A}, 106^{A}
		150 µg	*89*	*5*	*1.1*	WDN#, 92^{A}, 85^{A}
		50 µg	*92*	*16*	*1.1*	85^{A}, 81^{A}, 110^{A}
	Water	100 µL	*81*	*10*		85^{A}, 69^{A}, 88^{A}
TA1535	**PAGN**	5000 µg	*15*	*3*	*1.1*	13^{A}, 19^{A}, 13^{A}
		1500 µg	*14*	*1*	*1.0*	15^{A}, 13^{A}, 13^{A}
		500 µg	*14*	*1*	*1.0*	13^{A}, 15^{A}, 13^{A}
		150 µg	*13*	*5*	*0.9*	19^{A}, 9^{A}, 11^{A}
		50 µg	*9*	*5*	*0.6*	11^{A}, 4^{A}, 13^{A}
	Water	100 µL	*14*	*3*		11^{A}, 16^{A}, 15^{A}
TA1537	**PAGN**	5000 µg	*4*	*0*	*0.7*	4^{A}, 4^{A}, 4^{A}
		1500 µg	*8*	*1*	*1.3*	8^{A}, 7^{A}, 8^{A}
		500 µg	*6*	*3*	*1.0*	3^{A}, 8^{A}, 8^{A}
		150 µg	*8*	*4*	*1.3*	12^{A}, 7^{A}, 4^{A}
		50 µg	*4*	*1*	*0.7*	3^{A}, 4^{A}, 5^{A}
	Water	100 µL	*6*	*1*		7^{A}, 5^{A}, 5^{A}
WP2*uvrA*	**PAGN**	5000 µg	*23*	*5*	*0.7*	21^{A}, 19^{A}, 28^{A}
		1500 µg	*28*	*4*	*0.9*	32^{A}, 25^{A}, 28^{A}
		500 µg	*29*	*3*	*0.9*	32^{A}, 27^{A}, 29^{A}
		150 µg	*26*	*5*	*0.8*	28^{A}, 29^{A}, 20^{A}
		50 µg	*26*	*4*	*0.8*	29^{A}, 28^{A}, 21^{A}
	Water	100 µL	*32*	*8*		37^{A}, 36^{A}, 23^{A}

Key to Plate Postfix Codes

WD	Water damaged plate
N#	Not counted

Table 3 cont.
Confirmatory Mutagenicity Assay without S9 activation

Study Number: (b) (4) Study Code: (b) (4)
Experiment: B2 Date Plated: 7/22/2011
Exposure Method: Plate incorporation assay Evaluation Period: 7/28/2011

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98	**2NF**	1.0 µg	*314*	*76*	*22.4*	306^{A}, 243^{A}, 394^{A}
TA100	**SA**	1.0 µg	*746*	*239*	*9.2*	1008^{A}, 690^{A}, 540^{A}
TA1535	**SA**	1.0 µg	*636*	*522*	*45.4*	33^{A}, 926^{A}, 948^{A}
TA1537	**9AAD**	75 µg	*707*	*101*	*117.8*	633^{A}, 822^{A}, 666^{A}
WP2*uvr*A	**MMS**	1000 µg	*192*	*11*	*6.0*	194^{A}, 180^{A}, 202^{A}

Key to Positive Controls

2NF	2-nitrofluorene
SA	sodium azide
9AAD	9-Aminoacridine
MMS	methyl methanesulfonate

Key to Automatic & Manual Count Flags

^{M}: Manual count ^{A}: Automatic count

Table 4
Confirmatory Mutagenicity Assay with S9 activation

Study Number: (b) (4)
Experiment: B2
Exposure Method: Plate incorporation assay
Study Code: (b) (4)
Date Plated: 7/22/2011
Evaluation Period: 7/28/2011

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98	**PAGN**	5000 µg	*19*	*3*	*0.9*	16^{M}, 19^{M}, 21^{M}
		1500 µg	*24*	*3*	*1.1*	28^{M}, 22^{M}, 23^{M}
		500 µg	*19*	*1*	*0.9*	18^{M}, 19^{M}, 20^{M}
		150 µg	*22*	*5*	*1.0*	24^{M}, 26^{M}, 16^{M}
		50 µg	*24*	*1*	*1.1*	24^{M}, 25^{M}, 23^{M}
	Water	100 µL	*22*	*3*		21^{M}, 25^{M}, 20^{M}
TA100	**PAGN**	5000 µg	*175*	*1*	*1.2*	176^{A}, 175^{A}, 174^{A}
		1500 µg	*162*	*31*	*1.1*	126^{A}, 175^{A}, 184^{A}
		500 µg	*160*	*13*	*1.1*	175^{A}, 151^{A}, 155^{A}
		150 µg	*164*	*12*	*1.1*	159^{A}, 156^{A}, 178^{A}
		50 µg	*145*	*4*	*1.0*	146^{A}, 149^{A}, 141^{A}
	Water	100 µL	*151*	*14*		135^{A}, 155^{A}, 162^{A}
TA1535	**PAGN**	5000 µg	*16*	*6*	*0.9*	13^{A}, 23^{A}, 12^{A}
		1500 µg	*11*	*6*	*0.6*	16^{A}, 4^{A}, 12^{A}
		500 µg	*14*	*7*	*0.8*	7^{A}, 20^{A}, 15^{A}
		150 µg	*14*	*6*	*0.8*	19^{A}, 8^{A}, 16^{A}
		50 µg	*13*	*5*	*0.7*	16^{A}, 16^{A}, 7^{A}
	Water	100 µL	*18*	*6*		24^{A}, 17^{A}, 13^{A}
TA1537	**PAGN**	5000 µg	*12*	*6*	*1.3*	7^{A}, 19^{A}, 11^{A}
		1500 µg	*8*	*4*	*0.9*	8^{A}, 11^{A}, 4^{A}
		500 µg	*14*	*1*	*1.6*	13^{A}, 15^{A}, 15^{A}
		150 µg	*6*	*2*	*0.7*	4^{A}, 8^{A}, 7^{A}
		50 µg	*12*	*5*	*1.3*	11^{A}, 8^{A}, 17^{A}
	Water	100 µL	*9*	*2*		8^{A}, 8^{A}, 11^{A}
WP2*uvr*A	**PAGN**	5000 µg	*23*	*3*	*1.0*	25^{A}, 24^{A}, 19^{A}
		1500 µg	*26*	*10*	*1.1*	21^{A}, 20^{A}, 37^{A}
		500 µg	*31*	*9*	*1.3*	31^{A}, 23^{A}, 40^{A}
		150 µg	*32*	*8*	*1.3*	41^{A}, 25^{A}, 31^{A}
		50 µg	*23*	*10*	*1.0*	13^{A}, 32^{A}, 24^{A}
	Water	100 µL	*24*	*4*		23^{A}, 29^{A}, 21^{A}

Table 4 cont.
Confirmatory Mutagenicity Assay with S9 activation

Study Number: (b) (4)
Experiment: B2
Exposure Method: Plate incorporation assay
Study Code: (b) (4)
Date Plated: 7/22/2011
Evaluation Period: 7/28/2011

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98	**2AA**	1.0 µg	*298*	*18*	*13.5*	293^{A}, 282^{A}, 318^{A}
TA100	**2AA**	2.0 µg	*750*	*77*	*5.0*	814^{A}, 772^{A}, 664^{A}
TA1535	**2AA**	1.0 µg	*124*	*52*	*6.9*	66^{A}, 167^{A}, 139^{A}
TA1537	**2AA**	1.0 µg	*42*	*11*	*4.7*	33^{A}, 40^{A}, 54^{A}
WP2*uvrA*	**2AA**	15 µg	*87*	*18*	*3.6*	70^{A}, 105^{A}, 85^{A}

Key to Positive Controls
2AA 2-aminoanthracene
Key to Automatic & Manual Count Flags
^{M}: Manual count ^{A}: Automatic count

In Vitro Assays in Mammalian Cells

Study title: *In Vitro* Mammalian Chromosome Aberration Test

Study no.:	(b) (4)
Study report location:	N/A
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 27, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Phenylacetylglutamine (PAGN) UXW-M0053-SD2-1-6-41 and 90.98%

Key Study Findings

Methods

Cell line:	Chinese hamster ovary (CHO) cells
Concentrations in definitive study:	520, 1040, 1480, 2110, and 2643 µg/ml with and without S-9
Basis of concentration selection:	cell growth inhibition
Negative control:	Water
Positive control:	Mitomycin C 0.1-0.2 µg/ml Cyclophosphamide 10-15 µg/ml

Formulation/Vehicle:	Water
Incubation & sampling time:	The cells were treated for 4 or 20 hours. All cells were harvested 20 hours after treatment

Study Validity

The positive and solvent controls fulfilled the requirements for a valid test.

Results

The results indicated that phenylacetylglutamine (PAGN) did not significantly increase the proportion of cells with aberrations in the presence or absence of S-9.

4. Studies with Phenylacetylglycine (PAG)

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Bacterial Reverse Mutation Assay with n-Phenylacetylglycine (Phenaceturic Acid)

Study no.:	(b) (4)
Study report location:	N/A
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 13, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	n-Phenylacetylglycine (Phenaceturic Acid) / FC002

Key Study Findings

Methods

Strains:	TA98, TA100, TA1535 and TA1537 and *Escherichia coli* WP2 *uvr*A
Concentrations in definitive study:	1.5, 5.0, 15, 50, 150, 500, 1500 and 5000 µg per plate
Basis of concentration selection:	the maximum dose of 5000 µg per plate was tested.
Negative control:	Dimethyl sulfoxide (DMSO)
Positive control:	See table below
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Incubated for 48-72 hours using the plate incorporation method

Strain	S9 Activation	Positive Control	Concentration (µg/plate)
TA98, TA1535 and TA1537	Rat	2-aminoanthracene (b) (4) Lot No. 03403ED Exp. Date 22-Jan-2012 CAS No. 613-13-8 Purity 99.8%	1.0
TA100			2.0
WP2 *uvr*A			15
TA98	None	2-nitrofluorene (b) (4) Lot No. S43858 Exp. Date 31-Jan-2014 CAS No. 607-57-8 Purity 97.9%	1.0
TA100, TA1535		sodium azide (b) (4) Lot No. A23U048 Exp. Date 04-Dec-2012 CAS No. 26628-22-8 Purity 100.0%	1.0
TA1537		9-aminoacridine (b) (4) Lot No. 07620TD Exp. Date 31-Nov-2013 CAS No. 52417-22-8 Purity 99.9%	75
WP2 *uvr*A		methyl methanesulfonate (b) (4) Lot No. A0274779 Exp. Date 05-Jan-2013 CAS No. 66-27-3 Purity 99.8%	1,000

Study Validity

The positive controls significantly increased the colonies compared to the solvent controls.

Results

The results suggest that the test article, n-phenylacetylglycine, was not mutagenic under the assay conditions. The results were summarized in the sponsor's table below.

Table 3
Confirmatory Mutagenicity Assay without S9 activation

Study Number: (b) (4) Study Code: (b) (4)
Experiment: B2 Date Plated: 9/29/2011
Exposure Method: Plate incorporation assay Evaluation Period: 10/3/2011

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98	**n-Phenylacetylglycine (Phenaceturic Acid)**	5000 µg	*15*	*4*	*0.8*	12^A, 19^A, 15^A
		1500 µg	*15*	*2*	*0.8*	13^A, 16^A, 17^A
		500 µg	*19*	*10*	*1.0*	29^A, 9^A, 19^A
		150 µg	*16*	*5*	*0.8*	12^A, 21^A, 15^A
		50 µg	*14*	*3*	*0.7*	17^A, 11^A, 15^A
	DMSO	50 µL	*20*	*4*		20^A, 17^A, 24^A
TA100	**n-Phenylacetylglycine (Phenaceturic Acid)**	5000 µg	*89*	*16*	*1.0*	105^A, 89^A, 74^A
		1500 µg	*93*	*10*	*1.1*	94^A, 82^A, 102^A
		500 µg	*89*	*8*	*1.0*	98^A, 84^A, 84^A
		150 µg	*88*	*14*	*1.0*	101^A, 73^A, 89^A
		50 µg	*90*	*19*	*1.0*	109^A, 72^A, 90^A
	DMSO	50 µL	*87*	*7*		84^A, 81^A, 95^A
TA1535	**n-Phenylacetylglycine (Phenaceturic Acid)**	5000 µg	*11*	*2*	*0.8*	13^A, 12^A, 9^A
		1500 µg	*14*	*6*	*1.1*	12^A, 9^A, 20^A
		500 µg	*10*	*5*	*0.8*	16^A, 8^A, 7^A
		150 µg	*13*	*4*	*1.0*	15^A, 15^A, 8^A
		50 µg	*10*	*1*	*0.8*	9^A, 9^A, 11^A
	DMSO	50 µL	*13*	*4*		9^A, 13^A, 16^A
TA1537	**n-Phenylacetylglycine (Phenaceturic Acid)**	5000 µg	*4*	*1*	*0.8*	4^A, 4^A, 5^A
		1500 µg	*3*	*3*	*0.6*	0^A, 5^A, 3^A
		500 µg	*8*	*4*	*1.6*	5^A, 7^A, 12^A
		150 µg	*7*	*2*	*1.4*	7^A, 9^A, 5^A
		50 µg	*4*	*3*	*0.8*	7^A, 3^A, 1^A
	DMSO	50 µL	*5*	*1*		5^A, 4^A, 5^A

Table 3 cont.
Confirmatory Mutagenicity Assay without S9 activation

Study Number: (b) (4) Study Code: (b) (4)
Experiment: B2 Date Plated: 9/29/2011
Exposure Method: Plate incorporation assay Evaluation Period: 10/3/2011

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
WP2*uvr*A	**n-Phenylacetylglycine (Phenaceturic Acid)**	5000 µg	*23*	*5*	*0.9*	28^{A}, 19^{A}, 21^{A}
		1500 µg	*23*	*3*	*0.9*	27^{A}, 21^{A}, 21^{A}
		500 µg	*21*	*2*	*0.8*	24^{A}, 20^{A}, 20^{A}
		150 µg	*25*	*3*	*1.0*	27^{A}, 21^{A}, 27^{A}
		50 µg	*18*	*3*	*0.7*	20^{A}, 15^{A}, 19^{A}
	DMSO	50 µL	*25*	*9*		34^{A}, 25^{A}, 17^{A}
TA98	**2NF**	1.0 µg	*175*	*5*	*8.8*	174^{A}, 170^{A}, 180^{A}
TA100	**SA**	1.0 µg	*788*	*42*	*9.1*	765^{A}, 837^{A}, 763^{A}
TA1535	**SA**	1.0 µg	*571*	*18*	*43.9*	550^{A}, 578^{A}, 584^{A}
TA1537	**9AAD**	75 µg	*202*	*43*	*40.4*	232^{A}, 153^{A}, 221^{A}
WP2*uvr*A	**MMS**	1000 µg	*337*	*19*	*13.5*	328^{A}, 325^{A}, 359^{A}

Key to Positive Controls

2NF	2-nitrofluorene
SA	sodium azide
9AAD	9-Aminoacridine
MMS	methyl methanesulfonate

Key to Automatic & Manual Count Flags

^{M}: Manual count ^{A}: Automatic count

Table 4
Confirmatory Mutagenicity Assay with S9 activation

Study Number: (b) (4) Study Code: (b) (4)
Experiment: B2 Date Plated: 9/29/2011
Exposure Method: Plate incorporation assay Evaluation Period: 10/3/2011

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98	**n-Phenylacetylglycine (Phenaceturic Acid)**	5000 µg	*17*	*6*	*1.0*	23^A, 17^A, 12^A
		1500 µg	*21*	*5*	*1.2*	15^A, 24^A, 24^A
		500 µg	*24*	*1*	*1.4*	25^A, 24^A, 23^A
		150 µg	*19*	*6*	*1.1*	23^A, 23^A, 12^A
		50 µg	*21*	*5*	*1.2*	15^A, 23^A, 24^A
	DMSO	50 µL	*17*	*1*		16^A, 17^A, 17^A
TA100	**n-Phenylacetylglycine (Phenaceturic Acid)**	5000 µg	*129*	*8*	*1.0*	123^A, 138^A, 125^A
		1500 µg	*115*	*12*	*0.9*	111^A, 105^A, 129^A
		500 µg	*125*	*3*	*1.0*	126^A, 127^A, 121^A
		150 µg	*131*	*20*	*1.0*	117^A, 153^A, 122^A
		50 µg	*130*	*7*	*1.0*	137^A, 131^A, 123^A
	DMSO	50 µL	*127*	*7*		131^A, 130^A, 119^A
TA1535	**n-Phenylacetylglycine (Phenaceturic Acid)**	5000 µg	*11*	*3*	*0.8*	8^A, 13^A, 11^A
		1500 µg	*14*	*4*	*1.1*	11^A, 12^A, 19^A
		500 µg	*8*	*5*	*0.6*	8^A, 13^A, 4^A
		150 µg	*11*	*4*	*0.8*	9^A, 15^A, 8^A
		50 µg	*11*	*3*	*0.8*	7^A, 13^A, 12^A
	DMSO	50 µL	*13*	*7*		7^A, 13^A, 20^A
TA1537	**n-Phenylacetylglycine (Phenaceturic Acid)**	5000 µg	*4*	*3*	*0.6*	1^A, 5^A, 7^A
		1500 µg	*9*	*3*	*1.3*	12^A, 7^A, 8^A
		500 µg	*7*	*2*	*1.0*	8^A, 4^A, 8^A
		150 µg	*10*	*4*	*1.4*	15^A, 9^A, 7^A
		50 µg	*8*	*4*	*1.1*	4^A, 9^A, 11^A
	DMSO	50 µL	*7*	*2*		5^A, 8^A, 8^A

Table 4 cont.
Confirmatory Mutagenicity Assay with S9 activation

Study Number: (b) (4)
Experiment: B2
Exposure Method: Plate incorporation assay
Study Code: (b) (4)
Date Plated: 9/29/2011
Evaluation Period: 10/3/2011

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
WP2*uvr*A	**n-Phenylacetylglycine (Phenaceturic Acid)**	5000 µg	*22*	*11*	*0.8*	32^{A}, 11^{A}, 24^{A}
		1500 µg	*27*	*10*	*1.0*	36^{A}, 29^{A}, 17^{A}
		500 µg	*22*	*2*	*0.8*	20^{A}, 24^{A}, 23^{A}
		150 µg	*30*	*6*	*1.1*	27^{A}, 37^{A}, 25^{A}
		50 µg	*27*	*7*	*1.0*	34^{A}, 27^{A}, 21^{A}
	DMSO	50 µL	*28*	*6*		33^{A}, 29^{A}, 21^{A}
TA98	**2AA**	1.0 µg	*295*	*8*	*17.4*	298^{A}, 286^{A}, 302^{A}
TA100	**2AA**	2.0 µg	*664*	*19*	*5.2*	642^{A}, 679^{A}, 671^{A}
TA1535	**2AA**	1.0 µg	*56*	*13*	*4.3*	41^{A}, 65^{A}, 61^{A}
TA1537	**2AA**	1.0 µg	*50*	*7*	*7.1*	54^{A}, 42^{A}, 54^{A}
WP2*uvr*A	**2AA**	15 µg	*254*	*16*	*9.1*	256^{A}, 268^{A}, 237^{A}

Key to Positive Controls

2AA 2-aminoanthracene

Key to Automatic & Manual Count Flags

^{M}: Manual count ^{A}: Automatic count

In Vitro Assays in Mammalian Cells

Study title: *In Vitro* Mammalian Chromosome Aberration Test

Study no.: (b) (4)
Study report location: N/A
Conducting laboratory and location: (b) (4)
Date of study initiation: September 9, 2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: n-Phenylacetylglycine (phenaceturic Acid) FC002

Key Study Findings

Methods

Cell line:	Chinese hamster ovary (CHO) cells
Concentrations in definitive study:	80, 162, 324, 460, 660, 950, 1350, and 1932 µg/ml with and without S-9
Basis of concentration selection:	cell growth inhibition
Negative control:	DMSO
Positive control:	Mitomycin C 0.1-0.2 µg/ml Cyclophosphamide 10-15 µg/ml
Formulation/Vehicle:	DMSO
Incubation & sampling time:	The cells were treated for 4 or 20 hours. All cells were harvested 20 hours after treatment

Study Validity

The positive and solvent controls fulfilled the requirements for a valid test.

Results

The results indicated that n-phenylacetylglycine did not significantly increase the proportion of cells with aberrations in the presence or absence of S-9.

7 Carcinogenicity

MOUSE:

Study title: HPN-100 (Glyceryl Tri-(4-Phenylbutyrate) [GT4P]: 26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 Mice

Study no.:	(b) (4)
Study report location:	N/A
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 15, 2010 (report dated May 03, 2011)
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lot # XA210B; 99.0%
CAC concurrence:	Yes (see meeting minutes from July 17, 2012 in Appendix)

Key Study Findings

HPN-100 was well tolerated at all dose levels (600 and 1000 mg/kg/day). The FDA statistical review concluded that HPN-100 did not produce any significant increase in tumor incidence.

Adequacy of Carcinogenicity Study

The carcinogenicity study was conducted appropriately.

Appropriateness of Test Models

The test model was appropriate.

Evaluation of Tumor Findings

The tumor incidences were within the historical control ranges from the testing laboratory. No statistically significant increase in tumors was observed in groups treated with HPN-100. Treatment with urethane (positive control) produced a high incidence of lung tumors and hemangiosarcoma in spleen. The Executive Carcinogenicity Assessment Committee concluded that there were no drug-related neoplasms.

Methods

Doses:	0 (water), 0 (water), 600, and 1000 mg/kg/day; 1000 mg/kg urethane (positive control)
Frequency of dosing:	daily
Dose volume:	0.91, 0.91, 0.54, and 0.91 ml/kg
Route of administration:	oral
Formulation/Vehicle:	HPN-100 was given as a neat liquid
Basis of dose selection:	MTD and minimum feasible dose (see Executive CAC minutes from February 16, 2010 in the appendix)
Species/Strain:	Hemizygous Tg.rasH2 mice Males (20.7-26.3 g) Females (15.1-21.1 g)
Number/Sex/Group:	25
Age:	9 weeks
Animal housing:	individually
Paradigm for dietary restriction:	none
Dual control employed:	no
Interim sacrifice:	no
Satellite groups:	5/sex/group
Deviation from study protocol:	Deviations did not have a significant impact on the study outcome.

Mice were treated with HPN-100 (neat) at dose levels of 600 and 1000 mg/kg/day via oral gavage for 26 weeks. The dose levels were recommended by the Executive

Carcinogenicity Assessment Committee, based on MTD and the minimum feasible dose. Two water control groups were included. The positive control animals received urethane at 1000 mg/kg via intraperitoneal injection on Days 1, 3 and 5. The toxicokinetic evaluation (exposure study) was conducted in hybrid CByB6F1 (nontransgenic) mice (5 mice/sex/group). The study design was summarized in Text Table 7 from the study report (shown below).

Text Table 7. Experimental Design for Carcinogenicity Assessment and Exposure to HPN-100 in Mice

Group	Treatment	Dose levels (mg/kg/day)	Dose Volume (mL/kg/day)	Number of Animals			
				Main Study (Tg.rasH2)		Exposure Study (wild type littermates)**	
				Male	Female	Male	Female
Group 1 (Water Control)	Water Control	0	0.91	25	25	5	5
Group 2 (water Control)	Water Control	0	0.91	25	25	5 -	5 -
Group 3 (Low Dose)	HPN-100	600	0.54	25	25	5	5
Group 4 (High Dose)	HPN-100	1000	0.91	25	25	5	5
Group 5	urethane	1000 (urethane)*	10	16	15	-	-
Total				116	115	20	20

*The positive control animals were administered a total of 3 intraperitoneal (i.p.) injections (one each on Study Days (SD) 1, 3, and 5).

**Exposure bleeds were performed on Day 183 or 184 (3 mice/sex, except 5 males for Group 1, at 2 hours post-dose). Extra animals (2/sex) were assigned to the study to try to ensure that adequate animals were available at the end of the study.

Clinical signs of toxicity and mortality were observed daily. Body weights and food consumption were determined. All animals were necropsied at termination. Complete histopathological examination was performed on all treated animals in all main study groups. The tumor data were analyzed using the Peto prevalence method, Peto death rate method, and Peto combined analysis (incidental and fatal tumors).

Observations and Results

Mortality: Two high-dose females died before study termination. Malignant tumors were found in these females and were considered as the cause of death (multicentric

lymphoma in the female that died on day 49, and primary malignant hemangiosarcoma of the liver in the female that died on day 164). One control female was found dead on day 181. This female had malignant multicentric mesothelioma of the nasal cavity and lung. One low-dose male was found dead on day 28. This male had axonal degeneration of the spinal cord.

The mortality information was summarized in the following table (taken from the study report).

TABLE 1 - SUMMARY OF MORTALITY (MAIN STUDY)

MALES

Day of Death	Mode of Death	Group 1	Group 2	Group 3	Group 4	Group 5*	COD
Day 28	Found Dead	-	-	1/25	-	-	SPINE
Various Days	Positive Control						
Between Day 6 and Day 107	Early Death (Found Dead or Moribund Sacrifice)	-	-	-	-	6	PC††
Day 110	Scheduled sacrifice	-	-	-	-	1	
Day 117	Scheduled Sacrifice	-	-	-	-	9	
Day 183 or 184	Terminal Sacrifice	25/25	25/25	24/25	25/25	-	
	TOTAL:	**25/25**	**25/25**	**25/25**	**25/25**	**16/16†**	

FEMALES

Day of Death	Mode of Death	Group 1	Group 2	Group 3	Group 4	Group 5*	COD
Day 49	Moribund Sacrifice	-	-	-	1/25	-	LYMPH
Day 164	Found Dead	-	-	-	1/25	-	HEMAN
Day 181	Found Dead	1/25	-	-	-	-	MESO
Various Days	Positive Control						
Between Day 43 and Day 114	Early Death (Found Dead or Moribund Sacrifice)	-	-	-	-	8	PC
Day 115	Scheduled Sacrifice	-	-	-	-	7	
Day 183 or 184	Terminal Sacrifice	24/25	25/25	25/25	23/25	-	
	TOTAL:	**25/25**	**25/25**	**25/25**	**25/25**	**15/15**	

COD = Cause of Early Death PC: the expected sequelae of the positive control caused early death
MESO: nasal cavity, lungs with bronchi and trachea: mesothelioma; malignant; multicentric
SPINE: spinal cord, thoracic & lumbar; degeneration; axonal
LYMPH: malignant lymphoma, multicentric HEMAN: liver; hemangiosarcoma; malignant; primary
Notes: Represents the number of animals affected / the number of animals started on test.
There was no evidence of gavage error in any animal that died early.
†An extra male was added to Group 5 to replace an animal that was found dead on Day 6.
†† The cause of death for #2103 was entered as "undetermined" by the pathologist, but is still considered to be caused by treatment with the test article.
*p<0.05 (Fisher's Exact Test): Early death in this group was significantly increased compared to the vehicle control mice (Group 1 and 2 combined).
Nominal Dose: Group 1 - 0 mg/kg/day Group 2 - 0 mg/kg/day
Group 3 - 600 mg/kg/day Group 4 - 1000 mg/kg/day
Group 5 - positive control (urethane, 1000 mg/kg via i.p. administration one each on Days 1, 3 and 5

Clinical Signs: Hyperactivity was significantly increased in the treatment groups as compared to the control groups.

Body Weight: The initial and final body weights for the control animals were 23.1-23.4 and 27-27.4 g, respectively, for males and 18.4-18.7 and 22.4-22.7 g, respectively, for females. The terminal body weight gains were 3.98, 3.88, 3.42, 4.72 g in control 1,

control 2, low, and high dose males, respectively, and 3.88, 3.86, 4.24, 4.8 g in control 1, control 2, low, and high dose females, respectively. The body weight gain was higher in the high dose males, and in females in both HPN-100-treated groups, as compared to the controls. The growth curves were not provided.

Feed Consumption: There were no treatment-related changes.

Gross Pathology: No treatment-related changes were observed.

Histopathology

Peer Review: Yes.

Non-Neoplastic Changes: There were no treatment-related changes.

Neoplastic Changes:

The positive control article produced a marked increase in the incidence of lung tumors, whereas HPN-100 had no effects on the incidence of lung tumors. The incidence of pulmonary tumors was summarized in the following table (taken from the study report).

Lung Tumors

Text Table 2

MALE						
	Group 1	Group 2	Group 3	Group 4	Group 5	HCR
Adenoma, single	3	5	0	1	0	0-6
Adenoma, multiple	0	0	0	1	15	0-1
Carcinoma	0	0	0	0	6	0-2
All Lung Tumors	3	5	0	2	15*	0-6
FEMALE						
	Group 1	Group 2	Group 3	Group 4	Group 5	HCR
Adenoma, single	1	1	0	2	0	0-6
Adenoma, multiple	0	0	0	0	15	0-1
Carcinoma	0	0	0	0	9	0-1
All Lung Tumors	1	1	0	2	15*	0-6

Dose group 1: water control
Dose group 2: water control
Dose group 3: HPN-100, 600 mg/kg/day
Dose group 4: HPN-100, 1000 mg/kg/day
Dose group 5: Urethane
Number of animals examined: 25, groups 1, 2, 3 and 4
Number of animals examined: 15, group 5
HCR: Historical Control Range for vehicle control animals (See Appendix 2).
*: Multiple adenomas and/or carcinomas were present in some of the same animals in Urethane treated mice

The positive control article produced a marked increase in the splenic hemangiosarcoma rate, whereas no effect was observed with HPN-100, as shown the table below (taken from the study report).

Spleen Tumors

Text Table 3

MALE						
	Group 1	Group 2	Group 3	Group 4	Group 5	HCR
Hemangiosarcoma	1	0	0	0	14	0-4
FEMALE						
	Group 1	Group 2	Group 3	Group 4	Group 5	HCR
Hemangiosarcoma	1	1	1	2	14	0-4

Dose group 1: water control
Dose group 2: water control
Dose group 3: HPN-100, 600 mg/kg/day
Dose group 4: HPN-100, 1000 mg/kg/day
Dose group 5: Urethane
Number of animals examined: 25, groups 1, 2, 3 and 4
Number of animals examined: 15, group 5
HCR: Historical Control Range for vehicle control animals (See Appendix 2).

The combined incidence of hemangiomas and hemangiosarcomas in multiple organs is summarized in the following table. The treatment with HPN-100 did not significantly increase the combined incidence of hemangiomas and hemangiosarcoma as compared to the control groups.

Hemangiomas and Hemangiosarcomas

Text Table 4

MALE					
	Group 1	Group 2	Group 3	Group 4	HCR
Hemangiomas or Hemangiosarcomas					
Spleen	1	0	0	0	0-4
Lung	0	0	1	0	0-1
Skin	0	0	0	1	0-1
Combined Incidence	1	0	1	1	0-4
FEMALE					
	Group 1	Group 2	Group 3	Group 4	HCR
Hemangiomas or Hemangiosarcomas					
Spleen	1	1	1	2	0-4
Liver	0	0	0	1	NR
Ovary #	0	0	1	0	0-1
Uterus	0	1	0	0	0-2
Combined Incidence	1	2	2	3	0-5

Dose group 1: water control
Dose group 2: water control
Dose group 3: HPN-100, 600 mg/kg/day
Dose group 4: HPN-100, 1000 mg/kg/day
Number of animals examined: 25, groups 1, 2, 3 and 4
Number of animals examined: 15, group 5
HCR: Historical Control Range for vehicle control animals (See Appendix 2).
NR: Not recorded in our historical control data base.
#: Hemangioma recorded in ovary, hemangiosarcomas recorded in all other tissues.

The incidences of other types of tumors (non-vascular and non-pulmonary) were presented in the following table (taken from the study report). The treatment with HPN-100 did not significantly increase the incidence of these tumors as compared to the control groups.

Non-Vascular and Non-Pulmonary Tumors

Text Table 5

Male					
	Group 1	Group 2	Group 3	Group 4	HCR
Liver, adenoma	0	0	0	1	NR
Female					
	Group 1	Group 2	Group 3	Group 4	HCR
Harderian gland, adenoma	0	1	0	2	0-4
Lymphoma, multicentric	0	0	0	1	0-1
Thymus, thymoma	1	0	2	0	NR
Ear, papilloma	0	0	1	0	NR
Multicentric mesothelioma	1	0	0	1	0-1
Ear, squamous cell carcinoma	0	0	0	1	0-1

Dose group 1: water control
Dose group 2: water control
Dose group 3: HPN-100, 600 mg/kg/day
Dose group 4: HPN-100, 1000 mg/kg/day
Number of animals examined: 25, groups 1, 2, 3 and 4
Number of animals examined: 15, group 5
HCR: Historical Control Range for vehicle control animals (See Appendix 2).
NR: Not recorded in our historical control data base.

The tumor incidences were within the historical control ranges from the testing laboratory. The FDA statistical review of this study concluded that treatment with HPN-100 did not significantly increase the tumor incidences in both males and females as compared to each of the water controls and the combined water controls (see review by Dr. Min Min).

Toxicokinetics: HPN-100 is rapidly converted to PBA (4-phenylbutyric acid) in the GI tract. PBA is oxidized to PAA (phenylacetic acid). In mice, PAA conjugates with glycine forming PAG (phenylacetylglycine). The plasma concentrations of the above mentioned metabolites were analyzed in this study and the results were summarized in the following table (taken from the study report).

Table 2: Tabulation of Plasma Concentrations

		Dose HPN-100 (mg/kg)							
		0	0	600	1000	0	0	600	1000
		Males				Females			
PBA	µg/mL	BQL	BQL	1.273	25.415	BQL	BQL	24.547	13.957
		BQL	BQL	5.916	17.620	BQL	BQL	7.820	5.248
		BQL	BQL	11.226	8.331	BQL	BQL	6.662	7.127
	Average	0.000	0.000	6.138	17.122	0.000	0.000	13.010	8.777
	SD	0.000	0.000	4.980	8.553	0.000	0.000	10.008	4.583
	N	3	3	3	3	3	3	3	3
PAA	µg/mL	BQL	BQL	50.233	123.570	BQL	BQL	248.863	286.500
		BQL	BQL	86.029	560.323	BQL	BQL	329.643	479.881
		BQL	BQL	BQL	131.951	BQL	BQL	343.712	745.387
	Average	0.000	0.000	68.131	271.948	0.000	0.000	307.406	503.923
	SD	0.000	0.000	25.312	249.775	0.000	0.000	51.185	230.386
	N	3	3	2	3	3	3	3	3
PAG	µg/mL	BQL	BQL	4.675	19.493	BQL	BQL	12.086	16.717
		BQL	BQL	14.516	39.741	BQL	BQL	22.630	14.301
		BQL	BQL	12.884	18.567	BQL	BQL	17.209	26.039
	Average	0.000	0.000	10.692	25.934	0.000	0.000	17.308	19.019
	SD	0.000	0.000	5.274	11.966	0.000	0.000	5.273	6.198
	N	3	3	3	3	3	3	3	3

Dosing Solution Analysis: The test article was a neat liquid, and was stable throughout the study period.

RAT:

Study title: HPN-100 (Glyceryl Tri-(4-Phenylbutyrate) [GT4P]: 24-Month Repeated Dose Oral Carcinogenicity Study in Crl:CD(SD) Rats

Study no.:	(b) (4) 671007
Study report location:	N/A
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 22, 2008 (report dated September 14, 2011)
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lot # XA171; 98.8-101.2% Lot # XA179; 98.3-103.9%
CAC concurrence:	Yes (see meeting minutes from July 17, 2012 in Appendix)

Key Study Findings

HPN-100 did not produce statistically significant changes in mortality. The terminal body weight was 7% and 11% lower in the high dose males and females, respectively, as compared to the water control group. The terminal body weight gain was 13% and 21% lower in the high dose males and females, respectively, as compared to the water control group. Treatment-related non-neoplastic changes included focal hypertrophy in the adrenal cortex, pancreatic acinar cell hyperplasia, follicular cell hyperplasia in the thyroid gland, cystic endometrial hyperplasia of the uterus, Zymbal's gland hyperplasia, basophilic foci in the liver, and retinal atrophy.

The Executive Carcinogenicity Assessment Committee concluded that HPN-100 increased the incidence of the following neoplasms, as indicated by statistical significance in both the dose-response and pair-wise tests using the water control group, with exception of Zymbal's gland carcinoma in males: in males pancreatic acinar cell adenoma, carcinoma and combined adenoma or carcinoma at the high dose and Zymbal's gland carcinoma at the middle and high doses, and in females, pancreatic acinar cell adenoma, carcinoma and combined adenoma or carcinoma at the high dose, thyroid follicular cell adenoma, carcinoma and combined adenoma or carcinoma at the high dose, adrenal cortical combined adenoma or carcinoma at the high dose, uterine endometrial stromal polyp and combined polyp or sarcoma at the high dose, and Zymbal's gland carcinoma at the high dose. The increased incidence of Zymbal's gland carcinoma in males was considered to be drug-related, based on the very low incidence of this neoplasm in historical control data.

Adequacy of Carcinogenicity Study

The study was conducted appropriately.

Appropriateness of Test Models

The test model was appropriate.

Evaluation of Tumor Findings

Statistically significant dose-response relationships were found for the following tumors, based on comparison to the water control group: acinar cell adenoma, carcinoma and combined adenoma or carcinoma in pancreas in both sexes, follicular cell adenoma in thyroid in both sexes, malignant schwannoma in skin in males, malignant lymphoma in males, adenoma and combined adenoma or carcinoma in adrenal cortex in females, hepatocellular adenoma in females, follicular cell carcinoma and combined adenoma or carcinoma in thyroid in females, polyp and combined polyp or sarcoma in uterus, and carcinoma in Zymbal's glands in females (see statistical review by Dr. Min Min).

The FDA statistical review also found significant increases in the following tumors, based on pair-wise comparison to the water control group: acinar cell adenoma, carcinoma and combined adenoma or carcinoma in pancreas in high-dose groups for both sexes, follicular cell adenoma in thyroid in high-dose groups for both sexes, combined adenoma or carcinoma in adrenal cortex in high-dose females, follicular cell carcinoma and combined follicular cell adenoma or carcinoma in thyroid in high-dose females, polyp and combined polyp or sarcoma in uterus in high-dose females, and carcinoma in the Zymbal's glands in high-dose females.

Methods

Doses:	Males: 0 (water), 0 (corn oil), 70, 210, and 650 mg/kg/day Females: 0 (water), 0 (corn oil), 100, 300, and 900 mg/kg/day
Frequency of dosing:	daily
Dose volume:	See study design table below
Route of administration:	oral gavage
Formulation/Vehicle:	HPN-100 was given as a neat liquid
Basis of dose selection:	MTD in males, single-dose lethality in females (see Executive CAC meeting minutes from August 12, 2008 in the appendix)
Species/Strain:	Crl:CD(SD) rats Males (209-292 g) Females (150-196 g)
Number/Sex/Group:	65
Age:	7 weeks
Animal housing:	individually
Paradigm for dietary restriction:	none
Dual control employed:	water and corn oil
Interim sacrifice:	no
Satellite groups:	6/sex/group
Deviation from study protocol:	Deviations did not have a significant impact on the study outcome.

Toxicology Groups ([(b) (4)]671007M and [(b) (4)]671007F)

Group Number	Treatment	Dosage Level (mg/kg/day)		Dose Volume (mL/kg)		Number of Animals [a]	
		Males	Females	Males	Females	Males	Females
1	Control 1	0	0	0.59	0.82	65	65
2	Control 2	0	0	0.59	0.82	65	65
3	HPN-100	70	100	0.06	0.09	65	65
4	HPN-100	210	300	0.19	0.27	65	65
5	HPN-100	650	900	0.59	0.82	65	65

In this study, clinical signs of toxicity and mortality were observed daily. Body weights and food consumption were determined. All animals were necropsied at termination. Complete histopathological examination was performed on all treated animals in all main study groups. The tumor data were analyzed using the Peto's mortality-prevalence method.

Observations and Results

Mortality: There were no statistically significant changes in survival rates. The mortality information was summarized in the following table and figures (taken from the study report).

Table 4.1.1 Kaplan-Meier Estimates of Survival

		Kaplan-Meier Estimates and P-values					Overall / Trend
Sex	Week	Control 1	Control 2	Low	Mid	High	
M	52	92	89	88	83	85	
	78	75	77	64	66	69	
	92	65	42	44	44	48	
	End of Study	38	27	28	30	26	
	p-value (1)		0.0502	NT	NT	NT	0.1163 (O) 0.0882 (T)
	p-value (2)			NT	NT	NT	0.9881 (O) 0.9276 (T)
F	52	94	98	92	98	89	
	78	68	71	68	57	69	
	92	43	38	43	38	38	
	End of Study	21	27	35	28	28	
	p-value (1)		0.8296	NT	NT	NT	0.7706 (O) 0.4921 (T)
	p-value (2)			NT	NT	NT	0.6399 (O) 0.3644 (T)

p-values:
(1): Comparisons using control group 1
(2): Comparisons using control group 2
* - statistically significant at the 0.05 significance level. NT = Not tested per statistical methodology.

Figure 5.1.3 Kaplan-Meier Estimates of Survival: Males

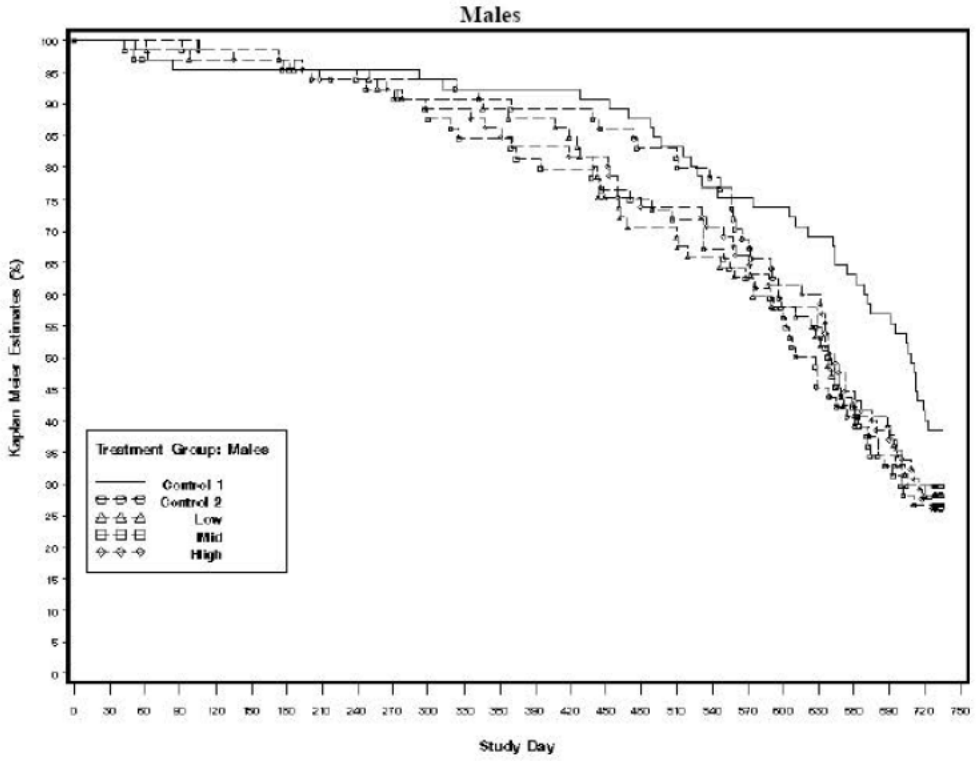
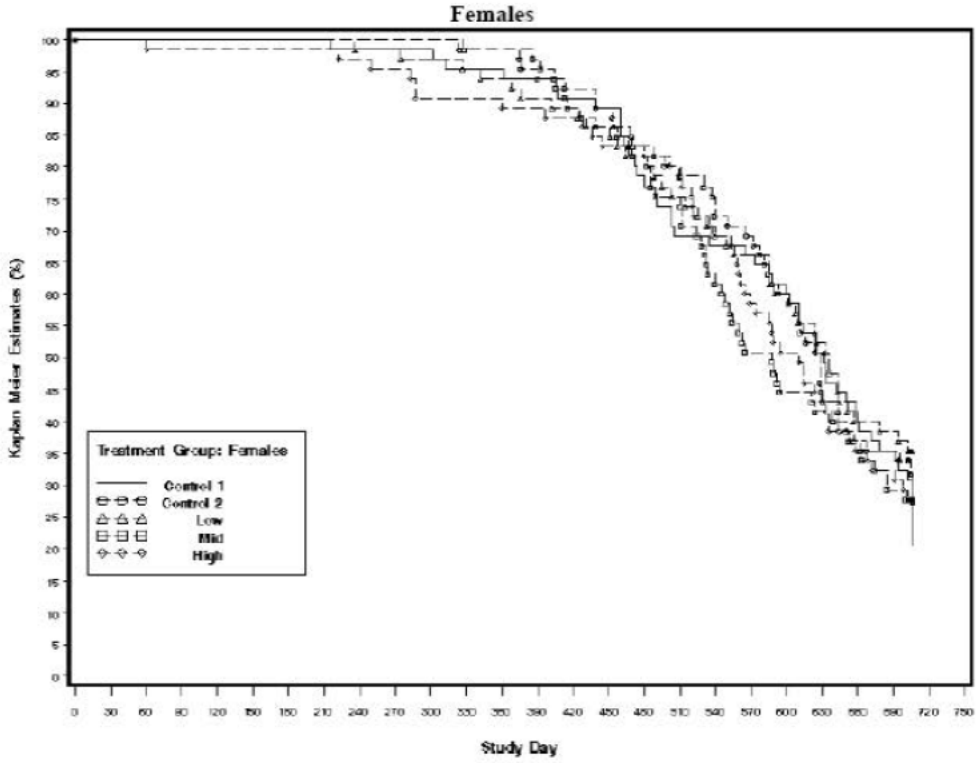
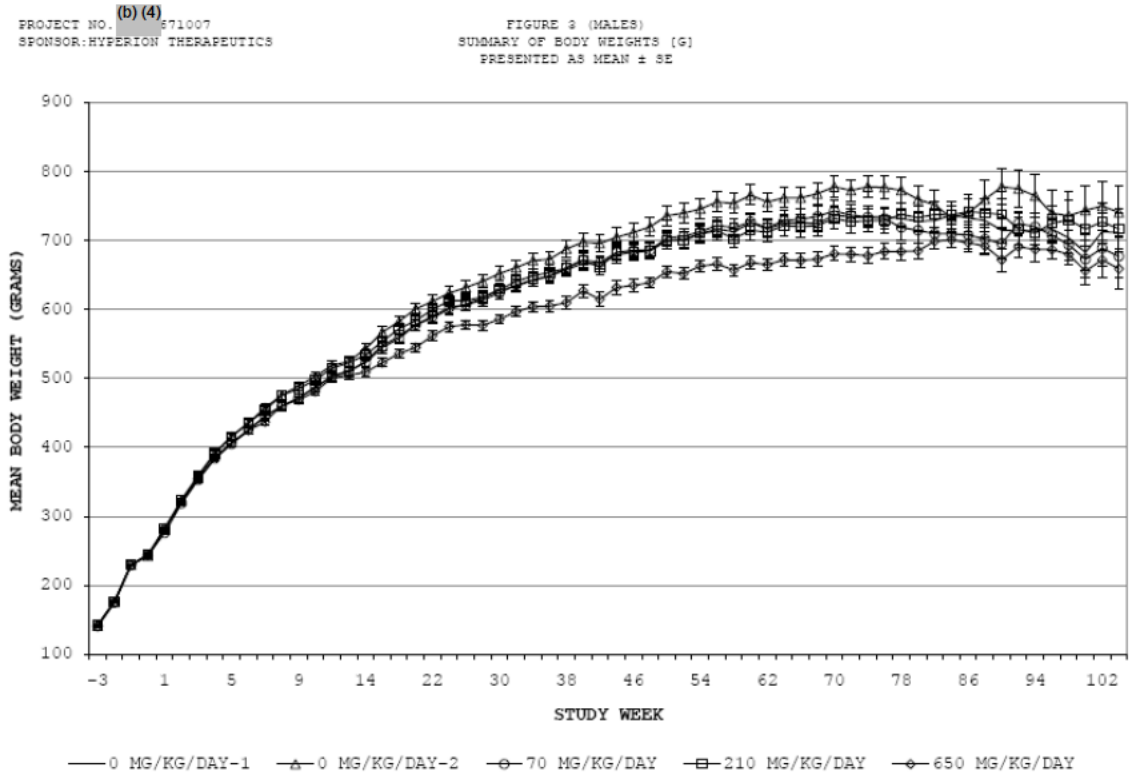


Figure 5.1.4 Kaplan-Meier Estimates of Survival: Females



Clinical Signs: Hypoactivity, rigid muscle tone, and impaired muscle coordination were observed in the first 1-5 days of dosing in the treatment groups. In addition, clear, yellow, red, and/or brown material around the mouth, ventral trunk, and/or anogenital area and reddened ears were noted in the high dose group. Yellow material around the urogenital area was noted in the middle- and high-dose groups.

Body Weight: The initial and final body weights for the control animals were 243 and 712-741 g, respectively, for males (weeks 0-104), and 175 and 422-459 g, respectively, for females (weeks 0-100). The terminal body weight was 7% and 11% lower in the high dose males and females, respectively, as compared to the control group (control 1). The terminal body weight gains were 472, 499, 437, 475, and 412 g in control 1, control 2, low, middle, and high dose males, respectively, and 293, 251, 335, 296, and 232 g in control 1, control 2, low, middle, and high dose females, respectively. The terminal body weight gain was 13% and 21% lower in the high dose males and females, respectively, as compared to the control group (control 1). The growth curves are attached below (taken from the study report).



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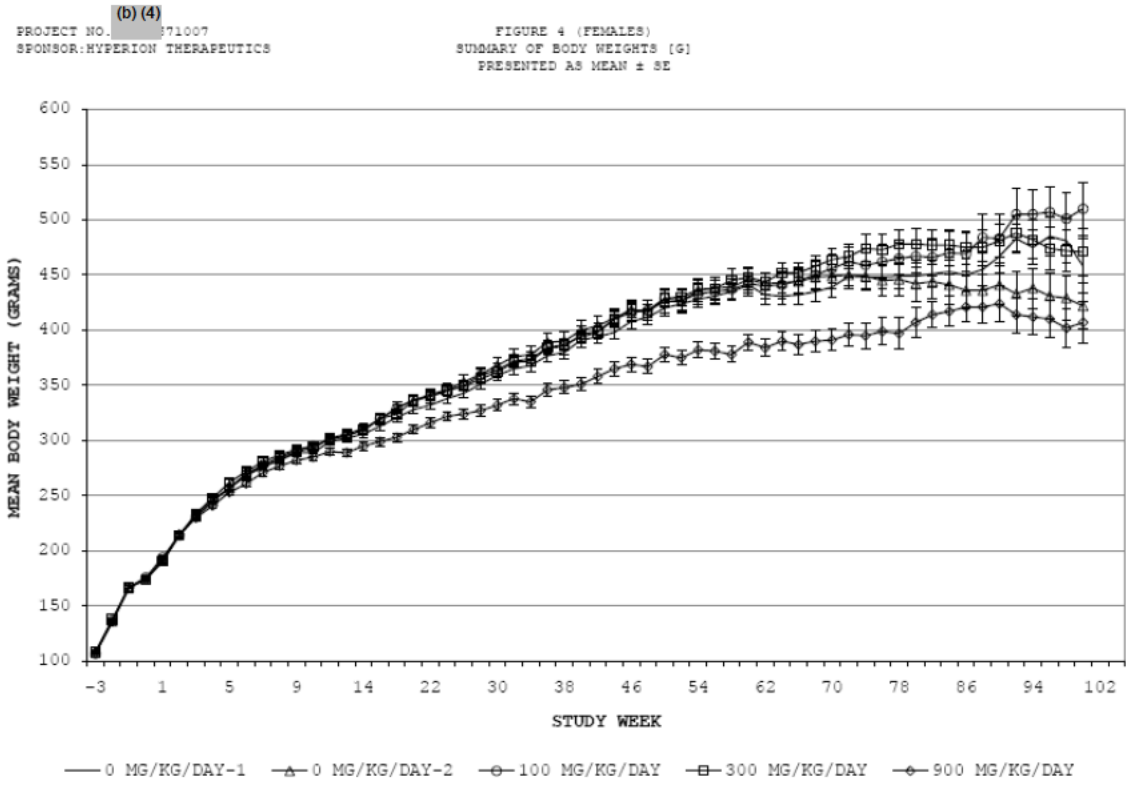

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Feed Consumption: There were no treatment-related changes.

Gross Pathology:

For males, there were higher incidences of gross findings in the pancreas, adrenal glands, mammary gland, and skin in the treatment groups, as summarized in the sponsor's table below.

Text Table 9. Selected Macroscopic Findings - Males, All Necropsies

Dose (mg/kg/day)	Control 1	Control 2	70	210	650
Number of Animals in Group	65	65	65	65	65
Pancreas					
Mass	2	1	1	0	6
Nodule	2	1	1	1	7
Adrenal Gland					
Mass	0	0	1	4	2
Enlarged	3	1	7	4	6
Area, dark red	1	1	1	3	4
Mottled	2	1	1	3	6
Skin					
Mass	10	8	10	12	17
Mammary Gland					
Mass	4	5	11	7	13

For females, there were higher incidences of gross findings in the pancreas, adrenal gland, uterus, and cervix in the treatment groups, as summarized in the sponsor's table below.

Text Table 10. Selected Macroscopic Findings - Females, All Necropsies

Dose (mg/kg/day)	Control 1	Control 2	100	300	900
Number of Animals in Group	65	65	65	65	65
Pancreas					
Mass	1	0	1	1	5
Nodule	0	0	1	2	5
Adrenal Gland					
Mass	0	3	2	1	5
Enlarged	14	10	22	26	35
Lobulated	0	1	10	14	21
Uterus					
Cyst(s)	9	8	18	18	26
Cervix					
Mass	2	1	0	6	4
Enlarged	1	1	4	2	2
Thickened	1	1	1	2	0

Histopathology

Peer Review: Yes.

Non-Neoplastic Changes: Treatment-related changes include focal hypertrophy in the adrenal cortex, pancreatic acinar cell hyperplasia, follicular cell hyperplasia in the thyroid gland, cystic endometrial hyperplasia of the uterus, Zymbal's gland hyperplasia, basophilic foci in the liver, and retinal atrophy in the eye. The incidences of these changes are summarized in the following tables (taken from the study report).

Text Table 12. Incidence of Selected Non-Neoplastic Findings, All Animals

	Males					Females				
Dosage (mg/kg/day):	**0**	**0**	**70**	**210**	**650**	**0**	**0**	**100**	**300**	**900**
Adrenal Cortex [a]	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**
Hypertrophy, focal, zona fasciculata	22	25	27	31	38	23	18	31	37	36
Minimal	11	14	11	9	7	4	9	3	1	0
Mild	8	9	12	16	16	15	5	15	16	7
Moderate	3	2	3	5	14	4	4	11	18	27
Severe	0	0	1	1	1	0	0	2	2	2
Pancreas [a]	**64**	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**
Hyperplasia, acinar cell	3	5	4	14	27	0	0	4	3	23
Minimal	2	4	3	9	9	-	-	3	2	7
Mild	1	1	1	5	8	-	-	1	1	10
Moderate	0	0	0	0	8	-	-	0	0	6
Severe	0	0	0	0	2	-	-	0	0	0
Thyroid Gland [a]	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**
Hyperplasia, follicular cell	1	3	4	6	8	0	1	3	5	10
Minimal	0	0	0	3	4	-	0	2	3	5
Mild	1	1	4	2	3	-	1	1	1	2
Moderate	0	2	0	1	1	-	0	0	1	3

[a] = Number of tissues examined from each group.

Text Table 12 (continued). Incidence of Selected Non-Neoplastic Findings, All Animals

	Males					Females				
Dosage (mg/kg/day):	**0**	**0**	**70**	**210**	**650**	**0**	**0**	**100**	**300**	**900**
Uterus [a]	**0**	**0**	**0**	**0**	**0**	**65**	**65**	**65**	**65**	**65**
Hyperplasia, cystic endometrial	0	0	0	0	0	14	16	26	26	41
Minimal	-	-	-	-	-	8	9	11	8	10
Mild	-	-	-	-	-	5	6	12	13	19
Moderate	-	-	-	-	-	1	1	3	5	9
Severe	-	-	-	-	-	0	0	0	0	3
Zymbal's Gland [a]	**62**	**56**	**62**	**59**	**58**	**63**	**64**	**64**	**65**	**62**
Hyperplasia	0	0	0	0	2	0	0	0	1	0
Minimal	-	-	-	-	1	-	-	-	0	-
Mild	-	-	-	-	1	-	-	-	0	-
Moderate	-	-	-	-	0	-	-	-	1	-
Liver [a]	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**
Focus, basophilic cell	17	13	13	10	17	19	17	23	32	40
Minimal	15	12	12	9	16	18	10	18	20	25
Mild	2	1	1	1	1	0	6	3	8	11
Moderate	0	0	0	0	0	0	1	2	3	4
Severe	0	0	0	0	0	1	0	0	1	0
Eye [a]	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**
Atrophy, retinal	3	4	1	1	2	3	4	1	8	29
Minimal	1	1	0	0	1	0	2	1	3	4
Mild	0	1	1	1	1	3	2	0	5	9
Moderate	2	2	0	0	0	0	0	0	0	16

[a] = Number of tissues examined from each group.

Neoplastic Changes: The incidences of selected tumors are summarized in the following table (taken from the study report).

Text Table 11. Incidence of Selected Neoplastic Findings, All Animals

	Males					Females				
Dosage (mg/kg/day):	**0**	**0**	**70**	**210**	**650**	**0**	**0**	**100**	**300**	**900**
Adrenal Cortex [a]	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**
Adenoma	1	1	2	1	1	1	1	2	1	7*†
Carcinoma	1	0	1	4*	5*†	0	2	1	2	3
Adenoma/Carcinoma	2	1	3	5*	6	0	3	3	3	10*†
Pancreas [a]	**64**	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**
Adenoma, acinar cell	1	1	0	3	8*†	0	0	0	0	6*†
Carcinoma, acinar cell	0	0	0	0	6*†	0	0	0	2	6*†
Adenoma/Carcinoma, acinar cell	1	2	0	3	14*†	0	0	0	2	12*†
Thyroid Gland [a]	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**
Adenoma, follicular cell	0	1	3	3	6*	0	1	1	2	9*†
Carcinoma, follicular cell	2	2	1	1	1	0	1	2	2	5*†
Adenoma/Carcinoma, follicular cell	2	3	4	4	7	0	2	3	4	14*†
Uterus [a]	**0**	**0**	**0**	**0**	**0**	**65**	**65**	**65**	**65**	**65**
Polyp, endometrial stromal	0	0	0	0	0	2	1	5	4	12*†
Sarcoma, endometrial stromal	0	0	0	0	0	0	0	0	0	1
Zymbal's Gland [a]	**62**	**56**	**62**	**59**	**58**	**63**	**64**	**64**	**65**	**62**
Carcinoma	1	1	2	5	5	0	1	1	2	5*†
Cervix [a]	**0**	**0**	**0**	**0**	**0**	**65**	**65**	**65**	**65**	**64**
Schwannoma, malignant	0	0	0	0	0	2	0	1	8*	1

[a] = Number of tissues examined from each group.
* = Statistically significant when compared with control Group 1 and/or control Group 2.
† = Statistically significant for dose response when compared with control Group 1 and/or control Group 2.

The results of the sponsor's statistical analysis including pair-wise and trend tests are summarized in the following tables (taken from the study report).

Table 4.2.3 Statistically Significant Tumor Findings: Males

Organ	Tumor	Low	Mid	High	Trend
Adrenal Cortex	#M Carcinoma	NS	*	*	*
	Carcinoma/Adenoma	NS	*	NS	NS
Brain	#B Granular Cell Tumor, Benign	*	NS	NS	NS
Pancreas	#M Carcinoma, Acinar Cell	NS	NS	*	*
	#M Adenoma, Acinar Cell	NS	NS	*	*
	Carcinoma/Adenoma, Acinar Cell	NS	NS	*	*
Skin	#M Schwannoma, Malignant	NS	NS	NS	*
Thyroid Glands	#B Adenoma, Follicular Cell	NS	NS	*	NS

*: Statistically significant when compared with control group 1 and/or control group 2
NS: Not statistically significant when compared with both control groups 1 and 2

Table 4.2.4 Statistically Significant Tumor Findings: Females

Organ	Tumor	Low	Mid	High	Trend
Adrenal Cortex	#B Adenoma	NS	NS	*	*
	Carcinoma/Adenoma	NS	NS	*	*
Cervix	#M Schwannoma, Malignant	NS	*	NS	NS
Liver	#B Adenoma, Hepatocellular	NS	NS	NS	*
	Carcinoma/Adenoma, Hepatocellular	NS	NS	NS	*
Mammary Gland	#B Fibroadenoma	*	NS	NS	NS
Pancreas	#M Carcinoma, Acinar Cell	NS	NS	*	*
	#M Adenoma, Acinar Cell	NS	NS	*	*
	Carcinoma/Adenoma, Acinar Cell	NS	NS	*	*
Thyroid Glands	#M Carcinoma, Follicular Cell	NS	NS	*	*
	#B Adenoma, Follicular Cell	NS	NS	*	*
	Carcinoma/Adenoma, Follicular Cell	NS	NS	*	*
Uterus	#B Polyp, Endometrial Stromal	NS	NS	*	*
Zymbal's Gland	#M Carcinoma	NS	NS	*	*

*: Statistically significant when compared with control group 1 and/or control group 2
NS: Not statistically significant when compared with both control groups 1 and 2

The sponsor's statistical analysis indicated that the following tumors show positive dose-response trends: adrenal cortical carcinomas in males, adrenal cortical adenomas in females, adrenal cortical adenomas + carcinomas in females, pancreatic acinar cell adenomas in males and females, pancreatic acinar cell carcinomas in males and females, pancreatic acinar cell adenomas + carcinomas in males and females, thyroid follicular cell adenomas in females, thyroid follicular cell carcinomas in females, thyroid follicular cell adenomas + carcinomas in females, benign endometrial stromal polyps of the uterus, Zymbal's gland carcinomas in females, hepatocellular adenomas in females, hepatocellular adenomas + carcinomas in females, and skin schwannoma in males. Each of these tumors, except for the liver tumors and skin schwannoma, was significantly increased compared to the control groups, based on a pair-wise test.

The FDA statistical review showed significant dose-response relationships for the following tumors, based on comparison to the water control group: acinar cell adenoma, carcinoma and combined adenoma or carcinoma in pancreas in both sexes, follicular cell adenoma in thyroid in both sexes, malignant schwannoma in skin in males, malignant lymphoma in males, adenoma and combined adenoma or carcinoma in adrenal cortex in females, hepatocellular adenoma in females, follicular cell carcinoma and combined adenoma or carcinoma in thyroid in females, polyp and combined polyp or sarcoma in uterus, and carcinoma in Zymbal's glands in females.

The FDA statistical review also found significant increases in the following tumors, based on pair-wise comparison to the water control group: acinar cell adenoma, carcinoma and combined adenoma or carcinoma in pancreas in high-dose groups for both sexes, follicular cell adenoma in thyroid in high-dose groups for both sexes, combined adenoma or carcinoma in adrenal cortex in high-dose females, follicular cell carcinoma and combined follicular cell adenoma or carcinoma in thyroid in high-dose females, polyp and combined polyp or sarcoma in uterus in high-dose females, and

carcinoma in the Zymbal's glands in high-dose females (see statisical review by Dr. Min Min).

The FDA statistical analysis was summarized in the following table.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pair-wise Comparisons

=			0 mg	70 mg	210 mg	650 mg				
			Water Cont	Low	Med	High	P_Value	P_Value	P_Value	P_Value
	Organ Name	Tumor Name	N=65	N=65	N=65	N=65	Dos Resp	C vs. L	C vs. M	C vs. H
Male	ADRENAL CORTEX	#M CARCINOMA	1	1	4	5	0.027	0.699	0.122	0.070
	LIVER	#M CARCINOMA, HEPATO	1	6	1	0	0.964	0.035	0.699	1.000
	PANCREAS	#B ADENOMA, ACINAR C	1	0	3	8	0.000	1.000	0.243	0.008
		#M CARCINOMA, ACINAR	0	0	0	6	0.000	.	.	0.008
		ACINAR_CELL_ADENOMA+ CARCINOMA	1	0	3	14	0.000	1.000	0.243	0.000
	SKIN	#M SCHWANNOMA, MALIG	0	0	1	3	0.018	.	0.448	0.102
	SOFT TISSUE- TH	#M HIBERNOMA, MALIGN	3	0	1	5	0.045	1.000	0.909	0.298
	SOFT_TISSUE	HIBERNOMAS	3	1	1	6	0.032	0.909	0.909	0.192
	SYSTEMIC TUMORS	#M LYMPHOMA, MALIGNA	0	0	1	3	0.018	.	0.448	0.102
	THYROID GLANDS	#B ADENOMA, FOLLICUL	0	3	3	6	0.014	0.086	0.090	0.008
		FOLLICULAR_CELL ADENOMA+CARCINOMA	2	4	4	7	0.041	0.256	0.256	0.052
			0 mg	70 mg	210 mg	650 mg				

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The incidence of Zymbal's gland carcinoma in males was 1/62 (water control), 2/62 (LD), 5/59 (MD) and 5/58 (HD). Although the incidence of this tumor was not significant in either the dose-response or pair-wise test, the Executive CAC concluded that the increased incidence in the mid- and high-dose males was drug-related, based on the very low incidence of this neoplasm in historical control data.

			0 mg Water Cont N-65	100 mg Low N-65	300 mg Med N-65	900 mg High N-65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Female	ADRENAL CORTEX	#B ADENOMA	1	2	1	7	0.004	0.509	0.735	0.027
		#M CARCINOMA	0	1	2	3	0.048	0.506	0.235	0.112
	ADRENAL_CORTEX	ADENOMA+CARCINOMA	1	3	3	10	0.001	0.317	0.282	0.003
	ADRENAL_MEDULLA	PHEOCHROMOCYTOMA_B+M	1	0	2	5	0.008	1.000	0.482	0.096
	CERVIX	#M SCHWANNOMA, MALIG	2	1	8	1	0.630	0.879	0.038	0.866
	LIVER	#B ADENOMA, HEPATOCE HEPATOCELLULAR	0	1	1	4	0.013	0.506	0.488	0.055
		ADENOMA+CARCINOMA	0	1	3	4	0.027	0.506	0.112	0.055
	OVARIES	#B GRANULOSA CELL TU	0	1	0	3	0.032	0.506	.	0.116
	PANCREAS	#B ADENOMA, ACINAR C	0	0	0	6	0.000	.	.	0.013
		#M CARCINOMA, ACINAR	0	0	2	6	0.001	.	0.235	0.012
		ACINAR_CELL_ADENOMA+ CARCINOMA	0	0	2	12	0.000	.	0.235	0.000
	SOFT_TISSUE	HIBERNOMAS	1	1	2	5	0.022	0.758	0.482	0.107
	THYROID GLANDS	#B ADENOMA, FOLLICUL	0	1	2	9	0.000	0.506	0.235	0.001
		#M CARCINOMA, FOLLIC	0	2	2	5	0.012	0.253	0.235	0.024
	THYROID_GLANDS	FOLLICULAR_CELL ADENOMA+CARCINOMA	0	3	4	14	0.000	0.129	0.053	0.000
	UTERUS	#B POLYP, ENDOMETRIA	2	5	4	12	0.001	0.217	0.305	0.004
		POLYP+SARCOMA	2	5	4	13	0.001	0.217	0.305	0.002
	ZYMBAL'S GLANDS	#M CARCINOMA	0	1	2	5	0.006	0.506	0.235	0.026

The number of Zymbal's glands examined in females was 63 (water control), 64 (LD), 65 (MD), and 62 (HD).

The FDA statistician also performed analysis on the tumor incidences based on comparison to the corn oil control and the combined water and corn oil control groups (see review by Dr. Min Min).

The overall neoplastic changes were summarized in the following tables (Table S48 for males and Table S50 for females, taken from the study report).

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SPONSOR:HYPERION THERAPEUTICS — A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

----- MALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
ADIPOSE TISSUE					
TOTAL NUMBER EXAMINED	NA	4	2	1	6
EXAMINED, UNREMARKABLE	NA	0	0	0	1
-#S CARCINOMA, ACINAR CELL; PANCREAS	NA	0	0	0	1
PRESENT	NA	NA	NA	NA	1
ADRENAL CORTEX					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	17	20	16	15	11
-#B ADENOMA	1	1	2	1	1
INCIDENTAL	NONE	1	2	1	1
SCHEDULED SACRIFICE	1	NONE	NONE	NONE	NONE
-#M CARCINOMA	1	0	1	4	5
INCIDENTAL	NONE	NONE	NONE	NONE	1
FATAL	1	NONE	1	NONE	2
SCHEDULED SACRIFICE	NONE	NONE	NONE	4	2
ADRENAL MEDULLA					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	53	51	53	53	47
-#B PHEOCHROMOCYTOMA, BENIGN	3	6	3	3	3
INCIDENTAL	2	3	2	3	2
SCHEDULED SACRIFICE	1	3	1	NONE	1
-#B PHEOCHROMOCYTOMA, COMPLEX, BENIGN	1	0	0	0	0
SCHEDULED SACRIFICE	1	NONE	NONE	NONE	NONE

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 70 MG/KG/DAY 4- 210 MG/KG/DAY 5- 650 MG/KG/DAY
# = NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC
NA = NOT APPLICABLE

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PROJECT NO. (b) (4) 71007M — TABLE S48 (ALL ANIMALS - MALES) — PAGE 2
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SUMMARY OF NEOPLASTIC FINDINGS

----- MALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
ADRENAL MEDULLA - CONTINUED					
-#M PHEOCHROMOCYTOMA, MALIGNANT	1	1	1	2	2
INCIDENTAL	NONE	1	NONE	1	NONE
FATAL	NONE	NONE	NONE	NONE	1
SCHEDULED SACRIFICE	1	NONE	1	1	1
AORTA					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	60	62	61	62	64
-#M HIBERNOMA, MALIGNANT	0	1	0	0	0
INCIDENTAL	NONE	1	NONE	NONE	NONE
BONE					
TOTAL NUMBER EXAMINED	1	1	NA	1	NA
EXAMINED, UNREMARKABLE	1	0	NA	0	NA
-#M OSTEOSARCOMA	0	0	NA	1	NA
FATAL	NA	NA	NA	1	NA
BRAIN					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	51	45	49	54	51
-#B GRANULAR CELL TUMOR, BENIGN	1	1	4	0	1
FATAL	NONE	NONE	1	NONE	NONE
SCHEDULED SACRIFICE	1	1	3	NONE	1

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 70 MG/KG/DAY 4- 210 MG/KG/DAY 5- 650 MG/KG/DAY
# = NEOPLASM, B = BENIGN, M = MALIGNANT
NA = NOT APPLICABLE

PROJECT NO. (b) (4)71007M — TABLE S48 (ALL ANIMALS - MALES) — PAGE 3
SPONSOR:HYPERION THERAPEUTICS — A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

----- MALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
BRAIN - CONTINUED					
-#B SCHWANNOMA, BENIGN	0	0	1	0	0
FATAL	NONE	NONE	1	NONE	NONE
-#M ASTROCYTOMA, MALIGNANT	0	2	2	2	3
INCIDENTAL	NONE	NONE	1	NONE	1
FATAL	NONE	2	1	2	1
SCHEDULED SACRIFICE	NONE	NONE	NONE	NONE	1
DIAPHRAGM					
TOTAL NUMBER EXAMINED	1	NA	NA	NA	1
EXAMINED, UNREMARKABLE	0	NA	NA	NA	0
-#S CARCINOMA, ACINAR; PANCREAS	0	NA	NA	NA	1
PRESENT	NA	NA	NA	NA	1
DUODENUM					
TOTAL NUMBER EXAMINED	63	62	60	62	59
EXAMINED, UNREMARKABLE	62	60	59	61	57
TOO AUTOLYZED TO EXAMINE	2	3	5	3	6
-#M LEIOMYOSARCOMA	0	0	0	0	1
FATAL	NONE	NONE	NONE	NONE	1
EARS					
TOTAL NUMBER EXAMINED	NA	NA	NA	1	NA
EXAMINED, UNREMARKABLE	NA	NA	NA	0	NA
-#S CARCINOMA; ZYMBAL'S GLAND	NA	NA	NA	1	NA
PRESENT	NA	NA	NA	1	NA

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 70 MG/KG/DAY 4- 210 MG/KG/DAY 5- 650 MG/KG/DAY
# = NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC
NA = NOT APPLICABLE

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SPONSOR:HYPERION THERAPEUTICS — A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

----- MALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
EPIDIDYMIDES					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	49	48	41	50	37
-#S CARCINOMA, ACINAR CELL; PANCREAS	0	0	0	0	2
PRESENT	NONE	NONE	NONE	NONE	2
EYES/OPTIC N.					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	58	57	63	59	53
-#M MELANOMA, AMELANOTIC, MALIGNANT	0	0	0	0	2
INCIDENTAL	NONE	NONE	NONE	NONE	2
HARDERIAN GLANDS					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	47	44	48	44	31
-#M CARCINOMA, SQUAMOUS CELL	0	0	0	1	0
FATAL	NONE	NONE	NONE	1	NONE
HEART					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	13	13	13	18	10
-#M MESOTHELIOMA, ATRIOCAVAL, MALIGNANT	0	0	1	0	0
SCHEDULED SACRIFICE	NONE	NONE	1	NONE	NONE
-#S HIBERNOMA, MALIGNANT; SOFT TISSUE, THORAX	0	1	0	0	1
PRESENT	NONE	1	NONE	NONE	1

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 70 MG/KG/DAY 4- 210 MG/KG/DAY 5- 650 MG/KG/DAY
= NEOPLASM, M = MALIGNANT, S = METASTATIC

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TABLE S48 (ALL ANIMALS - MALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

PAGE 5

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
HEART - CONTINUED					
-#S LEIOMYOSARCOMA, STOMACH	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
KIDNEYS					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	4	5	3	5	9
-#B ADENOMA	0	1	0	0	0
INCIDENTAL	NONE	1	NONE	NONE	NONE
-#B LIPOMA	0	0	0	2	0
SCHEDULED SACRIFICE	NONE	NONE	NONE	2	NONE
-#B ONCOCYTOMA	0	0	0	0	1
INCIDENTAL	NONE	NONE	NONE	NONE	1
-#M OSTEOSARCOMA	0	0	0	1	0
SCHEDULED SACRIFICE	NONE	NONE	NONE	1	NONE
LAC. GLAND EXOR					
TOTAL NUMBER EXAMINED	2	NA	NA	NA	1
EXAMINED, UNREMARKABLE	0	NA	NA	NA	0
-#S CARCINOMA, ZYMBAL'S GLAND	0	NA	NA	NA	1
PRESENT	NA	NA	NA	NA	1

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 70 MG/KG/DAY 4- 210 MG/KG/DAY 5- 650 MG/KG/DAY
# = NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC
NA = NOT APPLICABLE

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TABLE S48 (ALL ANIMALS - MALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

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GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
LIVER					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	3	5	6	4	5
-#B ADENOMA, HEPATOCELLULAR	0	1	1	3	1
INCIDENTAL	NONE	1	1	NONE	1
SCHEDULED SACRIFICE	NONE	NONE	NONE	3	NONE
-#B CHOLANGIOMA	1	0	0	0	0
SCHEDULED SACRIFICE	1	NONE	NONE	NONE	NONE
-#M CARCINOMA, HEPATOCELLULAR	1	2	6	1	0
INCIDENTAL	NONE	NONE	2	1	NONE
FATAL	NONE	1	3	NONE	NONE
SCHEDULED SACRIFICE	1	1	1	NONE	NONE
-#S HIBERNOMA, MALIGNANT; SOFT TISSUE, THORAX	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
-#S LEIOMYOSARCOMA; STOMACH	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
LN, RENAL					
TOTAL NUMBER EXAMINED	2	4	3	5	1
EXAMINED, UNREMARKABLE	0	0	0	0	0
-#S CARCINOMA; ADRENAL CORTEX	0	0	0	1	0
PRESENT	NA	NA	NA	1	NA
-#S HIBERNOMA, MALIGNANT; SOFT TISSUE, THORAX	0	0	0	1	0
PRESENT	NA	NA	NA	1	NA

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 70 MG/KG/DAY 4- 210 MG/KG/DAY 5- 650 MG/KG/DAY
# = NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC
NA = NOT APPLICABLE

PROJECT NO. (b) (4) 71007M
SPONSOR:HYPERION THERAPEUTICS

TABLE S48 (ALL ANIMALS - MALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

PAGE 7

----- MALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
LUNGS					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	37	24	37	31	27
-#M CARCINOMA, BRONCHIOLO-ALVEOLAR	0	0	0	0	1
INCIDENTAL	NONE	NONE	NONE	NONE	1
-#S ADENOCARCINOMA; SEMINAL VESICLES	1	0	0	0	0
PRESENT	1	NONE	NONE	NONE	NONE
-#S CARCINOMA; ADRENAL CORTEX	0	0	1	0	1
PRESENT	NONE	NONE	1	NONE	1
-#S FIBROSARCOMA; SKIN	0	0	1	0	0
PRESENT	NONE	NONE	1	NONE	NONE
-#S HIBERNOMA, MALIGNANT; SOFT TISSUE, THORAX	1	1	0	1	1
PRESENT	1	1	NONE	1	1
LYMPH NODE, MAND					
TOTAL NUMBER EXAMINED	65	65	65	65	64
EXAMINED, UNREMARKABLE	44	47	49	47	40
NOT PRESENT FOR EXAMINATION	0	0	0	0	1
-#S CARCINOMA, SQUAMOUS CELL; TONGUE	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
-#S CARCINOMA; ZYMBAL'S GLAND	1	0	0	0	0
PRESENT	1	NONE	NONE	NONE	NONE
-#S SCHWANNOMA, MALIGNANT; SKIN	0	0	0	1	0
PRESENT	NONE	NONE	NONE	1	NONE

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 70 MG/KG/DAY 4- 210 MG/KG/DAY 5- 650 MG/KG/DAY
= NEOPLASM, M = MALIGNANT, S = METASTATIC

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PROJECT NO. (b) (4) 71007M
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TABLE S48 (ALL ANIMALS - MALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

PAGE 8

----- MALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
LYMPH NODE, MES					
TOTAL NUMBER EXAMINED	63	65	63	64	65
EXAMINED, UNREMARKABLE	44	51	47	42	43
TOO AUTOLYZED TO EXAMINE	1	0	2	0	0
NOT PRESENT FOR EXAMINATION	1	0	0	1	0
-#S CARCINOMA, ACINAR CELL; PANCREAS	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
MESENTERY					
TOTAL NUMBER EXAMINED	1	1	NA	NA	1
EXAMINED, UNREMARKABLE	0	0	NA	NA	0
-#S CARCINOMA, ISLET CELL; PANCREAS	1	0	NA	NA	1
PRESENT	1	NA	NA	NA	1
PANCREAS					
TOTAL NUMBER EXAMINED	64	65	65	65	65
EXAMINED, UNREMARKABLE	28	36	44	40	26
NOT PRESENT FOR EXAMINATION	1	0	0	0	0
-#B ADENOMA, ACINAR CELL	1	1	0	3	8
INCIDENTAL	1	NONE	NONE	3	2
SCHEDULED SACRIFICE	NONE	1	NONE	NONE	6
-#B ADENOMA, ISLET CELL	3	4	3	2	0
INCIDENTAL	2	1	1	1	NONE
SCHEDULED SACRIFICE	1	3	2	1	NONE

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 70 MG/KG/DAY 4- 210 MG/KG/DAY 5- 650 MG/KG/DAY
# = NEOPLASM, B = BENIGN, S = METASTATIC
NA = NOT APPLICABLE

PROJECT NO. (b) (4) 671007M
SPONSOR:HYPERION THERAPEUTICS

TABLE S48 (ALL ANIMALS - MALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

PAGE 9

----- MALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
PANCREAS - CONTINUED					
-#M CARCINOMA, ACINAR CELL	0	0	0	0	6
INCIDENTAL	NONE	NONE	NONE	NONE	2
FATAL	NONE	NONE	NONE	NONE	2
SCHEDULED SACRIFICE	NONE	NONE	NONE	NONE	2
-#M CARCINOMA, ISLET CELL	4	2	0	0	0
INCIDENTAL	2	1	NONE	NONE	NONE
FATAL	1	NONE	NONE	NONE	NONE
SCHEDULED SACRIFICE	1	1	NONE	NONE	NONE
PARATHYROIDS					
TOTAL NUMBER EXAMINED	61	58	62	59	61
EXAMINED, UNREMARKABLE	47	46	44	50	54
TOO AUTOLYZED TO EXAMINE	1	0	0	0	0
NOT PRESENT FOR EXAMINATION	3	7	3	6	4
-#B ADENOMA	1	1	0	0	0
SCHEDULED SACRIFICE	1	1	NONE	NONE	NONE
PITUITARY					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	11	11	19	23	27
-#B ADENOMA, PARS DISTALIS	43	40	34	27	24
INCIDENTAL	10	10	9	9	9
FATAL	12	19	11	8	8
SCHEDULED SACRIFICE	20	11	14	10	7

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 70 MG/KG/DAY 4- 210 MG/KG/DAY 5- 650 MG/KG/DAY
= NEOPLASM, B = BENIGN, M = MALIGNANT

PROJECT NO. (b) (4) 71007M
SPONSOR:HYPERION THERAPEUTICS

TABLE S48 (ALL ANIMALS - MALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

PAGE 10

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----- MALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
PITUITARY - CONTINUED					
-#B ADENOMA, PARS INTERMEDIA	0	0	1	0	0
SCHEDULED SACRIFICE	NONE	NONE	1	NONE	NONE
-#M CARCINOMA, PARS DISTALIS	0	1	0	0	1
FATAL	NONE	NONE	NONE	NONE	1
SCHEDULED SACRIFICE	NONE	1	NONE	NONE	NONE
PREPUTIAL GLANDS					
TOTAL NUMBER EXAMINED	64	64	65	65	64
EXAMINED, UNREMARKABLE	50	48	46	47	46
NOT PRESENT FOR EXAMINATION	1	1	0	0	1
-#B ADENOMA	0	0	1	0	0
SCHEDULED SACRIFICE	NONE	NONE	1	NONE	NONE
PROSTATE					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	17	12	19	22	32
-#M ADENOCARCINOMA	0	0	2	0	0
FATAL	NONE	NONE	2	NONE	NONE
-#M LEIOMYOSARCOMA	0	0	0	0	1
SCHEDULED SACRIFICE	NONE	NONE	NONE	NONE	1
-#S ADENOCARCINOMA; SEMINAL VESICLES	1	0	0	0	0
PRESENT	1	NONE	NONE	NONE	NONE

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 70 MG/KG/DAY 4- 210 MG/KG/DAY 5- 650 MG/KG/DAY
= NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC

PROJECT NO. (b) (4) 671007M
SPONSOR:HYPERION THERAPEUTICS

TABLE S48 (ALL ANIMALS - MALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

PAGE 11

----- MALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
SAL. GLAND MAND					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	64	63	65	64	62
-#S SCHWANNOMA, MALIGNANT; SKIN	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
SEMINAL VESICLES					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	52	50	47	49	49
-#N ADENOCARCINOMA	1	0	0	0	0
FATAL	1	NONE	NONE	NONE	NONE
-#S ADENOCARCINOMA; PROSTATE	0	0	1	0	0
PRESENT	NONE	NONE	1	NONE	NONE
SKELETAL MUSCLE					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	43	37	49	46	53
-#N SARCOMA, UNDIFFERENTIATED	1	0	0	0	0
INCIDENTAL	1	NONE	NONE	NONE	NONE
-#N SCHWANNOMA, MALIGNANT	2	0	0	0	0
FATAL	1	NONE	NONE	NONE	NONE
SCHEDULED SACRIFICE	1	NONE	NONE	NONE	NONE
-#S CARCINOMA, ACINAR CELL; PANCREAS	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 70 MG/KG/DAY 4- 210 MG/KG/DAY 5- 650 MG/KG/DAY
= NEOPLASM, M = MALIGNANT, S = METASTATIC

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PROJECT NO. (b) (4) 671007M
SPONSOR:HYPERION THERAPEUTICS

TABLE S48 (ALL ANIMALS - MALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

PAGE 12

----- MALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
SKELETAL MUSCLE - CONTINUED					
-#S HIBERNOMA, MALIGNANT; SOFT TISSUE, THORAX	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
SKIN					
TOTAL NUMBER EXAMINED	65	65	65	64	65
EXAMINED, UNREMARKABLE	52	54	47	47	43
NOT PRESENT FOR EXAMINATION	0	0	0	1	0
-#B ADENOMA, SEBACEOUS CELL	0	0	1	2	1
INCIDENTAL	NONE	NONE	NONE	1	1
SCHEDULED SACRIFICE	NONE	NONE	1	1	NONE
-#B FIBROMA	3	1	4	5	3
INCIDENTAL	2	NONE	1	NONE	2
FATAL	NONE	NONE	1	1	NONE
SCHEDULED SACRIFICE	1	1	2	4	1
-#B KERATOACANTHOMA, BENIGN	2	5	7	4	6
INCIDENTAL	NONE	3	7	NONE	4
SCHEDULED SACRIFICE	2	2	NONE	4	2
-#B LIPOMA	1	0	0	0	0
INCIDENTAL	1	NONE	NONE	NONE	NONE
-#B NEURAL CREST TUMOR, BENIGN	0	0	0	1	0
INCIDENTAL	NONE	NONE	NONE	1	NONE
-#B PAPILLOMA, SQUAMOUS CELL	0	0	2	1	1
INCIDENTAL	NONE	NONE	1	NONE	1
SCHEDULED SACRIFICE	NONE	NONE	1	1	NONE

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 70 MG/KG/DAY 4- 210 MG/KG/DAY 5- 650 MG/KG/DAY
= NEOPLASM, B = BENIGN, S = METASTATIC

PROJECT NO. (b) (4) 71007M — TABLE S48 (ALL ANIMALS - MALES) — PAGE 13
SPONSOR:HYPERION THERAPEUTICS — A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

----- MALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
SKIN - CONTINUED					
-#B TRICHOEPITHELIOMA	0	0	1	0	0
SCHEDULED SACRIFICE	NONE	NONE	1	NONE	NONE
-#M CARCINOMA, BASAL CELL	0	0	1	1	2
INCIDENTAL	NONE	NONE	1	1	1
SCHEDULED SACRIFICE	NONE	NONE	NONE	NONE	1
-#M CARCINOMA, SQUAMOUS CELL	1	0	0	0	0
SCHEDULED SACRIFICE	1	NONE	NONE	NONE	NONE
-#M FIBROSARCOMA	2	0	1	1	2
INCIDENTAL	1	NONE	1	1	NONE
FATAL	1	NONE	NONE	NONE	1
SCHEDULED SACRIFICE	NONE	NONE	NONE	NONE	1
-#M MYXOSARCOMA	1	2	0	0	1
INCIDENTAL	NONE	1	NONE	NONE	NONE
FATAL	1	NONE	NONE	NONE	1
SCHEDULED SACRIFICE	NONE	1	NONE	NONE	NONE
-#M OSTEOSARCOMA	1	1	1	0	1
INCIDENTAL	NONE	NONE	1	NONE	1
SCHEDULED SACRIFICE	1	1	NONE	NONE	NONE
-#M SCHWANNOMA, MALIGNANT	0	2	0	1	3
INCIDENTAL	NONE	1	NONE	NONE	NONE
FATAL	NONE	NONE	NONE	1	3
SCHEDULED SACRIFICE	NONE	1	NONE	NONE	NONE
-#S LEIOMYOSARCOMA; STOMACH	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 70 MG/KG/DAY 4- 210 MG/KG/DAY 5- 650 MG/KG/DAY
= NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC

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PROJECT NO. (b) (4) 71007M — TABLE S48 (ALL ANIMALS - MALES) — PAGE 14
SPONSOR:HYPERION THERAPEUTICS — A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

----- MALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
SOFT TISSUE, OR					
TOTAL NUMBER EXAMINED	NA	1	NA	NA	NA
EXAMINED, UNREMARKABLE	NA	0	NA	NA	NA
-#M OSTEOSARCOMA	NA	1	NA	NA	NA
INCIDENTAL	NA	1	NA	NA	NA
SOFT TISSUE- AB					
TOTAL NUMBER EXAMINED	NA	NA	NA	NA	5
EXAMINED, UNREMARKABLE	NA	NA	NA	NA	1
-#B HIBERNOMA, BENIGN	NA	NA	NA	NA	1
INCIDENTAL	NA	NA	NA	NA	1
SOFT TISSUE- TH					
TOTAL NUMBER EXAMINED	4	2	1	1	6
EXAMINED, UNREMARKABLE	0	0	0	0	1
-#B HIBERNOMA, BENIGN	0	1	1	0	0
FATAL	NA	1	1	NA	NA
-#M HIBERNOMA, MALIGNANT	3	1	0	1	5
FATAL	3	1	NA	1	5
SPLEEN					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	35	37	34	35	38
-#S PHEOCHROMOCYTOMA, MALIGNANT; ADRENAL MEDULLA	0	0	0	1	0
PRESENT	NONE	NONE	NONE	1	NONE

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 70 MG/KG/DAY 4- 210 MG/KG/DAY 5- 650 MG/KG/DAY
# = NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC
NA = NOT APPLICABLE

PROJECT NO. (b) (4) 571007M — TABLE S48 (ALL ANIMALS - MALES) — PAGE 15
SPONSOR:HYPERION THERAPEUTICS — A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

----- MALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
STOMACH, GLAN					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	56	58	57	57	55
-#M LEIOMYOSARCOMA	0	0	0	0	1
FATAL	NONE	NONE	NONE	NONE	1
-#S CARCINOMA, ACINAR CELL; PANCREAS	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
STOMACH, NON					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	58	56	60	59	54
-#M CARCINOMA, SQUAMOUS CELL	0	0	0	0	1
SCHEDULED SACRIFICE	NONE	NONE	NONE	NONE	1
-#S CARCINOMA, ACINAR CELL; PANCREAS	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
SYSTEMIC TUMORS					
TOTAL NUMBER EXAMINED	6	4	2	5	10
EXAMINED, UNREMARKABLE	0	0	0	0	0
-#B HEMANGIOMA	0	1	0	0	0
SCHEDULED SACRIFICE	NA	1	NA	NA	NA
-#B MESOTHELIOMA, BENIGN	0	1	0	0	0
SCHEDULED SACRIFICE	NA	1	NA	NA	NA
-#M FIBROUS HISTIOCYTOMA, MALIGNANT	2	0	0	0	2
INCIDENTAL	NA	NA	NA	NA	1
FATAL	2	NA	NA	NA	NA
SCHEDULED SACRIFICE	NA	NA	NA	NA	1

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 70 MG/KG/DAY 4- 210 MG/KG/DAY 5- 650 MG/KG/DAY
# = NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC
NA = NOT APPLICABLE

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PROJECT NO. (b) (4) 571007M — TABLE S48 (ALL ANIMALS - MALES) — PAGE 16
SPONSOR:HYPERION THERAPEUTICS — A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

----- MALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
SYSTEMIC TUMORS - CONTINUED					
-#M HEMANGIOSARCOMA	1	0	0	1	0
FATAL	1	NA	NA	NA	NA
SCHEDULED SACRIFICE	NA	NA	NA	1	NA
-#M LYMPHOMA, MALIGNANT	0	2	0	1	3
FATAL	NA	2	NA	1	3
-#M MESOTHELIOMA, MALIGNANT	1	0	0	1	0
INCIDENTAL	1	NA	NA	NA	NA
SCHEDULED SACRIFICE	NA	NA	NA	1	NA
-#M SARCOMA, HISTIOCYTIC	2	1	2	2	5
INCIDENTAL	1	NA	NA	NA	NA
FATAL	1	1	2	2	5
TAIL					
TOTAL NUMBER EXAMINED	28	20	23	22	29
EXAMINED, UNREMARKABLE	0	0	1	1	1
NOT PRESENT FOR EXAMINATION	0	1	0	1	0
-#B KERATOACANTHOMA, BENIGN	1	0	0	0	1
SCHEDULED SACRIFICE	1	NA	NA	NA	1
-#B NEURAL CREST TUMOR, BENIGN	1	0	0	0	0
SCHEDULED SACRIFICE	1	NA	NA	NA	NA

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 70 MG/KG/DAY 4- 210 MG/KG/DAY 5- 650 MG/KG/DAY
# = NEOPLASM, B = BENIGN, M = MALIGNANT
NA = NOT APPLICABLE

PROJECT NO. (b) (4) 71007M — TABLE S48 (ALL ANIMALS - MALES) — PAGE 17
SPONSOR:HYPERION THERAPEUTICS — A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

	----- MALE -----				
GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
TESTES					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	52	49	51	49	46
-#B INTERSTITIAL CELL TUMOR, BENIGN	1	2	1	3	2
INCIDENTAL	NONE	NONE	NONE	1	2
SCHEDULED SACRIFICE	1	2	1	2	NONE
-#B SEMINOMA, BENIGN	0	1	0	0	0
INCIDENTAL	NONE	1	NONE	NONE	NONE
THYMUS					
TOTAL NUMBER EXAMINED	64	64	63	65	63
EXAMINED, UNREMARKABLE	2	4	3	4	4
TOO AUTOLYZED TO EXAMINE	0	0	1	0	0
NOT PRESENT FOR EXAMINATION	1	1	1	0	2
-#B THYMOMA, BENIGN	0	0	0	0	1
INCIDENTAL	NONE	NONE	NONE	NONE	1
-#M CARCINOMA, SQUAMOUS CELL	0	0	0	0	1
INCIDENTAL	NONE	NONE	NONE	NONE	1
-#M THYMOMA, MALIGNANT	0	0	0	1	0
SCHEDULED SACRIFICE	NONE	NONE	NONE	1	NONE
THYROID GLANDS					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	17	19	17	19	19
-#B ADENOMA, C-CELL	5	7	3	7	3
INCIDENTAL	2	7	2	3	2
SCHEDULED SACRIFICE	3	NONE	1	4	1

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 70 MG/KG/DAY 4- 210 MG/KG/DAY 5- 650 MG/KG/DAY
= NEOPLASM, B = BENIGN, M = MALIGNANT

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PROJECT NO. (b) (4) 671007M — TABLE S48 (ALL ANIMALS - MALES) — PAGE 18
SPONSOR:HYPERION THERAPEUTICS — A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

	----- MALE -----				
GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
THYROID GLANDS - CONTINUED					
-#B ADENOMA, FOLLICULAR CELL	0	1	3	3	6
INCIDENTAL	NONE	1	2	2	5
SCHEDULED SACRIFICE	NONE	NONE	1	1	1
-#M CARCINOMA, C-CELL	3	0	0	0	1
INCIDENTAL	1	NONE	NONE	NONE	1
SCHEDULED SACRIFICE	2	NONE	NONE	NONE	NONE
-#M CARCINOMA, FOLLICULAR CELL	2	2	1	1	1
INCIDENTAL	NONE	1	1	1	NONE
SCHEDULED SACRIFICE	2	1	NONE	NONE	1
TONGUE					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	63	62	63	63	64
-#M CARCINOMA, SQUAMOUS CELL	0	0	0	0	1
FATAL	NONE	NONE	NONE	NONE	1
URINARY BLADDER					
TOTAL NUMBER EXAMINED	64	65	65	65	64
EXAMINED, UNREMARKABLE	56	58	59	58	56
TOO AUTOLYZED TO EXAMINE	0	0	0	0	1
NOT PRESENT FOR EXAMINATION	1	0	0	0	0
-#B PAPILLOMA	0	1	0	0	0
SCHEDULED SACRIFICE	NONE	1	NONE	NONE	NONE

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 70 MG/KG/DAY 4- 210 MG/KG/DAY 5- 650 MG/KG/DAY
= NEOPLASM, B = BENIGN, M = MALIGNANT

PROJECT NO. (b) (4) 671007M — TABLE S48 (ALL ANIMALS - MALES) — PAGE 19
SPONSOR:HYPERION THERAPEUTICS — A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

	----- MALE -----				
GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
ZYMBAL'S GLANDS					
TOTAL NUMBER EXAMINED	62	56	62	59	58
EXAMINED, UNREMARKABLE	61	55	60	54	50
NOT PRESENT FOR EXAMINATION	3	9	3	6	7
-#N CARCINOMA	1	1	2	5	5
INCIDENTAL	NONE	NONE	1	2	2
FATAL	1	1	1	2	3
SCHEDULED SACRIFICE	NONE	NONE	NONE	1	NONE

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 70 MG/KG/DAY 4- 210 MG/KG/DAY 5- 650 MG/KG/DAY
= NEOPLASM, M = MALIGNANT

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PROJECT NO (b) (4) 571007F — TABLE S50 (ALL ANIMALS - FEMALES) — PAGE 1
SPONSOR:HYPERION THERAPEUTICS — A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

GROUP:	1	2	3	4	5
	----- FEMALE -----				
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
ADIPOSE TISSUE					
TOTAL NUMBER EXAMINED	1	1	2	3	1
EXAMINED, UNREMARKABLE	0	0	0	0	1
-#S SCHWANNOMA, MALIGNANT; UTERUS	0	0	0	1	0
PRESENT	NA	NA	NA	1	NA
ADRENAL CORTEX					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	4	3	3	0	3
-#B ADENOMA	1	1	2	1	7
INCIDENTAL	1	NONE	2	NONE	5
SCHEDULED SACRIFICE	NONE	1	NONE	1	2
-#M CARCINOMA	0	2	1	2	3
INCIDENTAL	NONE	NONE	NONE	2	1
FATAL	NONE	1	NONE	NONE	1
SCHEDULED SACRIFICE	NONE	1	1	NONE	1
-#S ADENOCARCINOMA, MUCINOUS; DUODENUM	0	0	1	0	0
PRESENT	NONE	NONE	1	NONE	NONE
ADRENAL MEDULLA					
TOTAL NUMBER EXAMINED	65	65	59	61	63
EXAMINED, UNREMARKABLE	62	61	56	55	57
NOT PRESENT FOR EXAMINATION	0	0	6	4	2
-#B PHEOCHROMOCYTOMA, BENIGN	1	1	0	2	3
INCIDENTAL	NONE	NONE	NONE	NONE	2
SCHEDULED SACRIFICE	1	1	NONE	2	1

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
# = NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC
NA = NOT APPLICABLE

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PROJECT NO (b) (4) 571007F — TABLE S50 (ALL ANIMALS - FEMALES) — PAGE 2
SPONSOR:HYPERION THERAPEUTICS — A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

GROUP:	1	2	3	4	5
	----- FEMALE -----				
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
ADRENAL MEDULLA - CONTINUED					
-#M OSTEOSARCOMA	0	0	0	0	1
INCIDENTAL	NONE	NONE	NONE	NONE	1
-#M PHEOCHROMOCYTOMA, MALIGNANT	0	0	0	0	2
INCIDENTAL	NONE	NONE	NONE	NONE	1
SCHEDULED SACRIFICE	NONE	NONE	NONE	NONE	1
BILE DUCT					
TOTAL NUMBER EXAMINED	NA	NA	NA	1	NA
EXAMINED, UNREMARKABLE	NA	NA	NA	0	NA
-#S SCHWANNOMA, MALIGNANT; UTERUS	NA	NA	NA	1	NA
PRESENT	NA	NA	NA	1	NA
BRAIN					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	23	25	37	37	53
-#B GRANULAR CELL TUMOR, BENIGN	0	0	1	0	0
INCIDENTAL	NONE	NONE	1	NONE	NONE
-#M ASTROCYTOMA, MALIGNANT	1	1	0	0	0
INCIDENTAL	1	NONE	NONE	NONE	NONE
FATAL	NONE	1	NONE	NONE	NONE

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
# = NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC
NA = NOT APPLICABLE

PROJECT NO. (b) (4) 71007F
SPONSOR:HYPERION THERAPEUTICS

TABLE S50 (ALL ANIMALS - FEMALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

PAGE 3

----- FEMALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
CECUM					
TOTAL NUMBER EXAMINED	59	59	57	60	59
EXAMINED, UNREMARKABLE	56	58	55	59	59
TOO AUTOLYZED TO EXAMINE	6	6	8	5	6
-#S SCHWANNOMA, MALIGNANT; CERVIX	0	0	1	0	0
PRESENT	NONE	NONE	1	NONE	NONE
-#S SCHWANNOMA, MALIGNANT; UTERUS	0	0	0	1	0
PRESENT	NONE	NONE	NONE	1	NONE
CERVIX					
TOTAL NUMBER EXAMINED	65	65	65	65	64
EXAMINED, UNREMARKABLE	57	60	56	54	53
NOT PRESENT FOR EXAMINATION	0	0	0	0	1
-#B GRANULAR CELL TUMOR, BENIGN	2	1	1	0	1
INCIDENTAL	NONE	NONE	1	NONE	1
SCHEDULED SACRIFICE	2	1	NONE	NONE	NONE
-#B LEIOMYOMA	0	0	0	0	1
INCIDENTAL	NONE	NONE	NONE	NONE	1
-#B POLYP	0	1	0	0	0
INCIDENTAL	NONE	1	NONE	NONE	NONE
-#M SARCOMA, UNDIFFERENTIATED	0	0	0	0	1
INCIDENTAL	NONE	NONE	NONE	NONE	1
-#M SCHWANNOMA, MALIGNANT	2	0	1	8	1
FATAL	2	NONE	NONE	3	NONE
SCHEDULED SACRIFICE	NONE	NONE	1	5	1

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
= NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC

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PROJECT NO. (b) (4) 71007F
SPONSOR:HYPERION THERAPEUTICS

TABLE S50 (ALL ANIMALS - FEMALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

PAGE 4

----- FEMALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
CLITORAL GLANDS					
TOTAL NUMBER EXAMINED	62	64	65	65	64
EXAMINED, UNREMARKABLE	58	59	56	56	57
NOT PRESENT FOR EXAMINATION	3	1	0	0	1
-#S SCHWANNOMA, MALIGNANT; SKIN	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
COLON					
TOTAL NUMBER EXAMINED	65	63	65	65	65
EXAMINED, UNREMARKABLE	64	63	64	63	63
TOO AUTOLYZED TO EXAMINE	0	2	0	0	0
-#B LEIOMYOMA	0	0	0	0	1
INCIDENTAL	NONE	NONE	NONE	NONE	1
-#M ADENOCARCINOMA, MUCINOUS	0	0	0	0	1
FATAL	NONE	NONE	NONE	NONE	1
-#S SCHWANNOMA, MALIGNANT; CERVIX	0	0	1	0	0
PRESENT	NONE	NONE	1	NONE	NONE
DIAPHRAGM					
TOTAL NUMBER EXAMINED	1	NA	1	2	2
EXAMINED, UNREMARKABLE	0	NA	0	0	0
-#S ADENOCARCINOMA, MUCINOUS; COLON	0	NA	0	0	1
PRESENT	NA	NA	NA	NA	1
-#S ADENOCARCINOMA, MUCINOUS; DUODENUM	0	NA	1	0	0
PRESENT	NA	NA	1	NA	NA

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
# = NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC
NA = NOT APPLICABLE

(b) (4)
PROJECT NO. 71007F
SPONSOR:HYPERION THERAPEUTICS

TABLE S50 (ALL ANIMALS - FEMALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

PAGE 5

----- FEMALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
DIAPHRAGM - CONTINUED					
-#S SCHWANNOMA, MALIGNANT; UTERUS	0	NA	0	1	0
PRESENT	NA	NA	NA	1	NA
DUODENUM					
TOTAL NUMBER EXAMINED	63	63	62	64	64
EXAMINED, UNREMARKABLE	62	63	61	64	62
TOO AUTOLYZED TO EXAMINE	2	2	3	1	1
-#M ADENOCARCINOMA, MUCINOUS	0	0	1	0	1
FATAL	NONE	NONE	1	NONE	NONE
SCHEDULED SACRIFICE	NONE	NONE	NONE	NONE	1
EARS					
TOTAL NUMBER EXAMINED	1	1	1	1	NA
EXAMINED, UNREMARKABLE	0	0	0	0	NA
-#B NEURAL CREST TUMOR, BENIGN	0	0	0	1	NA
INCIDENTAL	NA	NA	NA	1	NA
HEART					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	36	30	30	22	17
-#M SCHWANNOMA, MALIGNANT	0	1	0	0	0
INCIDENTAL	NONE	1	NONE	NONE	NONE
-#S ADENOCARCINOMA, MUCINOUS; COLON	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
# = NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC
NA = NOT APPLICABLE

(b) (4)
PROJECT NO. 71007F
SPONSOR:HYPERION THERAPEUTICS

TABLE S50 (ALL ANIMALS - FEMALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

PAGE 6

----- FEMALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
HEART - CONTINUED					
-#S ADENOCARCINOMA, MUCINOUS; DUODENUM	0	0	1	0	0
PRESENT	NONE	NONE	1	NONE	NONE
-#S ADENOCARCINOMA; MAMMARY GLAND	0	0	0	1	0
PRESENT	NONE	NONE	NONE	1	NONE
-#S CARCINOMA; ADRENAL CORTEX	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
ILEUM					
TOTAL NUMBER EXAMINED	60	60	56	57	60
EXAMINED, UNREMARKABLE	59	60	54	56	58
TOO AUTOLYZED TO EXAMINE	5	5	9	7	5
NOT PRESENT FOR EXAMINATION	0	0	0	1	0
-#S SCHWANNOMA, MALIGNANT; CERVIX	0	0	1	0	0
PRESENT	NONE	NONE	1	NONE	NONE
JEJUNUM					
TOTAL NUMBER EXAMINED	53	58	54	50	52
EXAMINED, UNREMARKABLE	50	58	52	49	50
TOO AUTOLYZED TO EXAMINE	12	7	11	15	13
-#M ADENOCARCINOMA	1	0	0	0	1
SCHEDULED SACRIFICE	1	NONE	NONE	NONE	1
-#S SCHWANNOMA, MALIGNANT; CERVIX	0	0	1	0	0
PRESENT	NONE	NONE	1	NONE	NONE

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
= NEOPLASM, M = MALIGNANT, S = METASTATIC

TABLE S50 (ALL ANIMALS - FEMALES)
PROJECT NO. (b) (4) 671007F — A 24-MONTH ORAL STUDY OF HPN-100 IN RATS — PAGE 7
SPONSOR:HYPERION THERAPEUTICS — SUMMARY OF NEOPLASTIC FINDINGS

----- FEMALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
KIDNEYS					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	1	4	11	11	10
-#B ADENOMA	0	0	1	0	0
INCIDENTAL	NONE	NONE	1	NONE	NONE
-#S ADENOCARCINOMA, MUCINOUS; DUODENUM	0	0	1	0	0
PRESENT	NONE	NONE	1	NONE	NONE
-#S ADENOCARCINOMA; MAMMARY GLAND	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
LIVER					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	6	9	5	9	4
-#B ADENOMA, HEPATOCELLULAR	0	0	1	1	4
INCIDENTAL	NONE	NONE	NONE	NONE	2
SCHEDULED SACRIFICE	NONE	NONE	1	1	2
-#B CHOLANGIOMA	0	0	0	0	1
INCIDENTAL	NONE	NONE	NONE	NONE	1
-#M CARCINOMA, HEPATOCELLULAR	0	0	0	2	0
INCIDENTAL	NONE	NONE	NONE	2	NONE
-#M CHOLANGIOCARCINOMA	1	0	0	0	0
INCIDENTAL	1	NONE	NONE	NONE	NONE
-#S CARCINOMA, ACINAR CELL; PANCREAS	0	0	0	1	1
PRESENT	NONE	NONE	NONE	1	1

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
= NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC

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TABLE S50 (ALL ANIMALS - FEMALES)
PROJECT NO. (b) (4) 671007F — A 24-MONTH ORAL STUDY OF HPN-100 IN RATS — PAGE 8
SPONSOR:HYPERION THERAPEUTICS — SUMMARY OF NEOPLASTIC FINDINGS

----- FEMALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
LIVER - CONTINUED					
-#S CARCINOMA; ADRENAL CORTEX	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
-#S PHEOCHROMOCYTOMA, MALIGNANT; ADRENAL MEDULLA	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
LN, AXILLARY					
TOTAL NUMBER EXAMINED	NA	NA	NA	2	NA
EXAMINED, UNREMARKABLE	NA	NA	NA	0	NA
NOT PRESENT FOR EXAMINATION	NA	NA	1	0	1
-#S ADENOCARCINOMA; MAMMARY GLAND	NA	NA	NA	1	NA
PRESENT	NA	NA	NA	1	NA
LN, BRONCHIAL					
TOTAL NUMBER EXAMINED	NA	NA	NA	NA	1
EXAMINED, UNREMARKABLE	NA	NA	NA	NA	0
-#S ADENOCARCINOMA, MUCINOUS; COLON	NA	NA	NA	NA	1
PRESENT	NA	NA	NA	NA	1
LN, ILIAC					
TOTAL NUMBER EXAMINED	1	NA	2	1	6
EXAMINED, UNREMARKABLE	0	NA	0	0	0
-#M SCHWANNOMA, MALIGNANT	0	NA	0	0	1
FATAL	NA	NA	NA	NA	1

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
# = NEOPLASM, M = MALIGNANT, S = METASTATIC
NA = NOT APPLICABLE

PROJECT NO. (b) (4) 571007F
SPONSOR:HYPERION THERAPEUTICS

TABLE S50 (ALL ANIMALS - FEMALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

GROUP:	1	2	3	4	5
	----- FEMALE -----				
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
LN, ILIAC - CONTINUED					
-#S FIBROSARCOMA; PAWS	0	NA	0	0	1
PRESENT	NA	NA	NA	NA	1
LN, MEDIASTINAL					
TOTAL NUMBER EXAMINED	NA	NA	2	2	3
EXAMINED, UNREMARKABLE	NA	NA	0	0	0
-#S CARCINOMA; ADRENAL CORTEX	NA	NA	0	0	1
PRESENT	NA	NA	NA	NA	1
LN, RENAL					
TOTAL NUMBER EXAMINED	NA	NA	2	NA	2
EXAMINED, UNREMARKABLE	NA	NA	0	NA	0
-#S CARCINOMA; ADRENAL CORTEX	NA	NA	0	NA	1
PRESENT	NA	NA	NA	NA	1
LUNGS					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	37	37	40	36	35
-#S ADENOCARCINOMA, MUCINOUS; COLON	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
-#S ADENOCARCINOMA; MAMMARY GLAND	0	2	1	1	2
PRESENT	NONE	2	1	1	2
-#S ADENOCARCINOMA; UTERUS	0	0	0	1	0
PRESENT	NONE	NONE	NONE	1	NONE

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
# = NEOPLASM, S = METASTATIC
NA = NOT APPLICABLE

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PROJECT NO. (b) (4) 571007F
SPONSOR:HYPERION THERAPEUTICS

TABLE S50 (ALL ANIMALS - FEMALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

GROUP:	1	2	3	4	5
	----- FEMALE -----				
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
LUNGS - CONTINUED					
-#S CARCINOMA, C-CELL; THYROID	1	0	0	0	0
PRESENT	1	NONE	NONE	NONE	NONE
-#S CARCINOMA; ADRENAL CORTEX	0	1	0	0	1
PRESENT	NONE	1	NONE	NONE	1
-#S FIBROSARCOMA; PAWS	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
-#S HIBERNOMA, MALIGNANT; SOFT TISSUE THORAX	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
-#S SARCOMA, UNDIFFERENTIATED; SOFT TISSUE, THORAX	0	0	1	0	0
PRESENT	NONE	NONE	1	NONE	NONE
-#S SCHWANNOMA, MALIGNANT; SKIN	0	0	1	1	0
PRESENT	NONE	NONE	1	1	NONE
LYMPH NODE, MAND					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	38	41	51	44	39
-#S ADENOCARCINOMA; MAMMARY GLAND	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
LYMPH NODE, MES					
TOTAL NUMBER EXAMINED	65	65	65	64	65
EXAMINED, UNREMARKABLE	37	36	46	42	41
NOT PRESENT FOR EXAMINATION	0	0	0	1	0
-#S SCHWANNOMA, MALIGNANT; CERVIX	0	0	0	1	0
PRESENT	NONE	NONE	NONE	1	NONE

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
= NEOPLASM, S = METASTATIC

PROJECT NO. (b) (4) 671007F
SPONSOR:HYPERION THERAPEUTICS

TABLE S50 (ALL ANIMALS - FEMALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

PAGE 11

----- FEMALE -----					
GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
MAMMARY GLAND					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	21	24	19	20	31
-#B ADENOMA	4	4	2	1	5
INCIDENTAL	2	3	2	1	4
SCHEDULED SACRIFICE	2	1	NONE	NONE	1
-#B FIBROADENOMA	30	23	36	32	20
INCIDENTAL	16	13	17	18	13
FATAL	NONE	1	1	NONE	1
SCHEDULED SACRIFICE	14	9	18	14	6
-#B LIPOMA	0	0	0	1	0
INCIDENTAL	NONE	NONE	NONE	1	NONE
-#M ADENOCARCINOMA	9	9	9	12	12
INCIDENTAL	5	3	3	5	5
FATAL	NONE	3	2	1	4
SCHEDULED SACRIFICE	4	3	4	6	3
MESENTERY					
TOTAL NUMBER EXAMINED	1	NA	2	3	1
EXAMINED, UNREMARKABLE	1	NA	0	0	0
-#B LIPOMA	0	NA	0	1	0
SCHEDULED SACRIFICE	NA	NA	NA	1	NA
-#S ADENOCARCINOMA, MUCINOUS; DUODENUM	0	NA	1	0	0
PRESENT	NA	NA	1	NA	NA

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
# = NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC
NA = NOT APPLICABLE

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PROJECT NO. (b) (4) 671007F
SPONSOR:HYPERION THERAPEUTICS

TABLE S50 (ALL ANIMALS - FEMALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

PAGE 12

----- FEMALE -----					
GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
MESENTERY - CONTINUED					
-#S CARCINOMA, ADRENAL CORTEX	0	NA	0	0	1
PRESENT	NA	NA	NA	NA	1
-#S SCHWANNOMA, MALIGNANT; CERVIX	0	NA	1	0	0
PRESENT	NA	NA	1	NA	NA
-#S SCHWANNOMA, MALIGNANT; UTERUS	0	NA	0	1	0
PRESENT	NA	NA	NA	1	NA
OVARIES					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	29	33	22	30	28
-#B ADENOMA	0	1	0	0	1
SCHEDULED SACRIFICE	NONE	1	NONE	NONE	1
-#B GRANULOSA CELL TUMOR, BENIGN	0	0	1	0	3
INCIDENTAL	NONE	NONE	1	NONE	3
-#B LEIOMYOMA	0	1	0	0	0
SCHEDULED SACRIFICE	NONE	1	NONE	NONE	NONE
-#B THECOMA, BENIGN	0	0	0	0	2
INCIDENTAL	NONE	NONE	NONE	NONE	1
SCHEDULED SACRIFICE	NONE	NONE	NONE	NONE	1
-#M THECOMA, MALIGNANT	0	1	0	0	0
FATAL	NONE	1	NONE	NONE	NONE
-#S ADENOCARCINOMA, MUCINOUS; COLON	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
# = NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC
NA = NOT APPLICABLE

PROJECT NO. (b) (4) 71007F
SPONSOR:HYPERION THERAPEUTICS

TABLE S50 (ALL ANIMALS - FEMALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

PAGE 13

GROUP:	1	2	3	4	5
	----- FEMALE -----				
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
OVARIES - CONTINUED					
-#S ADENOCARCINOMA, MUCINOUS; DUODENUM	0	0	1	0	0
PRESENT	NONE	NONE	1	NONE	NONE
PANCREAS					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	56	52	48	48	33
-#B ADENOMA, ACINAR CELL	0	0	0	0	6
INCIDENTAL	NONE	NONE	NONE	NONE	3
SCHEDULED SACRIFICE	NONE	NONE	NONE	NONE	3
-#B ADENOMA, ISLET CELL	0	2	2	2	0
INCIDENTAL	NONE	1	NONE	NONE	NONE
SCHEDULED SACRIFICE	NONE	1	2	2	NONE
-#M CARCINOMA, ACINAR CELL	0	0	0	2	6
INCIDENTAL	NONE	NONE	NONE	NONE	3
FATAL	NONE	NONE	NONE	1	1
SCHEDULED SACRIFICE	NONE	NONE	NONE	1	2
-#M CARCINOMA, ISLET CELL	1	0	3	0	0
INCIDENTAL	1	NONE	NONE	NONE	NONE
SCHEDULED SACRIFICE	NONE	NONE	3	NONE	NONE
-#S ADENOCARCINOMA, MUCINOUS; COLON	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
-#S ADENOCARCINOMA, MUCINOUS; DUODENUM	0	0	1	0	0
PRESENT	NONE	NONE	1	NONE	NONE

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
= NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC

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PROJECT NO. (b) (4) 71007F
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TABLE S50 (ALL ANIMALS - FEMALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

PAGE 14

GROUP:	1	2	3	4	5
	----- FEMALE -----				
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
PANCREAS - CONTINUED					
-#S ADENOCARCINOMA; UTERUS	0	0	0	1	0
PRESENT	NONE	NONE	NONE	1	NONE
-#S SCHWANNOMA, MALIGNANT; CERVIX	1	0	1	1	0
PRESENT	1	NONE	1	1	NONE
-#S SCHWANNOMA, MALIGNANT; UTERUS	0	0	0	1	0
PRESENT	NONE	NONE	NONE	1	NONE
PAWS					
TOTAL NUMBER EXAMINED	5	8	11	13	17
EXAMINED, UNREMARKABLE	0	0	0	0	0
NOT PRESENT FOR EXAMINATION	1	0	0	0	1
-#M FIBROSARCOMA	0	0	0	0	1
FATAL	NA	NA	NA	NA	1
PITUITARY					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	1	2	1	4	19
-#B ADENOMA, PARS DISTALIS	62	58	58	52	31
INCIDENTAL	6	8	6	12	9
FATAL	39	33	30	25	16
SCHEDULED SACRIFICE	17	17	22	15	6
-#B ADENOMA, PARS INTERMEDIA	0	0	0	1	0
FATAL	NONE	NONE	NONE	1	NONE

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
# = NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC
NA = NOT APPLICABLE

PROJECT NO. (b) (4)671007F
SPONSOR:HYPERION THERAPEUTICS

TABLE S50 (ALL ANIMALS - FEMALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
PITUITARY - CONTINUED					
-#M CARCINOMA, PARS DISTALIS	1	0	3	2	0
FATAL	1	NONE	3	2	NONE
SAL. GLAND MAND					
TOTAL NUMBER EXAMINED	65	65	65	64	65
EXAMINED, UNREMARKABLE	63	63	62	62	63
NOT PRESENT FOR EXAMINATION	0	0	0	1	0
-#M ADENOCARCINOMA	0	0	0	0	1
SCHEDULED SACRIFICE	NONE	NONE	NONE	NONE	1
SKELETAL MUSCLE					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	61	56	61	60	59
-#M SARCOMA, UNDIFFERENTIATED	0	0	0	1	0
FATAL	NONE	NONE	NONE	1	NONE
-#S ADENOCARCINOMA, MUCINOUS; DUODENUM	0	0	1	0	0
PRESENT	NONE	NONE	1	NONE	NONE
SKIN					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	63	60	57	58	58
-#B ADENOMA, SEBACEOUS CELL	0	1	0	0	0
INCIDENTAL	NONE	1	NONE	NONE	NONE

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
= NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC

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PROJECT NO. (b) (4)671007F
SPONSOR:HYPERION THERAPEUTICS

TABLE S50 (ALL ANIMALS - FEMALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
SKIN - CONTINUED					
-#B FIBROMA	0	0	0	1	1
INCIDENTAL	NONE	NONE	NONE	1	1
-#M ADENOCARCINOMA, SEBACEOUS CELL	0	0	0	0	1
SCHEDULED SACRIFICE	NONE	NONE	NONE	NONE	1
-#M CARCINOMA, SQUAMOUS CELL	0	2	0	0	0
INCIDENTAL	NONE	1	NONE	NONE	NONE
FATAL	NONE	1	NONE	NONE	NONE
-#M FIBROSARCOMA	0	0	0	1	0
FATAL	NONE	NONE	NONE	1	NONE
-#M MYXOSARCOMA	0	0	0	0	1
FATAL	NONE	NONE	NONE	NONE	1
-#M SCHWANNOMA, MALIGNANT	0	1	1	1	2
INCIDENTAL	NONE	1	NONE	NONE	2
FATAL	NONE	NONE	1	1	NONE
SOFT TISSUE- AB					
TOTAL NUMBER EXAMINED	NA	NA	5	1	3
EXAMINED, UNREMARKABLE	NA	NA	0	0	0
-#B LIPOMA	NA	NA	2	0	0
SCHEDULED SACRIFICE	NA	NA	2	NA	NA
-#S ADENOCARCINOMA, MUCINOUS; COLON	NA	NA	0	0	1
PRESENT	NA	NA	NA	NA	1
-#S ADENOCARCINOMA, MUCINOUS; DUODENUM	NA	NA	1	0	0
PRESENT	NA	NA	1	NA	NA

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
# = NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC
NA = NOT APPLICABLE

PROJECT NO. (b) (4) 571007F — TABLE S50 (ALL ANIMALS - FEMALES) — PAGE 17
SPONSOR:HYPERION THERAPEUTICS — A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

GROUP:	1	2	3	4	5
	----- FEMALE -----				
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
SOFT TISSUE- AB - CONTINUED					
-#S CARCINOMA, ACINAR CELL; PANCREAS	NA	NA	0	1	1
PRESENT	NA	NA	NA	1	1
-#S SCHWANNOMA, MALIGNANT; CERVIX	NA	NA	1	0	0
PRESENT	NA	NA	1	NA	NA
SOFT TISSUE- TH					
TOTAL NUMBER EXAMINED	1	NA	3	2	5
EXAMINED, UNREMARKABLE	0	NA	0	0	0
-#B HIBERNOMA, BENIGN	1	NA	0	1	3
FATAL	1	NA	NA	1	3
-#M HIBERNOMA, MALIGNANT	0	NA	1	1	2
FATAL	NA	NA	1	1	2
-#M SARCOMA, UNDIFFERENTIATED	0	NA	1	0	0
INCIDENTAL	NA	NA	1	NA	NA
-#S ADENOCARCINOMA, MUCINOUS; DUODENUM	0	NA	1	0	0
PRESENT	NA	NA	1	NA	NA
SPINAL CORD					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	20	17	21	27	22
-#M SCHWANNOMA, MALIGNANT	0	0	0	0	1
FATAL	NONE	NONE	NONE	NONE	1

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
# = NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC
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PROJECT NO. (b) (4) 571007F — TABLE S50 (ALL ANIMALS - FEMALES) — PAGE 18
SPONSOR:HYPERION THERAPEUTICS — A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

GROUP:	1	2	3	4	5
	----- FEMALE -----				
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
SPLEEN					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	16	13	14	8	11
-#M OSTEOSARCOMA	1	0	0	0	0
SCHEDULED SACRIFICE	1	NONE	NONE	NONE	NONE
-#S SCHWANNOMA, MALIGNANT; UTERUS	0	0	0	1	0
PRESENT	NONE	NONE	NONE	1	NONE
STOMACH, GLAN					
TOTAL NUMBER EXAMINED	65	65	65	64	65
EXAMINED, UNREMARKABLE	57	53	60	56	54
TOO AUTOLYZED TO EXAMINE	0	0	0	1	0
-#B LEIOMYOMA	1	0	0	0	0
INCIDENTAL	1	NONE	NONE	NONE	NONE
-#S ADENOCARCINOMA, MUCINOUS; DUODENUM	0	0	1	0	0
PRESENT	NONE	NONE	1	NONE	NONE
-#S SCHWANNOMA, MALIGNANT; CERVIX	0	0	1	0	0
PRESENT	NONE	NONE	1	NONE	NONE
-#S SCHWANNOMA, MALIGNANT; UTERUS	0	0	0	1	0
PRESENT	NONE	NONE	NONE	1	NONE
SYSTEMIC TUMORS					
TOTAL NUMBER EXAMINED	3	1	3	3	5
EXAMINED, UNREMARKABLE	0	0	0	0	0
-#M FIBROUS HISTIOCYTOMA, MALIGNANT	0	0	0	0	1
INCIDENTAL	NA	NA	NA	NA	1

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# = NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC
NA = NOT APPLICABLE

PROJECT NO (b) (4) 671007F
SPONSOR:HYPERION THERAPEUTICS

TABLE S50 (ALL ANIMALS - FEMALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

PAGE 19

----- FEMALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
SYSTEMIC TUMORS - CONTINUED					
-#M HEMANGIOSARCOMA	0	1	1	1	1
FATAL	NA	NA	1	1	1
SCHEDULED SACRIFICE	NA	1	NA	NA	NA
-#M LYMPHANGIOSARCOMA	0	0	0	1	0
FATAL	NA	NA	NA	1	NA
-#M LYMPHOMA, MALIGNANT	1	0	1	1	1
FATAL	1	NA	NA	1	1
SCHEDULED SACRIFICE	NA	NA	1	NA	NA
-#M LYMPHOMA, MALIGNANT (LARGE GRANULAR LYMPHOCYTE)	0	0	1	0	0
SCHEDULED SACRIFICE	NA	NA	1	NA	NA
-#M MESOTHELIOMA, MALIGNANT	1	1	0	0	0
INCIDENTAL	1	NA	NA	NA	NA
SCHEDULED SACRIFICE	NA	1	NA	NA	NA
-#M MYELOMA, PLASMA CELL	1	0	0	0	0
SCHEDULED SACRIFICE	1	NA	NA	NA	NA
-#M SARCOMA, HISTIOCYTIC	0	0	0	0	2
FATAL	NA	NA	NA	NA	2
TAIL					
TOTAL NUMBER EXAMINED	19	20	20	17	14
EXAMINED, UNREMARKABLE	0	0	0	0	0
-#B NEURAL CREST TUMOR, BENIGN	0	1	0	0	0
SCHEDULED SACRIFICE	NA	1	NA	NA	NA

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# = NEOPLASM, B = BENIGN, M = MALIGNANT
NA = NOT APPLICABLE

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PROJECT NO (b) (4) 671007F
SPONSOR:HYPERION THERAPEUTICS

TABLE S50 (ALL ANIMALS - FEMALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

PAGE 20

----- FEMALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
THYMUS					
TOTAL NUMBER EXAMINED	63	62	64	64	65
EXAMINED, UNREMARKABLE	2	1	1	3	6
NOT PRESENT FOR EXAMINATION	2	3	1	1	0
-#B THYMOMA, BENIGN	1	0	0	0	0
INCIDENTAL	1	NONE	NONE	NONE	NONE
-#S ADENOCARCINOMA, MUCINOUS; DUODENUM	0	0	1	0	0
PRESENT	NONE	NONE	1	NONE	NONE
-#S ADENOCARCINOMA; MAMMARY GLAND	0	0	0	0	1
PRESENT	NONE	NONE	NONE	NONE	1
-#S ADENOCARCINOMA; UTERUS	0	0	0	1	0
PRESENT	NONE	NONE	NONE	1	NONE
THYROID GLANDS					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	11	8	5	10	7
-#B ADENOMA, C-CELL	9	4	8	3	2
INCIDENTAL	3	1	5	1	1
SCHEDULED SACRIFICE	6	3	3	2	1
-#B ADENOMA, FOLLICULAR CELL	0	1	1	2	9
INCIDENTAL	NONE	1	1	NONE	5
SCHEDULED SACRIFICE	NONE	NONE	NONE	2	4
-#M CARCINOMA, C-CELL	3	0	0	1	0
INCIDENTAL	2	NONE	NONE	1	NONE
FATAL	1	NONE	NONE	NONE	NONE

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
= NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC

PROJECT NO. (b) (4) 571007F
SPONSOR:HYPERION THERAPEUTICS

TABLE S50 (ALL ANIMALS - FEMALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

GROUP:	1	2	3	4	5
	----- FEMALE -----				
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
THYROID GLANDS - CONTINUED					
-#M CARCINOMA, FOLLICULAR CELL	0	1	2	2	5
INCIDENTAL	NONE	NONE	1	1	NONE
SCHEDULED SACRIFICE	NONE	1	1	1	5
TONGUE					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	62	62	65	64	63
-#B PAPILLOMA, SQUAMOUS CELL	0	0	0	0	1
INCIDENTAL	NONE	NONE	NONE	NONE	1
URINARY BLADDER					
TOTAL NUMBER EXAMINED	65	65	64	65	65
EXAMINED, UNREMARKABLE	61	56	60	55	56
NOT PRESENT FOR EXAMINATION	0	0	1	0	0
-#B GRANULAR CELL TUMOR, BENIGN	0	0	0	1	1
INCIDENTAL	NONE	NONE	NONE	NONE	1
SCHEDULED SACRIFICE	NONE	NONE	NONE	1	NONE
-#B PAPILLOMA	0	0	0	1	0
SCHEDULED SACRIFICE	NONE	NONE	NONE	1	NONE
-#S CARCINOMA; ADRENAL CORTEX	0	0	0	1	0
PRESENT	NONE	NONE	NONE	1	NONE

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
= NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC

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PROJECT NO. (b) (4) 571007F
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TABLE S50 (ALL ANIMALS - FEMALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

GROUP:	1	2	3	4	5
	----- FEMALE -----				
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
UTERUS					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	44	45	36	35	17
-#B ADENOMA, ENDOMETRIAL	0	0	0	0	1
SCHEDULED SACRIFICE	NONE	NONE	NONE	NONE	1
-#B LEIOMYOMA	0	0	0	0	1
INCIDENTAL	NONE	NONE	NONE	NONE	1
-#B POLYP, ENDOMETRIAL STROMAL	2	1	5	4	12
INCIDENTAL	1	1	2	1	8
SCHEDULED SACRIFICE	1	NONE	3	3	4
-#M ADENOCARCINOMA	1	1	0	1	2
FATAL	NONE	NONE	NONE	1	1
SCHEDULED SACRIFICE	1	1	NONE	NONE	1
-#M SARCOMA, ENDOMETRIAL STROMAL	0	0	0	0	1
INCIDENTAL	NONE	NONE	NONE	NONE	1
-#M SCHWANNOMA, MALIGNANT	0	0	0	1	0
FATAL	NONE	NONE	NONE	1	NONE
-#S SCHWANNOMA, MALIGNANT; CERVIX	1	0	0	0	0
PRESENT	1	NONE	NONE	NONE	NONE
VAGINA					
TOTAL NUMBER EXAMINED	65	65	65	65	65
EXAMINED, UNREMARKABLE	59	59	58	61	56
-#B GRANULAR CELL TUMOR, BENIGN	0	0	0	1	1
INCIDENTAL	NONE	NONE	NONE	1	1

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
= NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC

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PROJECT NO. 571007F
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TABLE S50 (ALL ANIMALS - FEMALES)
A 24-MONTH ORAL STUDY OF HPN-100 IN RATS
SUMMARY OF NEOPLASTIC FINDINGS

PAGE 23

----- FEMALE -----

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	65	65	65	65	65
NUMBER OF ANIMALS (ALL TYPES OF DEATH COMBINED)	65	65	65	65	65
VAGINA - CONTINUED					
-#B LEIOMYOMA	0	1	0	0	1
INCIDENTAL	NONE	1	NONE	NONE	NONE
SCHEDULED SACRIFICE	NONE	NONE	NONE	NONE	1
-#B POLYP, VAGINAL	1	0	1	0	0
INCIDENTAL	NONE	NONE	1	NONE	NONE
FATAL	1	NONE	NONE	NONE	NONE
-#M CARCINOMA, SQUAMOUS CELL	0	0	1	0	0
SCHEDULED SACRIFICE	NONE	NONE	1	NONE	NONE
-#M LEIOMYOSARCOMA	0	0	0	0	1
INCIDENTAL	NONE	NONE	NONE	NONE	1
-#M SCHWANNOMA, MALIGNANT	0	0	0	0	2
FATAL	NONE	NONE	NONE	NONE	1
SCHEDULED SACRIFICE	NONE	NONE	NONE	NONE	1
-#S ADENOCARCINOMA; MAMMARY GLAND	0	1	0	0	0
PRESENT	NONE	1	NONE	NONE	NONE
-#S FIBROSARCOMA; SKIN	0	0	0	1	0
PRESENT	NONE	NONE	NONE	1	NONE
ZYMBAL'S GLANDS					
TOTAL NUMBER EXAMINED	63	64	64	65	62
EXAMINED, UNREMARKABLE	63	62	62	60	54
NOT PRESENT FOR EXAMINATION	2	1	1	0	3
-#M CARCINOMA	0	1	1	2	5
INCIDENTAL	NONE	1	NONE	1	2
FATAL	NONE	NONE	NONE	NONE	1
SCHEDULED SACRIFICE	NONE	NONE	1	1	2

1- 0 MG/KG/DAY-1 2- 0 MG/KG/DAY-2 3- 100 MG/KG/DAY 4- 300 MG/KG/DAY 5- 900 MG/KG/DAY
= NEOPLASM, B = BENIGN, M = MALIGNANT, S = METASTATIC

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Toxicokinetics: HPN-100 is rapidly converted to PBA (4-phenylbutyric acid) in the GI tract. PBA is oxidized to PAA (phenylacetic acid). In rats, PAA conjugates with glycine forming PAG (phenylacetylglycine). The plasma concentrations of the above mentioned metabolites plus phenylacetylglutamine (PAGN), phenylbutyrylglycine (PBG), and phenylbutyrylglutamine (PBGN) were analyzed, and the toxickinetic parameters were summarized in the following tables (taken from the study report). Plasma levels of PBG and PBGN were either at or below the lowest level of quantitation (1 µg/mL).

Text Table 5. Summary of Toxicokinetic Parameters, PBA

Dosage	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ug/mL)	C_{last} (ug/mL)	AUC_{last} (hr•ug/mL)	AUC_{all} (hr•ug/mL)	AUC_{∞} (hr•ug/mL)
Study day 0							
Males							
70 mg/kg/day	0.85	1	16.1	1.25	23.47	24.72	25.01
210 mg/kg/day	1.77	1	22.4	6.64	47.30	53.94	64.29
650 mg/kg/day	1.33	1	195.9	0.38	341.76	344.02	342.48
Females							
100 mg/kg/day	0.94	1	21.0	0.46	38.75	39.21	39.37
300 mg/kg/day	0.96	1	44.9	0.45	111.57	112.48	112.20
900 mg/kg/day	3.6	1	223.6	0.44	710.31	710.31	712.57
Study day 364							
Males							
70 mg/kg/day	1.24	1	14.8	2.44	23.91	26.34	28.27
210 mg/kg/day	2.21	1	37.1	1.31	71.51	74.12	75.68
650 mg/kg/day	4.54	1	34.1	4.48	111.11	137.98	140.41
Females							
100 mg/kg/day	1.86	1	41.3	2.47	99.04	103.97	105.65
300 mg/kg/day	1.41	1	123.9	0.40	230.66	233.06	231.48
900 mg/kg/day	2.60	1	120.4	3.38	290.78	311.08	303.48

Text Table 6. Summary of Toxicokinetic Parameters, PAA

Dosage	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ug/mL)	C_{last} (ug/mL)	AUC_{last} (hr•ug/mL)	AUC_{all} (hr•ug/mL)	AUC_{∞} (hr•ug/mL)
				Study day 0			
Males							
70 mg/kg/day	NA	1	36.1	5.19	38.67	43.86	NA
210 mg/kg/day	NA	2	113.3	69.84	287.82	357.66	NA
650 mg/kg/day	1.34	2	278.0	12.35	1914.00	1988.07	1937.86
Females							
100 mg/kg/day	2.90	1	62.3	23.48	105.93	129.41	204.20
300 mg/kg/day	2.87	4	102.2	38.86	519.88	597.60	680.62
900 mg/kg/day	6.01	6	318.7	160.26	2892.00	3853.54	4280.94
				Study day 364			
Males							
70 mg/kg/day	0.46	1	47.2	0.49	63.15	63.65	63.48
210 mg/kg/day	0.77	1	129.7	1.07	425.39	426.46	426.58
650 mg/kg/day	3.35	4	585.8	107.07	3993.13	4635.52	4510.15
Females							
100 mg/kg/day	1.41	1	66.6	6.30	160.18	166.48	173.01
300 mg/kg/day	14.77	1	268.2	178.16	1618.01	1974.32	5414.15
900 mg/kg/day	6.72	4	757.4	328.01	7106.03	9074.09	10284.20

NA = Not Applicable

Text Table 7. Summary of Toxicokinetic Parameters, PAG

Dosage	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ug/mL)	C_{last} (ug/mL)	AUC_{last} (hr•ug/mL)	AUC_{all} (hr•ug/mL)	AUC_{∞} (hr•ug/mL)
				Study day 0			
Males							
70 mg/kg/day	1.43	1	11.4	2.75	26.61	29.36	32.27
210 mg/kg/day	0.86	2	18.5	0.75	75.53	76.28	76.46
650 mg/kg/day	3.96	2	35.2	5.56	263.32	296.71	295.09
Females							
100 mg/kg/day	2.14	1	11.9	1.82	35.68	37.50	41.32
300 mg/kg/day	2.42	2	18.9	5.70	104.98	116.38	124.89
900 mg/kg/day	4.14	2	39.6	1.48	469.71	469.71	478.58
				Study day 364			
Males							
70 mg/kg/day	4.36	1	27.6	0.43	66.27	66.27	68.97
210 mg/kg/day	1.72	1	35.6	0.94	154.04	159.70	156.38
650 mg/kg/day	2.22	4	62.3	0.47	810.28	810.28	811.79
Females							
100 mg/kg/day	1.99	1	19.7	3.59	98.78	105.96	109.08
300 mg/kg/day	1.40	2	36.5	1.46	269.76	278.50	272.71
900 mg/kg/day	2.50	2	66.6	0.97	972.53	972.53	976.02

Text Table 8. Summary of Toxicokinetic Parameters, PAGN

Dosage	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ug/mL)	C_{last} (ug/mL)	AUC_{last} (hr•ug/mL)	AUC_{all} (hr•ug/mL)	AUC_{∞} (hr•ug/mL)
				Study day 364			
Males							
650 mg/kg/day	22.5	4	1.33	1.17	7.50	9.85	45.64
Females							
900 mg/kg/day	NA	8	1.25	1.25	3.34	5.84	NA

NA = Not Applicable

Dosing Solution Analysis: The test article was a neat liquid, which was stable throughout the study period.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: Fertility and general reproduction toxicity study in rats

Study no.:	MQY00011
Study report location:	N/A
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 10, 2007
GLP compliance:	YES
QA statement:	YES
Drug, lot #, and % purity:	HPN-100 / XA179 / 99.8%

Key Study Findings

Methods

Doses:	0.65, 0.9, and 1.2 g/kg/day HPN-100; corn oil was used as the control article
Frequency of dosing:	daily
Dose volume:	0.59, 0.82, and 1.09 for low, middle, and high dose, respectively
Route of administration:	oral
Formulation/Vehicle:	Neat liquid
Species/Strain:	Rat/Crl:CD(SD)
Number/Sex/Group:	25/sex/group
Satellite groups:	None
Study design:	See table below
Deviation from study protocol:	There were no deviations that had a significant impact on the study outcome.

The study design is shown in the tables below (taken from the study report).

5.5.1.1. Treated Male Rats

Dosage Group	Dosage[a] (g/kg/day)	Density (g/mL)	Dosage Volume (mL/kg)	Number of Rats	Assigned Male Rat Numbers
I	0 (Control Article)	0	1.09	25	4701 - 4725
II	0.65	1.1033	0.59	25	4726 - 4750
III	0.9	1.1033	0.82	25	4751 - 4775
IV	1.2	1.1033	1.09	25	4776 - 4800

a. The test article purity was considered 100% for purposes of dosage calculations. The Certificate of Analysis was provided for the lot: specifications are set > and = 97% potency and purity.

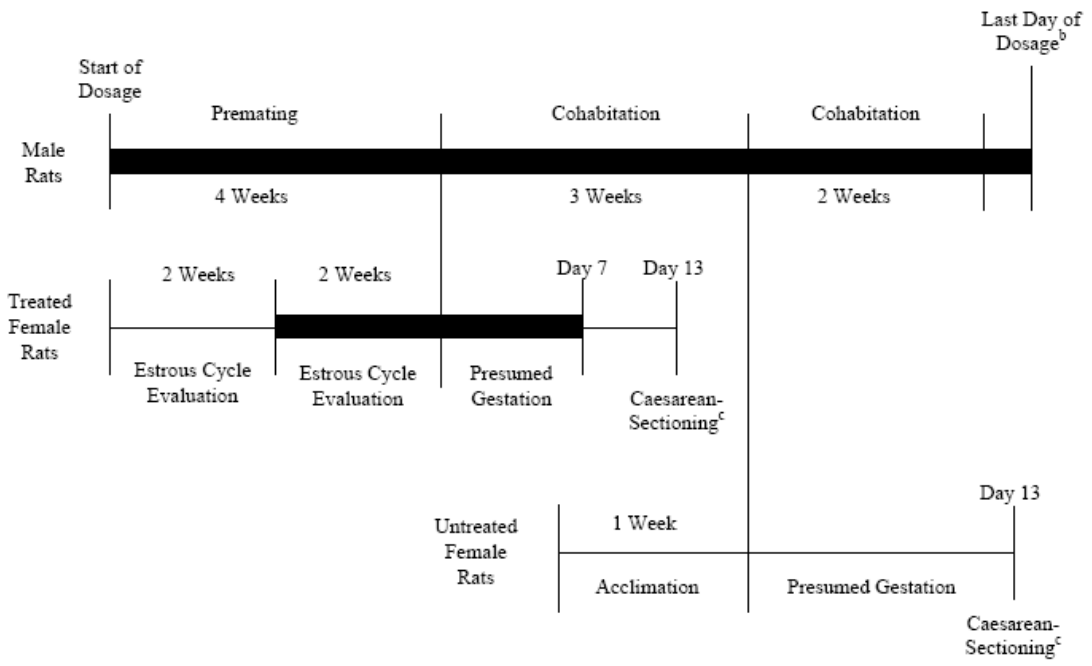
5.5.1.2. Treated Female Rats

Dosage Group	Dosage[a] (g/kg/day)	Density (g/mL)	Dosage Volume (mL/kg)	Number of Rats	Assigned Female Rat Numbers
I	0 (Control Article)	0	1.09	25	4801 - 4825
II	0.65	1.1033	0.59	25	4826 - 4850
III	0.9	1.1033	0.82	25	4851 - 4875
IV	1.2	1.1033	1.09	25	4876 - 4900

a. The test article purity was considered 100% for purposes of dosage calculations. The Certificate of Analysis was provided for the lot: specifications are set > 97% potency and purity.

Male rats were treated with the HPN-100 or corn oil once daily beginning 28 days before the first cohabitation (with treated females up to 15 days), through the second cohabitation (with untreated females up to 14 days). Treatment of males continued through the day before sacrifice. Treated female rats were given HPN-100 or corn oil once daily beginning 15 days before cohabitation through gestation day (DG) 7. The study design was summarized in the sponsor's table below.

Schematic of Study Design



a. For additional details see "Tests, Analyses and Measurements" section of the protocol.
b. Male rats sacrificed and sperm evaluations performed.
c. Female rats Caesarean-sectioned and examined for corpora lutea, implantation sites and viable and nonviable embryos.

The major finding in this study was a small but statistically significant increase in embryo-lethality in the high-dose group. Mating and fertility parameters were unaffected.

Observations and Results

Mortality: There were no treatment-related deaths. One low-dose male was sacrificed due to aspiration of the test drug. All females survived to termination.

Clinical Signs: Salivation and chromorhinorrhea were noted in the treatment groups (males and females). In addition, decreased motor activity, ataxia, and low carriage were noted in the high-dose females.

Body Weight: The terminal body weights in males (91 day treatment) were lower in the treatment groups (~96%, 92%, and 88% of the control group value for low, middle, and high dose groups, respectively). The terminal body weights in females (gestation day 13) were lower in the treatment groups (~98%, 94%, and 94% of the control group value for low, middle, and high dose groups, respectively).

Feed Consumption: Food consumption was lower in the treatment groups.

Toxicokinetics: Not measured.

Dosing Solution Analysis: Not applicable.

Necropsy:

All mating and fertility parameters including sperm parameters and all estrous cycling were not affected.

Pregnancy occurred in 23 (92.0%), 20 (80.0%), 23 (92%) and 23 (92%) of female rats that mated with treated males in the control, low, middle, and high dose groups, respectively. The number of viable embryos per litter was significantly reduced and the number of non-viable embryos per litter and percentage of non-viable embryos per litter significantly increased in the high-dose group. The results were summarized in the sponsor's table below.

TABLE B13 (PAGE 1): CAESAREAN-SECTIONING AND LITTER OBSERVATIONS - SUMMARY - TREATED FEMALE RATS

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)a		0 (CONTROL ARTICLE)	0.65	0.9	1.2
RATS TESTED	N	25	25	25	25
PREGNANT	N(%)	23(92.0)	20(80.0)	23(92.0)	23(92.0)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 13 OF GESTATION	N	23	20	23	23
CORPORA LUTEA	MEAN±S.D.	16.7 ± 2.8	16.6 ± 2.3	15.4 ± 2.1	15.5 ± 2.3
IMPLANTATIONS	MEAN±S.D.	15.5 ± 3.4	15.6 ± 2.0	14.3 ± 2.6	14.1 ± 3.0
VIABLE EMBRYOS	N	333	281	291	267
	MEAN±S.D.	14.5 ± 3.8	14.0 ± 2.1	12.6 ± 2.5	11.6 ± 2.8**
NONVIABLE EMBRYOS	N	23	31	39	57
	MEAN±S.D.	1.0 ± 1.3	1.6 ± 1.2	1.7 ± 1.4	2.5 ± 1.4**
DAMS WITH ANY NONVIABLE EMBRYOS	N(%)	14(60.9)	17(85.0)	18(78.3)	21(91.3)
DAMS WITH ALL NONVIABLE EMBRYOS	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
DAMS WITH VIABLE EMBRYOS	N(%)	23(100.0)	20(100.0)	23(100.0)	23(100.0)
% NONVIABLE EMBRYOS/LITTER	MEAN±S.D.	6.7 ± 9.8	9.9 ± 7.2	11.6 ± 9.3	17.4 ± 10.2**

a. Dosage occurred on day 1 of study through day 7 of gestation.
** Significantly different from the control group value ($p \leq 0.01$).

9.2 Embryonic Fetal Development

Study title: Oral developmental toxicity study in rats

Study no.:	MQY00008
Study report location:	N/A
Conducting laboratory and location:	(b) (4)
Date of study initiation:	January 7, 2008
GLP compliance:	YES
QA statement:	YES
Drug, lot #, and % purity:	HPN-100 / XA179 / 100%

Key Study Findings

Methods

Doses:	0.3, 0.65, and 0.9 g/kg/day HPN-100; corn oil was used as the control article
Frequency of dosing:	daily
Dose volume:	0.27, 0.59, 0.82 ml/kg for low, middle, and high dose groups, respectively
Route of administration:	oral
Formulation/Vehicle:	Neat liquid
Species/Strain:	Rat/Crl:CD(SD)
Number/Sex/Group:	25
Satellite groups:	6/sex/group
Study design:	See sponsor's table below
Deviation from study protocol:	There were no deviations that had a significant impact on the study outcome.

The study design is shown in the table below (taken from the study report).

Dosage Group	Dosage[a] (g/kg/day)	Density (g/mL)	Dosage Volume (mL/kg)	Number of Rats	Assigned Rat Numbers	
					Main Study	TK Study
I	0 (Control Article)	0	0.82	25 + 3[b]	8901 - 8925	676 - 678
II	0.3	1.1033	0.27	25 + 6[b]	8926 - 8950	679 - 684
III	0.65	1.1033	0.59	25 + 6[b]	8951 - 8975	685 - 690
IV	0.9	1.1033	0.82	25 + 6[b]	8976 - 9000	691 - 696

a. The test article was considered 100% pure for the purpose of dosage calculations.
b. Rats assigned to toxicokinetic sample collection.

Pregnant rats were treated with HPN-100 at oral doses of 0 (corn oil), 0.3, 0.65, and 0.9 g/kg/day during gestation days (DG) 7-17. The dose selection was based on the results of the dose-ranging study (MQY00007). In this study, doses of 0 (control article), 0.65, 0.9, 1.2, and 1.5 g/kg/day of glyceryl tri-(4-phenylbutyrate) (HPN-100) were given to

pregnant rats during gestation days 7-17. Significant clinical signs of maternal toxicity including ataxia, decreased motor activity, muscle rigidity, splayed limbs, low carriage, and cold to touch were observed at doses of 0.9 g/kg/day or higher. Decreases in mean maternal body weights and fetal loss were noted at doses of 1.2 and 1.5 g/kg/day. In the present study, the most common fetal effect was the presence of a cervical rib at the 7th cervical vertebra. This effect was dose-dependent. The litter incidence was statistically significant in the middle and high-dose groups, and fetal incidence was significant only in the high-dose group. Malformations were observed in the middle and high groups (3 and 2 fetuses, respectively), but were not statistically significant. Mild maternal toxicity was observed in the middle and high dose groups, based on reduction in weight gain. Reduced motor activity and splayed limbs were also noted in the high dose group.

Observations and Results

Mortality: No deaths occurred.

Clinical Signs: Decreased motor activity and splayed limbs were observed in the high dose group.

Body Weight: Body weight gains during DG 7-18 were reduced by 13% and 21% in the middle and high-dose groups, respectively, as compared to the control.

Feed Consumption: Food consumption was lower in the middle and high dose groups.

Toxicokinetics: Plasma levels of the major metabolites of HPN-100 were measured. The toxicokinetic results are shown in the table below (taken from the study report).

Analyte	Study Day	Dose mg/kg	T_{max} hr	C_{max} ug/ml	T_{last} hr	C_{last} ug/ml	AUC_{all} hr*ug/ml
PBA	7	300	0.5	125.63	8	10.42	418.67
PBA	7	650	0.5	228.36	8	35.96	873.24
PBA	7	900	2	316.53	24	0.57	1197.92
PBA	17	300	0.5	14.42	8	2.21	94.36
PBA	17	650	2	34.47	8	29.16	414.94
PBA	17	900	2	45.00	8	7.81	215.65
PAA	7	300	4	317.65	8	289.71	4244.03
PAA	7	650	4	386.16	8	363.23	5172.16
PAA	7	900	4	543.92	8	509.21	7192.33
PAA	17	300	2	181.15	8	75.48	1557.83
PAA	17	650	8	348.43	8	348.43	4632.81
PAA	17	900	8	471.54	8	471.54	6336.22
PAG	7	300	4	19.74	8	16.25	266.24
PAG	7	650	2	24.88	8	24.74	357.95
PAG	7	900	2	25.32	24	1.19	363.94
PAG	17	300	4	21.72	24	0.46	287.74
PAG	17	650	8	40.25	24	0.57	570.83
PAG	17	900	8	39.81	24	2.27	591.47

Dosing Solution Analysis: Not applicable.

Necropsy

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

Fetal body weights were slightly lower in the middle (6%) and high dose groups (10%), as compared to the control. There were no treatment-related effects on corpora lutea, implantations, litter sizes, live fetuses, early and late resorptions, percent resorbed conceptuses, and percent live male fetuses. The results were summarized in the sponsor's tables below.

TABLE 8 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)a		0 (CONTROL ARTICLE)	0.3	0.65	0.9
RATS TESTED	N	25	25	25	25
PREGNANT	N(%)	24(96.0)	22(88.0)	24(96.0)	24(96.0)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 21 OF GESTATION	N	24	22	24	24
CORPORA LUTEA	MEAN±S.D.	16.2 ± 2.0	16.3 ± 1.5	16.1 ± 3.0	15.2 ± 2.5
IMPLANTATIONS	MEAN±S.D.	15.8 ± 1.9	15.3 ± 2.9	14.8 ± 4.2	14.7 ± 3.0
LITTER SIZES	MEAN±S.D.	15.1 ± 1.9	14.9 ± 2.9	14.1 ± 4.0	13.9 ± 3.1
LIVE FETUSES	N	363	327	338	334
	MEAN±S.D.	15.1 ± 1.9	14.9 ± 2.9	14.1 ± 4.2	13.9 ± 3.1
DEAD FETUSES	N	0	0	1	0
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.2	0.0 ± 0.0
RESORPTIONS	MEAN±S.D.	0.6 ± 0.6	0.4 ± 0.7	0.6 ± 1.0	0.8 ± 1.1
EARLY RESORPTIONS	N	15	10	14	19
	MEAN±S.D.	0.6 ± 0.6	0.4 ± 0.7	0.6 ± 0.9	0.8 ± 1.1
LATE RESORPTIONS	N	0	0	1	0
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.2	0.0 ± 0.0
DAMS WITH ANY RESORPTIONS	N(%)	13(54.2)	7(31.8)	9(37.5)	12(50.0)
DAMS WITH ALL CONCEPTUSES DEAD OR RESORBED	N(%)	0(0.0)	0(0.0)	1(4.2)	0(0.0)
DAMS WITH VIABLE FETUSES	N(%)	24(100.0)	22(100.0)	23(95.8)	24(100.0)
PLACENTAE APPEARED NORMAL	N(%)	24(100.0)	22(100.0)	23(95.8)	24(100.0)

a. Dosage occurred on days 7 through 17 of gestation.

PROTOCOL MQY00008: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY OF GLYCERYL TRI-(4-PHENYLBUTYRATE) [HPN-100] IN GRAVID RATS

TABLE 9 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)a		0 (CONTROL ARTICLE)	0.3	0.65	0.9
LITTERS WITH ONE OR MORE LIVE FETUSES	N	24	22	23	24
IMPLANTATIONS	MEAN±S.D.	15.8 ± 1.9	15.3 ± 2.9	15.3 ± 3.1	14.7 ± 3.0
LIVE FETUSES	N	363	327	338	334
	MEAN±S.D.	15.1 ± 1.9	14.9 ± 2.9	14.7 ± 3.0	13.9 ± 3.1
LIVE MALE FETUSES	N	181	166	173	174
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	49.3 ± 14.6	50.6 ± 12.2	51.2 ± 13.5	53.7 ± 18.2
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	5.30 ± 0.24	5.22 ± 0.26	5.01 ± 0.25**	4.78 ± 0.44**
MALE FETUSES	MEAN±S.D.	5.47 ± 0.25	5.36 ± 0.26	5.14 ± 0.26**	4.93 ± 0.47**
FEMALE FETUSES	MEAN±S.D.	5.15 ± 0.25	5.08 ± 0.26	4.87 ± 0.26**	4.72 ± 0.31** [23]b
% DEAD OR RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	4.0 ± 4.2	2.8 ± 4.6	4.5 ± 6.6	5.3 ± 6.9

[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 17 of gestation.
b. Litter 8976 had no female fetuses.
** Significantly different from the control group value (p≤0.01).

Offspring (Malformations, Variations, etc.)

The number of litters with fetal alterations were 3 (12.5%), 8 (36.4%), 15 (65.2%) and 21 (87.5%) for the control, low, middle, and high dose groups, respectively. The number of fetuses with any alteration were 3 (0.8%), 15 (4.6%), 38 (11.2%) and 82 (24.6%), and the percentages of fetuses with any alteration per litter were 0.8, 4.2, 12.6, and 24.0 in the control, low, middle, and high dose groups, respectively. The results were summarized in the sponsor's table below.

TABLE 10 (PAGE 1): FETAL ALTERATIONS - CAESAREAN-DELIVERED LIVE FETUSES (DAY 21 OF GESTATION) - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)a		0 (CONTROL ARTICLE)	0.3	0.65	0.9
LITTERS EVALUATED	N	24	22	23b	24
FETUSES EVALUATED	N	363	327	339	334
LIVE	N	363	327	338	334
DEAD	N	0	0	1c	0
LITTERS WITH FETUSES WITH ANY ALTERATION OBSERVED	N(%)	3(12.5)	8(36.4)	15(65.2)**	21(87.5)**
FETUSES WITH ANY ALTERATION OBSERVED	N(%)	3(0.8)	15(4.6)	38(11.2)	82(24.6)**
% FETUSES WITH ANY ALTERATION/LITTER	MEAN±S.D.	0.8 ± 2.3	4.2 ± 7.2	12.6 ± 14.4**	24.0 ± 16.5**

a. Dosage occurred on days 7 through 17 of gestation.
b. Excludes values for litter 8964, which consisted of only one dead fetus.
c. Values for dead fetus were excluded from summarization and statistical analyses. Observations for this conceptus are cited on Table 23.
** Significantly different from the control group value ($p \leq 0.01$).

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External alterations:

Gross fetal alterations occurred in 1, 1, 2 and 5 fetuses from 1, 1, 2 and 4 litters in the control, low, middle, and high dose groups, respectively. The results were summarized in the sponsor's table below.

TABLE 11 (PAGE 1): FETAL GROSS EXTERNAL ALTERATIONS - CAESAREAN-DELIVERED LIVE FETUSES (DAY 21 OF GESTATION) - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)a		0 (CONTROL ARTICLE)	0.3	0.65	0.9
LITTERS EVALUATED	N	24	22	23b	24
FETUSES EVALUATED	N	363	327	339	334
LIVE	N	363	327	338	334
DEAD	N	0	0	1c	0
BODY: UMBILICAL HERNIA					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.3)
BODY: EDEMA					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.3)	0(0.0)	0(0.0)
TRUNK: SHORT					
LITTER INCIDENCE	N(%)	1(4.2)	0(0.0)	0(0.0)	1(4.2)
FETAL INCIDENCE	N(%)	1(0.3)	0(0.0)	0(0.0)	1(0.3)e
ANUS: NO OPENING PRESENT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.3)	1(4.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.3)d	1(0.3)f
TAIL: ABSENT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.3)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.3)	0(0.0)
TAIL: SHORT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.3)	2(8.3)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.3)d	2(0.6)e
TAIL: THREAD-LIKE					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	2(8.3)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	2(0.6)f

a. Dosage occurred on days 7 through 17 of gestation.
b. Excludes values for litter 8964, which consisted of only one dead fetus.
c. Values for dead fetus were excluded from summarization and statistical analyses. Observations for this conceptus are cited on Table 23.
d. Fetus 8960-6 had other gross external alterations.
e. Fetus 8994-8 had other gross external alterations.
f. Fetus 8994-9 had other gross external alterations.

The increase in the number of fetuses with gross alterations was mainly due to higher incidence of tail anomalies (short, threadlike) in the high dose group.

Fetal Soft Tissue Alterations:

One middle-dose fetus has interventricular septal defect and folded retina. This fetus also had whole body edema as reported under external alterations. One high dose fetus had undescended testes and other alterations such as short tail as described under external alterations.

The results were summarized in the sponsor's table below.

TABLE 12 (PAGE 1): FETAL SOFT TISSUE ALTERATIONS - CAESAREAN-DELIVERED LIVE FETUSES (DAY 21 OF GESTATION) - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)a		0 (CONTROL ARTICLE)	0.3	0.65	0.9
LITTERS EVALUATED	N	24	22	23	24
FETUSES EVALUATED	N	176	158	162	161
LIVE	N	176	158	162	161
EYES: RETINA FOLDED					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)b	0(0.0)	0(0.0)
HEART: INTERVENTRICULAR SEPTAL DEFECT					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)b	0(0.0)	0(0.0)
TESTES: UNDESCENDED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.6)

a. Dosage occurred on days 7 through 17 of gestation.
b. Fetus 8939-2 had other soft tissue alterations.

Fetal Skeletal Alterations:

Malformations were found in three middle-dose fetuses and two high-dose fetuses. The middle-dose fetuses with malformations included one fetus with a fused arch (cervical vertebrae) and a cervical rib present at the 7th cervical vertebrae, one fetus with a hemivertebra and only two caudal vertebrae (this fetus had other alterations such as no tail), and one fetus with a short digit and a cervical rib present at the 7th cervical vertebrae.

The two high-dose fetuses with malformations included one with fused ribs, cervical ribs at the 7th cervical vertebrae, a 6th cervical arch that had the appearance (shape and size) of the 7th arch, unilaterally ossified thoracic vertebral centrum, and a small thoracic vertebral arch. The other high-dose fetus had only two sacral vertebrae, no caudal vertebrae, and other alterations including a thread-like tail.

The most common skeletal alteration was the presence of a cervical rib at the 7th cervical vertebra. This effect was dose-dependent. The litter incidence was statistically significant in the middle and high-dose groups, and fetal incidence was significant only in the high-dose group. Thickened ribs and incomplete ossification of the pelvis occurred with low incidence in the high-dose group.

The results were summarized in the sponsor's table below.

TABLE 13 (PAGE 1): FETAL SKELETAL ALTERATIONS - CAESAREAN-DELIVERED LIVE FETUSES (DAY 21 OF GESTATION) - SUMMARY
(See footnotes on the last page of this table.)

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)a		0 (CONTROL ARTICLE)	0.3	0.65	0.9
LITTERS EVALUATED	N	24	22	23b	24
FETUSES EVALUATED c	N	187	169	177	173
LIVE	N	187	169	176	173
DEAD	N	0	0	1d	0
SKULL: PARIETAL, INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	2(8.7)	5(20.8)
FETAL INCIDENCE	N(%)	0(0.0)	2(1.2)	5(2.8)	5(2.9)
SKULL: SUPRAOCCIPITAL, INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)	0(0.0)	0(0.0)
SKULL: FRONTAL, INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.3)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	2(1.1)	0(0.0)
SKULL: MAXILLA, INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.3)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
SKULL: NASAL-FRONTAL SUTURE, LARGE					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	2(8.3)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	2(1.2)
CERVICAL VERTEBRAE: CERVICAL RIB PRESENT AT THE 7TH CERVICAL VERTEBRA					
LITTER INCIDENCE	N(%)	0(0.0)	7(31.8)	14(60.9)**	20(83.3)**
FETAL INCIDENCE	N(%)	0(0.0)	8(4.7)	27(15.3)	73(42.2)**
CERVICAL VERTEBRAE: ARCH, FUSED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.3)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
CERVICAL VERTEBRAE: 6TH CERVICAL ARCH HAS THE APPEARANCE OF THE 7TH					
LITTER INCIDENCE	N(%)	1(4.2)	0(0.0)	0(0.0)	2(8.3)
FETAL INCIDENCE	N(%)	1(0.5)	0(0.0)	0(0.0)	4(2.3)**
CERVICAL VERTEBRAE: ARCH, INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)	0(0.0)	0(0.0)

** Significantly different from the control group value ($p \leq 0.01$).

TABLE 13 (PAGE 2): FETAL SKELETAL ALTERATIONS - CAESAREAN-DELIVERED LIVE FETUSES (DAY 21 OF GESTATION) - SUMMARY
(See footnotes on the last page of this table.)

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)a		0 (CONTROL ARTICLE)	0.3	0.65	0.9
LITTERS EVALUATED	N	24	22	23b	24
FETUSES EVALUATED c	N	187	169	177	173
LIVE	N	187	169	176	173
DEAD	N	0	0	1d	0
THORACIC VERTEBRAE: CENTRUM, BIFID					
LITTER INCIDENCE	N(%)	0(0.0)	2(9.1)	2(8.7)	3(12.5)
FETAL INCIDENCE	N(%)	0(0.0)	2(1.2)	2(1.1)	4(2.3)
THORACIC VERTEBRAE: CENTRUM, UNILATERALLY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
THORACIC VERTEBRAE: ARCH, SMALL					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
LUMBAR VERTEBRAE: ARCH, INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
SACRAL VERTEBRAE: 2 PRESENT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
CAUDAL VERTEBRAE: HEMIVERTEBRA					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.3)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
CAUDAL VERTEBRAE: 2 PRESENT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.3)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
CAUDAL VERTEBRAE: 0 PRESENT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
RIBS: THICKENED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.3)	4(16.7)**
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)	4(2.3)**

** Significantly different from the control group value ($p \leq 0.01$).

TABLE 13 (PAGE 3): FETAL SKELETAL ALTERATIONS - CAESAREAN-DELIVERED LIVE FETUSES (DAY 21 OF GESTATION) - SUMMARY
(See footnotes on the last page of this table.)

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)a		0 (CONTROL ARTICLE)	0.3	0.65	0.9
LITTERS EVALUATED	N	24	22	23b	24
FETUSES EVALUATED c	N	187	169	177	173
LIVE	N	187	169	176	173
DEAD	N	0	0	1d	0
RIBS: SHORT					
LITTER INCIDENCE	N(%)	1(4.2)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.5)	0(0.0)	0(0.0)	0(0.0)
RIBS: WAVY					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	2(8.7)	1(4.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	4(2.3)**	1(0.6)
RIBS: INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.3)	1(4.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	3(1.7)	1(0.6)
RIBS: BENT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.3)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	2(1.1)	0(0.0)
RIBS: FUSED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
STERNAL CENTRA: SUMMARIZATION (SUMMARIZATION OF ASYMMETRIC, INCOMPLETELY OSSIFIED AND IRREGULARLY SHAPED)					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	1(4.3)	3(12.5)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)	1(0.6)	3(1.7)
STERNAL CENTRA: ASYMMETRIC					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.5)	0(0.0)	2(8.3)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.6)	0(0.0)	2(1.2)
STERNAL CENTRA: INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.3)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
STERNAL CENTRA: IRREGULARLY SHAPED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.6)

** Significantly different from the control group value ($p \leq 0.01$).

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TABLE 13 (PAGE 4): FETAL SKELETAL ALTERATIONS - CAESAREAN-DELIVERED LIVE FETUSES (DAY 21 OF GESTATION) - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)a		0 (CONTROL ARTICLE)	0.3	0.65	0.9
LITTERS EVALUATED	N	24	22	23b	24
FETUSES EVALUATED c	N	187	169	177	173
LIVE	N	187	169	176	173
DEAD	N	0	0	1d	0
FORELIMB: DIGIT, SHORT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.3)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
PELVIS: SUMMARIZATION (SUMMARIZATION OF PUBIS AND ISCHIUM INCOMPLETELY OSSIFIED)					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	2(8.3)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	5(2.9)**
PELVIS: PUBIS, INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	2(8.3)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	4(2.3)**
PELVIS: ISCHIUM, INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.2)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	3(1.7)**

a. Dosage occurred on days 7 through 17 of gestation.
b. Excludes values for litter 8964, which consisted of only one dead fetus.
c. See the individual fetal alterations table (Table 23) for fetuses with multiple skeletal alterations.
d. Values for dead fetus were excluded from summarization and statistical analyses. Observations for this conceptus are cited on Table 23.
** Significantly different from the control group value ($p \leq 0.01$).

Study title: Oral developmental toxicity study in rabbits

Study no.:	MQY00010
Study report location:	N/A
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 31, 2008
GLP compliance:	YES
QA statement:	YES
Drug, lot #, and % purity:	HPN-100 / XA179 / 99.8%

Key Study Findings

Methods

Doses:	0.15, 0.25, and 0.35 g/kg/day HPN-100; corn oil was used as the control article
Frequency of dosing:	daily
Dose volume:	0.14, 0.23, 0.32 ml/kg for low, middle, and high dose groups, respectively
Route of administration:	oral
Formulation/Vehicle:	Neat liquid
Species/Strain:	Rabbit/Hra:(NZW)SPF
Number/Sex/Group:	20
Satellite groups:	none
Study design:	See table below
Deviation from study protocol:	There were no deviations that had a significant impact on the study outcome.

The study design is shown in the sponsor's table below.

Dosage Group	Dosage[a] (g/kg/day)	Density (g/mL)	Dosage Volume (mL/kg)	Number of Rabbits[b]	Assigned Rabbit Numbers
I	0 (Control)	0	0.32	20	7001 - 7020
II	0.15	1.1033	0.14	20	7021 - 7040
III	0.25	1.1033	0.23	20	7041 - 7060
IV	0.35	1.1033	0.32	20	7061 - 7080

a. The test article purity was considered 99.8% for purposes of dosage calculations.
b. The last three rabbits in each dosage group had blood samples collected as described in section 4.5.5.

The pregnant rabbits were treated with HPN-100 or corn oil given via stomach tube once daily on gestation days (DG) 7 through 19 at dosages of 0 (corn oil), 0.15, 0.25, and 0.35 g/kg/day. The dose selection was based on the results of a dose range-finding study (b) (4) MYQ00009) in pregnant NZW rabbits. In this study, a dose of 0.6

g/kg/day given to pregnant rabbits during DG 7 through 19 induced marked mortality/morbidity. At lower doses of 0.2 and 0.4 g/kg/day, body weight gains were lower (-44% and -81%, respectively). One animal treated with 0.4 g/kg/day was sacrificed due to clinical signs of toxicity (soft or liquid feces, dehydration, decreased motor activity, ptosis, ataxia, pale, cold to touch, and tachypnea) and body weight loss. Fetal weights were reduced (10%) in the 0.4 g/kg/day group as compared to the control. Therefore, the selection of 0.35 g/kg/day as the high dose is acceptable. In the present study, there were no signs of maternal toxicity and no adverse effects in fetuses.

Observations and Results

Mortality: No deaths occurred.

Clinical Signs: There were no treatment-related clinical signs of toxicity.

Body Weight: There were no treatment-related effects.

Feed Consumption: There were no treatment-related effects.

Toxicokinetics: Plasma levels of the major metabolites of HPN-100 were measured. The toxicokinetic results are shown in the table below (taken from the study report).

Analyte	Study Day	Dose mg/kg	T_{max} hr	C_{max} ug/ml	AUC_{all} hr*ug/ml
PBA	19	150	1.33	13.70	31.52
PBA	19	250	1.67	29.40	62.46
PBA	19	350	1.50	21.33	49.44
PAA	19	150	4.67	179.00	872.66
PAA	19	250	4.00	308.73	1555.84
PAA	19	350	4.67	399.57	2298.31
PAG	19	150	5.33	7.53	48.36
PAG	19	250	3.33	10.47	67.64
PAG	19	350	4.00	10.00	78.96

Dosing Solution Analysis: Not applicable.

Necropsy

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

There were no treatment-related effects. The results were summarized in the sponsor's tables below.

PROTOCOL MQY00010: ORAL (STOMACH TUBE) DEVELOPMENTAL TOXICITY STUDY OF GLYCERYL TRI-(4-PHENYLBUTYRATE) [HPN-100] IN RABBITS INCLUDING A TOXICOKINETIC EVALUATION

TABLE 8 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)a		0 (CONTROL)	0.15	0.25	0.35
RABBITS TESTED	N	20	20	20	20
PREGNANT	N(%)	17(85.0)	18(90.0)	18(90.0)	16(80.0)
FOUND DEAD	N(%)	0(0.0)	0(0.0)	0(0.0)	1(6.2)
RABBITS PREGNANT AND CAESAREAN-SECTIONED ON DAY 29 OF GESTATION	N	17	18	18	15
CORPORA LUTEA	MEAN±S.D.	8.8 ± 1.1	8.1 ± 1.2	9.0 ± 1.9	8.3 ± 1.6
IMPLANTATIONS	MEAN±S.D.	8.2 ± 1.1	7.2 ± 2.2	8.7 ± 2.0	7.9 ± 1.3
LITTER SIZES	MEAN±S.D.	8.0 ± 1.2	7.0 ± 2.1	8.3 ± 2.0	7.6 ± 1.2
LIVE FETUSES	N	136	127	150	114
	MEAN±S.D.	8.0 ± 1.2	7.0 ± 2.1	8.3 ± 2.0	7.6 ± 1.2
DEAD FETUSES	N	1	0	0	0
	MEAN±S.D.	0.0 ± 0.2	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
RESORPTIONS	MEAN±S.D.	0.1 ± 0.3	0.2 ± 0.4	0.4 ± 0.6	0.3 ± 0.5
EARLY RESORPTIONS	N	0	3	3	5
	MEAN±S.D.	0.0 ± 0.0	0.2 ± 0.4	0.2 ± 0.4	0.3 ± 0.5*
LATE RESORPTIONS	N	2	0	4	0
	MEAN±S.D.	0.1 ± 0.3	0.0 ± 0.0	0.2 ± 0.5	0.0 ± 0.0
DOES WITH ANY RESORPTIONS	N(%)	2(11.8)	3(16.7)	6(33.3)	5(33.3)
DOES WITH ALL CONCEPTUSES DEAD OR RESORBED	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
DOES WITH VIABLE FETUSES	N(%)	17(100.0)	18(100.0)	18(100.0)	15(100.0)
PLACENTAE APPEARED NORMAL	N(%)	17(100.0)	18(100.0)	18(100.0)	15(100.0)

a. Dosage occurred on days 7 through 19 of gestation.
* Significantly different from the control group value ($p \leq 0.05$).

TABLE 9 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)a		0 (CONTROL)	0.15	0.25	0.35
LITTERS WITH ONE OR MORE LIVE FETUSES	N	17	18	18	15
IMPLANTATIONS	MEAN±S.D.	8.2 ± 1.1	7.2 ± 2.2	8.7 ± 2.0	7.9 ± 1.3
LIVE FETUSES	N	136	127	150	114
	MEAN±S.D.	8.0 ± 1.2	7.0 ± 2.1	8.3 ± 2.0	7.6 ± 1.2
LIVE MALE FETUSES	N	55	49	78	47
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	39.2 ± 17.6	35.8 ± 18.0	52.5 ± 20.2*	41.6 ± 16.6
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	43.80 ± 2.75	45.16 ± 5.62	42.14 ± 4.95	44.37 ± 4.97
MALE FETUSES	MEAN±S.D.	44.64 ± 3.86 [16]b	45.74 ± 5.75 [17]b	42.82 ± 4.91	45.21 ± 5.02
FEMALE FETUSES	MEAN±S.D.	43.31 ± 2.88	44.41 ± 5.88	41.26 ± 6.00 [17]c	44.46 ± 5.98
% DEAD OR RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	2.2 ± 5.0	2.1 ± 5.1	4.5 ± 7.1	4.1 ± 6.3

[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 7 through 19 of gestation.
b. Litters 7013 and 7023 had no male fetuses.
c. Litter 7043 had no female fetuses.
* Significantly different from the control group value ($p \leq 0.05$).

Offspring (Malformations, Variations, etc.)

There were no treatment-related effects. The results were summarized in the sponsor's tables below.

TABLE 11 (PAGE 1): FETAL GROSS EXTERNAL ALTERATIONS - CAESAREAN-DELIVERED LIVE FETUSES (DAY 29 OF GESTATION) - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)a		0 (CONTROL)	0.15	0.25	0.35
LITTERS EVALUATED	N	17	18	18	15
FETUSES EVALUATED	N	137	127	150	114
LIVE	N	136	127	150	114
DEAD b	N	1	0	0	0
NO FETAL ALTERATIONS WERE IDENTIFIED AT GROSS EXTERNAL EXAMINATION					

a. Dosage occurred on days 7 through 19 of gestation.
b. Dead fetus was excluded from summarization and statistical analyses. Observations for this conceptus are cited on Table 22.

TABLE 12 (PAGE 1): FETAL SOFT TISSUE ALTERATIONS - CAESAREAN-DELIVERED LIVE FETUSES (DAY 29 OF GESTATION) - SUMMARY
(See footnotes on the last page of this table.)

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)a		0 (CONTROL)	0.15	0.25	0.35
LITTERS EVALUATED	N	17	18	18	15
FETUSES EVALUATED	N	136	127	150	114
LIVE	N	136	127	150	114
EYES: SMALL					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(6.7)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.9)
EYES: CIRCUMCORNEAL HEMORRHAGE					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(6.7)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.9)
HEART: INTERVENTRICULAR SEPTAL DEFECT					
LITTER INCIDENCE	N(%)	2(11.8)	0(0.0)	1(5.6)	0(0.0)
FETAL INCIDENCE	N(%)	2(1.5)b,c	0(0.0)	1(0.7)d	0(0.0)
VESSELS: AORTA DISTENDED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(5.6)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.7)d	0(0.0)
VESSELS: PERSISTENT TRUNCUS ARTERIOSUS					
LITTER INCIDENCE	N(%)	1(5.9)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.7)c	0(0.0)	0(0.0)	0(0.0)
VESSELS: PULMONARY ARTERY CONSTRICTED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(6.7)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.9)
LUNGS: INTERMEDIATE LOBE ABSENT					
LITTER INCIDENCE	N(%)	1(5.9)	1(5.6)	1(5.6)	2(13.3)
FETAL INCIDENCE	N(%)	1(0.7)b	2(1.6)	1(0.7)d	3(2.6)
KIDNEYS: LOW SET					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(5.6)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.7)	0(0.0)

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TABLE 12 (PAGE 2): FETAL SOFT TISSUE ALTERATIONS - CAESAREAN-DELIVERED LIVE FETUSES (DAY 29 OF GESTATION) - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)a		0 (CONTROL)	0.15	0.25	0.35
LITTERS EVALUATED	N	17	18	18	15
FETUSES EVALUATED	N	136	127	150	114
LIVE	N	136	127	150	114
GALLBLADDER: ABSENT					
LITTER INCIDENCE	N(%)	1(5.9)	0(0.0)	0(0.0)	2(13.3)
FETAL INCIDENCE	N(%)	1(0.7)	0(0.0)	0(0.0)	5(4.4)**
GALLBLADDER: SMALL					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(5.6)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.7)d	0(0.0)

a. Dosage occurred on days 7 through 19 of gestation.
b. Fetus 7004-6 had other soft tissue alterations.
c. Fetus 7016-6 had other soft tissue alterations.
d. Fetus 7050-3 had other soft tissue alterations.
** Significantly different from the control group value ($p \leq 0.01$).

TABLE 13 (PAGE 1): FETAL SKELETAL ALTERATIONS - CAESAREAN-DELIVERED LIVE FETUSES (DAY 29 OF GESTATION) - SUMMARY
(See footnotes on the last page of this table.)

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)a		0 (CONTROL)	0.15	0.25	0.35
LITTERS EVALUATED	N	17	18	18	15
FETUSES EVALUATED	N	137	127	150	114
LIVE	N	136	127	150	114
DEAD b	N	1	0	0	0
SKULL: IRREGULAR OSSIFICATION c (SUMMARIZATION OF ALL IRREGULAR OSSIFICATION OF THE SKULL d; INDIVIDUAL SUBCATEGORIES CITED BELOW)					
LITTER INCIDENCE	N(%)	3(17.6)	2(11.1)	4(22.2)	0(0.0)
FETAL INCIDENCE	N(%)	3(2.2)	2(1.6)	4(2.7)	0(0.0)
SKULL: FRONTAL, CONTAINS AN INTRAFRONTAL					
LITTER INCIDENCE	N(%)	1(5.9)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.7)	0(0.0)	0(0.0)	0(0.0)
SKULL: NASAL(S), IRREGULAR OSSIFICATION (SUMMARIZATION OF NASALS MIDLINE SUTURE DISPLACED, NASAL - FRONTAL SUTURE IRREGULAR AND NASALS SUTURE IRREGULAR)					
LITTER INCIDENCE	N(%)	2(11.8)	2(11.1)	4(22.2)	0(0.0)
FETAL INCIDENCE	N(%)	2(1.5)	2(1.6)	4(0.7)	0(0.0)
SKULL: NASALS, MIDLINE SUTURE DISPLACED					
LITTER INCIDENCE	N(%)	1(5.9)	0(0.0)	4(22.2)**	0(0.0)
FETAL INCIDENCE	N(%)	1(0.7)	0(0.0)	4(2.7)	0(0.0)
SKULL: NASAL - FRONTAL, SUTURE IRREGULAR					
LITTER INCIDENCE	N(%)	0(0.0)	2(11.1)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	2(1.6)	0(0.0)	0(0.0)
SKULL: NASALS, SUTURE IRREGULAR					
LITTER INCIDENCE	N(%)	1(5.9)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.7)	0(0.0)	0(0.0)	0(0.0)
SKULL - OTHER ALTERATIONS: HYOID: ALA, ANGULATED					
LITTER INCIDENCE	N(%)	3(17.6)	2(11.1)	3(16.7)	3(20.0)
FETAL INCIDENCE	N(%)	5(3.7)	2(1.6)	6(4.0)	6(5.3)

** Significantly different from the control group value (p≤0.01).

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TABLE 13 (PAGE 2): FETAL SKELETAL ALTERATIONS - CAESAREAN-DELIVERED LIVE FETUSES (DAY 29 OF GESTATION) - SUMMARY
(See footnotes on the last page of this table.)

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)a		0 (CONTROL)	0.15	0.25	0.35
LITTERS EVALUATED	N	17	18	18	15
FETUSES EVALUATED	N	137	127	150	114
LIVE	N	136	127	150	114
DEAD b	N	1	0	0	0
THORACIC VERTEBRAE: HEMIVERTEBRA					
LITTER INCIDENCE	N(%)	0(0.0)	1(5.6)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.8)h	0(0.0)	0(0.0)
LUMBAR VERTEBRAE: ARCH, SMALL					
LITTER INCIDENCE	N(%)	1(5.9)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.7)g	0(0.0)	0(0.0)	0(0.0)
LUMBAR VERTEBRAE: CENTRUM, UNILATERAL OSSIFICATION					
LITTER INCIDENCE	N(%)	1(5.9)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.7)g	0(0.0)	0(0.0)	0(0.0)
CAUDAL VERTEBRAE: MISALIGNED					
LITTER INCIDENCE	N(%)	1(5.9)	1(5.6)	2(11.1)	2(13.3)
FETAL INCIDENCE	N(%)	1(0.7)	1(0.8)	2(1.3)	2(1.8)
RIBS: FLAT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	2(11.1)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	2(1.3)i,j	0(0.0)
RIBS: THICKENED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(5.6)	1(6.7)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.7)	1(0.9)
RIBS: FUSED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(5.6)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.7)	0(0.0)
RIBS: EXTRA					
LITTER INCIDENCE	N(%)	0(0.0)	1(5.6)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.8)h	0(0.0)	0(0.0)

TABLE 13 (PAGE 3): FETAL SKELETAL ALTERATIONS - CAESAREAN-DELIVERED LIVE FETUSES (DAY 29 OF GESTATION) - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)a		0 (CONTROL)	0.15	0.25	0.35
LITTERS EVALUATED	N	17	18	18	15
FETUSES EVALUATED	N	137	127	150	114
LIVE	N	136	127	150	114
DEAD b	N	1	0	0	0
MANUBRIUM: SMALL					
LITTER INCIDENCE	N(%)	1(5.9)	1(5.6)	1(5.6)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.7)f	1(0.8)	1(0.7)j	0(0.0)
MANUBRIUM: FUSED					
LITTER INCIDENCE	N(%)	1(5.9)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.7)f	0(0.0)	0(0.0)	0(0.0)
MANUBRIUM: IRREGULARLY SHAPED					
LITTER INCIDENCE	N(%)	0(0.0)	1(5.6)	1(5.6)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.8)	1(0.7)i	0(0.0)
STERNAL CENTRA: FUSED					
LITTER INCIDENCE	N(%)	4(23.5)	1(5.6)	4(22.2)	1(6.7)
FETAL INCIDENCE	N(%)	6(4.4)e	1(0.8)	8(5.3)i,j	1(0.9)
SIERNAL CENIRA: ASYMMETRIC					
LITTER INCIDENCE	N(%)	1(5.9)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.7)e	0(0.0)	0(0.0)	0(0.0)
XIPHOID: LARGE					
LITTER INCIDENCE	N(%)	0(0.0)	1(5.6)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.8)	0(0.0)	0(0.0)

a. Dosage occurred on days 7 through 19 of gestation.
b. Dead fetus was excluded from summarization and statistical analyses. Observations for this conceptus are cited on Table 22.
c. Fetuses with alterations of the skull and/or hyoid are not separately identified in this summarization, except when alterations of other ossification sites were also present.
d. Includes all alterations noted for the skull except hyoid, ala, angulated. This category is excluded because these alterations do not result from irregular ossification.
e. Fetus 7002-8 had other skeletal alterations.
f. Fetus 7004-6 had other skeletal alterations.
g. Fetus 7017-3 had other skeletal alterations.
h. Fetus 7031-1 had other skeletal alterations.
i. Fetus 7050-3 had other skeletal alterations.
j. Fetus 7053-4 had other skeletal alterations.

TABLE 14 (PAGE 1): FETAL OSSIFICATION SITES - CAESAREAN-DELIVERED LIVE FETUSES (DAY 29 OF GESTATION) - SUMMARY

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)a		0 (CONTROL)	0.15	0.25	0.35
LITTERS EXAMINED	N	17	18	18	15
FETUSES EXAMINED	N	136	127	150	114
OSSIFICATION SITES PER FETUS PER LITTER					
HYOID	MEAN±S.D.	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
VERTEBRAE					
CERVICAL	MEAN±S.D.	7.00 ± 0.00	7.00 ± 0.00	7.00 ± 0.00	7.00 ± 0.00
THORACIC	MEAN±S.D.	12.54 ± 0.28	12.59 ± 0.30	12.53 ± 0.30	12.61 ± 0.33
LUMBAR	MEAN±S.D.	6.45 ± 0.28	6.40 ± 0.30	6.46 ± 0.31	6.40 ± 0.33
SACRAL	MEAN±S.D.	3.00 ± 0.00	3.00 ± 0.00	3.00 ± 0.00	3.00 ± 0.00
CAUDAL	MEAN±S.D.	16.69 ± 0.36	16.79 ± 0.39	16.81 ± 0.34	16.67 ± 0.35
RIBS (PAIRS)	MEAN±S.D.	12.47 ± 0.26	12.51 ± 0.30	12.46 ± 0.27	12.52 ± 0.34
STERNUM					
MANUBRIUM	MEAN±S.D.	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
STERNAL CENTERS	MEAN±S.D.	3.98 ± 0.07	3.86 ± 0.24	3.98 ± 0.15	3.81 ± 0.24*
XIPHOID	MEAN±S.D.	0.92 ± 0.19	0.98 ± 0.05	0.90 ± 0.16	0.93 ± 0.10
FORELIMB b					
CARPALS	MEAN±S.D.	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
METACARPALS	MEAN±S.D.	4.92 ± 0.14	4.99 ± 0.02	4.98 ± 0.05	4.97 ± 0.07
DIGITS	MEAN±S.D.	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00
PHALANGES	MEAN±S.D.	13.90 ± 0.26	13.87 ± 0.23	13.86 ± 0.15	13.93 ± 0.12
HINDLIMB b					
TARSALS	MEAN±S.D.	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00
METATARSALS	MEAN±S.D.	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00
DIGITS	MEAN±S.D.	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00
PHALANGES	MEAN±S.D.	12.00 ± 0.00	12.00 ± 0.00	12.00 ± 0.00	12.00 ± 0.00

a. Dosage occurred on days 7 through 19 of gestation.
b. Calculated as average per limb.
* Significantly different from the control group value ($p \leq 0.05$).

9.3 Prenatal and Postnatal Development

Oral Peri- and Post-natal Reproduction Toxicity Study in Rats

Study No: MQY00012
Conducting Laboratory and Location:
[redacted] (b) (4)

Date of study initiation: September 2, 2009
Report date: August 6, 2010
GLP compliance: This study was conducted in accordance with Good Laboratory Practice Regulations of the United States Food and Drug Administration (21 CFR Part 58).
QA-Report Yes (x) No ()

Animals: Crl:CD(SD) rats
Weight: F0 females: 202-248 g on day 0 of gestation (DG0)
Drug lot#: XA171

Methods: GT4P was given to pregnant rats (25 females/group) by oral gavage at 0 (corn oil), 300, 600, and 900 mg/kg/day from DG7 through day 20 of lactation (DL20) or DG24 (rats that did not deliver a litter). The test article was undiluted colorless oil (neat). These rats (F0) were sacrificed either on DG25 or after the 21-day postpartum period. The number of rats that delivered litters and were

dosed through DL 20 was 24, 25, 25, and 24 in the 0 (corn oil), 300, 600, and 900 mg/kg/day groups, respectively.

For F0 females, the following parameters were observed: mortality, clinical signs, body weights, food consumption, maternal behavior, litter observation, natural delivery, pup body weights, dam and pup necropsy.

For the F1 generation, the following parameters were observed: mortality, clinical signs, body weights, food consumption, age at sexual maturity, passive avoidance and water-filled M-maze tests, mating, necropsy, testes and epididymides weights, and caesarean-sectioning. The F2 generation parameters included fetal body weights, fetal sex, and gross external alterations.

Results:

F0 females:

There were no deaths. At the high dose, the following clinical signs of toxicity were noted: ataxia, decreased motor activity, low carriage, and dehydration.

Reduced body weight gain and food consumption in the 600 and 900 mg/kg/day groups were noted during the treatment period. The body weight change from gestation days 0 to 20 was 146.2, 141.6, 130.8, and 119.6 g for the control, low, middle, and high dose groups, respectively. The absolute feed consumption from gestation days 0 to 20 were 21.2, 21.3, 20.4, and 19.2 g/day for the control, low, middle, and high dose groups, respectively.

F1 generation:

One control male was found dead on day 57 postpartum.

One high-dose male was sacrificed on day 92 postpartum due to moribund condition. Necropsy revealed broken incisors and palate.

Two middle-dose females were sacrificed due to moribund condition. These rats had broken palate with misaligned or broken incisors. The broken incisors or palate appear to be due to physical trauma.

One female each in the control, middle, and high dose group was sacrificed after early delivery on either DG 20 or 21.

No clear treatment-related changes were observed in sexual maturation, mating and fertility (evaluated starting on day 28 postpartum), pregnancy, learning ability

(passive avoidance and water maze tests), necropsy, or testes and epididymides weights.

The notable changes in the body weights were observed only on postpartum days 22, 29, and 36 in the high dose males and females. Body weight on postpartum days 22, 29, and 36 in the F1 high dose males (40.8, 82.8, and 139.6 g, respectively) was lower than the control (46.6, 91.5, and 151 g, respectively). Body weights on postpartum day 92 were 492.3, 493.6, 503.2, and 477.3 g for the control, low, middle, and high dose males, respectively.

Body weight on postpartum days 22, 29, and 36 in the F1 high dose females (39.8, 77.5, and 121.5 g) was lower than the control (45.2, 86, and 130.6 g). Body weights on postpartum day 92 were 276.1, 276.8, 294.8, and 276.8 g for the control, low, middle, and high dose females, respectively.

F2 generation: No clear treatment related changes were observed in the F2 fetuses.

In summary, GT4P was given to pregnant rats by oral gavage at 0 (corn oil), 300, 600, and 900 mg/kg/day from DG7 through DG24 or day 20 of lactation. Treatment with 600 and 900 mg/kg/day reduced the body weight gain of pregnant rats (F0 generation). No treatment-related effects were observed in the sexual maturation, mating and fertility, pregnancy, or learning ability of the F1 generation.

Study title: Oral (Gavage) Repeated-Dose Toxicity Study of HPN-100 [Glyceryl tri-(4-phenylbutyrate)] in Neonatal Rats

Study no.:	QBU00007
Study report location:	N/A
Conducting laboratory and location:	(b) (4)
Date of study initiation:	October 6, 2008
GLP compliance:	YES
QA statement:	YES
Drug, lot #, and % purity:	Glyceryl Tri (4-Phenylbutyrate), Lot no. XA171, 99.7%

Key Study Findings

Methods

Doses:	0.65, 0.9, and 1.2 g/kg/day (corn oil was administered to control group)
Frequency of dosing:	Daily
Route of administration:	Oral gavage
Dose volume:	0.59, 0.82, and 1.09 mL/kg for low, middle, and high dose groups, respectively
Formulation/Vehicle:	Neat liquid
Species/Strain:	Rat/Crl:CD(SD)
Number/Sex/Group:	25/sex/group
Age:	2 days old at initiation
Weight:	6.7-6.9 g for males or 6.9-7.2 g for males at initiation
Satellite groups:	Blood samples from the toxicity study animals were collected at termination for TK analysis.
Unique study design:	Study included 2 parts with different treatment durations (see description of Part A and B, below)
Deviation from study protocol:	There were no deviations that had a significant impact on the study outcome.

The study design is shown in the sponsor's table below.

Dosage Group	Number of F1-Generation Pups		Dosage (g/kg/day)	Density (g/mL)	Dosage Volume (mL/kg)
	Male	Female			
I	24	25	0 (Control)	0	1.09
II	25	25	0.65	1.1033	0.59
III	25	25	0.9	1.1033	0.82
IV	25	25	1.2	1.1033	1.09

Neonatal rats were treated with HPN-100 at 0.65, 0.9, and 1.2 g/kg/day by oral gavage from postnatal day (PND) 2 to 51 in Part A of the study (25/sex/group). The rats in Part B were treated from PND 2 through mating and day 20 of gestation, for a total of 125-127 days of treatment (25/sex/group). Mating of rats was initiated on 96-100 days of age.

No drug-related deaths occurred. In Part A, the major finding was periductal mixed cellular infiltrates in liver in all drug-treated animals, with no incidence in the control group. A reduction in neutrophils and lymphocytes occurred in the high-dose group.

In Part B, terminal body weights were decreased by approximately 10-16% in the middle and high-dose groups. Triglyceride levels were increased by more than 2-fold in females in all treatment groups. Fertility index was decreased to 70-78% in all treatment group females, compared to 96% in the control group. Sperm count and morphology were not evaluated in this study. C-sections showed a dose-dependent increase in post-implantation loss (i.e. resorptions) and a dose-dependent reduction in fetal weight in all treatment groups. The number of live fetuses per litter was significantly reduced in the middle and high dose groups. Preimplantation loss was increased with dose, but this change was not statistically significant.

Observations and Results

PART A: Treatment from PND 2 to 51

Mortality: Deaths occurred, but these were not dose dependent (see the sponsor's table below). Therefore, the deaths are not considered as treatment related.

Text Table 1: Mortality - Summary

	0 (control) g/kg/day		0.65 g/kg/day		0.9 g/kg/day		1.2 g/kg/day	
	Male	Female	Male	Female	Male	Female	Male	Female
Dosage Administered[a]	30	30	29	29	30	30	30	29
Assigned to Study[b]	24	25	25	25	25	25	25	25
Unscheduled Sacrificed	1	-	-	-	3	-	1	1
Found Dead	8	2	1	2	1	-	3	2
Missing / Presumed cannibalized	1	-	-	-	-	-	-	-
Total Deaths	10	2	1	2	4	0	4	3
Replaced	2	-	-	-	-	-	-	-
Death due to confirmed intubation accidents	4	1	-	1	3	-	-	2

Clinical Signs: There were no treatment-related effects.

Body Weights: There were no treatment-related changes.

Feed Consumption: There were no treatment-related changes.

Hematology: White blood cells, neutrophils, and lymphocytes were lower in the high dose group as compared to the control. The results were summarized in the sponsor's table below.

Text Table 4: Selected Hematological Values

Parameter	0 (Control) g/kg/day	0.65 g/kg/day	0.9 g/kg/day	1.2 g/kg/day
WBC				
Male	13.905	12.972 (93.3)	12.263 (88.2)	**10.567* (76.0)**
Female	11.308	11.082 (98.0)	10.021 (88.6)	**9.169 (81.1)**
Neut				
Male	1.383	1.346 (97.3)	1.170 (84.6)	**0.881* (63.7)**
Female	1.116	1.030 (93.3)	0.880 (78.8)	**0.770 (69.0)**
Lymph				
Male	11.744	10.963 (93.3)	10.406 (88.6)	**9.179* (78.1)**
Female	9.679	9.464 (97.8)	8.643 (89.3)	**7.953 (82.2)**
RBC				
Male	6.2220	5.937 (95.4)	5.995 (96.3)	6.088 (97.8)
Female	6.348	6.136 (96.7)	6.159 (97.0)	6.048 (95.3)
MCV				
Male	67.98	70.62 (103.9)	71.61 (105.3)	71.30 (104.9)
Female	65.58	68.19* (104.0)	69.08* (105.3)	69.73* (106.3)
MCHC				
Male	31.77	31.14* (98.0)	30.53* (96.1)	29.87* (94.0)
Female	32.16	31.52 (98.0)	30.62* (95.2)	30.27* (94.1)
Baso				
Male	0.100	0.101 (100)	0.082 (82.0)	0.069* (69.0)
Female	0.084	0.086 (102)	0.067 (79.8)	0.075 (89.3)
PT				
Male	16.58	17.64* (106.4)	18.07* (109.0)	18.27* (110.2)
Female	16.43	16.87 (102.7)	17.15* (104.4)	17.44* (106.1)

Bold - Considered Possibly Related to the Test Article
* Significantly different from the 0 (Control) at $p \leq 0.05$. (Percent of control)

Clinical Chemistry: Slightly increased AST and ALT values were noted in the middle and high dose females (ALT = 43-52 U/L or AST 76-86 U/L) as compared to the control (ALT = 36-45.5 U/L or AST = 66-75.4 U/L).

Gross Pathology: There were no treatment-related changes.

Organ Weights: Decreased weight of the adrenals, thymus, and ovaries were noted mainly in the middle and high-dose groups. The results were summarized in the sponsor's table below.

Text Table 2: Selected Organ Weights

Parameter	0 (Control) g/kg/day	0.65 g/kg/day	0.9 g/kg/day	1.2 g/kg/day
Liver				
Male	12.26	12.98 (105.9)	12.86 (104.9)	12.92 (105.4)
Female	9.87	9.02 (91.4)	9.84 (99.7)	9.42 (95.4)
Adrenals (paired)				
Male	0.052	0.044* (84.6)	0.040** (76.9)	**0.040** (76.9)**
% of TBW	0.022	0.018	0.017*	**0.016****
% of BrW	2.7	2.4	2.2**	**2.2****
Female	0.054	0.054 (100.0)	0.050 (92.6)	**0.043* (79.6)**
Thymus				
Male	0.88	0.82 (93.2)	0.72** (81.8)	0.65** (73.9)
% of TBW	0.357	0.327	0.296**	0.272**
% of BrW	45.8	44.0	39.8*	36.3**
Female	0.67	0.55** (82.1)	0.59 (88.0)	0.58* (86.6)
Heart				
Male	1.10	1.18 (107.3)	1.17 (106.4)	1.14 (103.6)
% of TBW	0.447	0.470	0.482	0.472
% of BrW	57.2	63.2*	64.7**	63.5*
Female	0.93	0.92 (98.9)	0.92 (98.9)	0.91 (97.8)
Ovary (paired)				
Female	0.090	0.088 (97.8)	0.075* (83.3)	**0.069** 76.7)**
% of TBW	0.048	0.050	0.042	**0.039***
% of BrW	5.0	5.0	4.2	**4.0****

Bold - Considered Possibly Related to the Test Article
* Significantly different from the 0 Control at $p \leq 0.05$.
** Significantly different from the 0 Control at $p \leq 0.01$.
(Percent of control)
TBW – Terminal Body Weight
BrW – Brain Weight

Histopathology: Minimal to mild periductal mixed cellular infiltrates in liver were noted in all drug-treated animals, with no incidence in the control group, as shown in the sponsor's table below.

Text Table 5: Summary of HPN-100 [Glyceryl tri-(4-phenylbutyrate)] - Related Lesions

Group	0 (Control)		0.65 g/kg/day		0.9 g/kg/day		1.2 g/kg/day	
Sex	M	F	M	F	M	F	M	F
Organ/Findings No. of Animals	10	10	10	10	10	10	10	10
Liver, periductal mixed cellular infiltrate								
Minimal	0	0	3	4	3	8	2	5
Mild	0	0	7	6	7	2	8	5

M - Male
F - Female

Toxicokinetics: TK parameters were summarized in the following sponsor's table.

Text Table 3: Toxicokinetic Parameters

Analyte	Sex	Dose g/kg/day	$t_{1/2}$ hr	T_{max} hr	C_{max} ug/ml	C_{last} ug/ml	AUC_{last} hr*ug/ml	AUC_{all} hr*ug/ml	AUC_{∞} hr*ug/ml
PAA	F	0.65	Missing	4	398.0	131.3	2253.4	3304.1	Missing
PAA	F	0.9	13.7	2	497.0	327.0	2295.0	4911.4	8774.9
PAA	F	1.2	Missing	4	660.9	556.4	4053.1	8504.3	Missing
PAA	M	0.65	Missing	4	376.4	90.0	2017.2	2737.6	Missing
PAA	M	0.9	Missing	4	593.7	84.7	2660.9	3338.6	Missing
PAA	M	1.2	10.4	2	673.5	448.2	3805.3	7390.6	10509.2
PAG	F	0.65	4.1	2	46.1	1.1	455.8	455.8	462.7
PAG	F	0.9	5.2	2	52.5	2.3	558.2	558.2	575.8
PAG	F	1.2	5.0	2	68.8	3.1	767.2	767.2	789.3
PAG	M	0.65	4.7	2	44.6	1.7	425.3	425.3	436.6
PAG	M	0.9	5.3	4	44.6	3.0	471.5	471.5	494.5
PAG	M	1.2	4.9	2	56.0	3.6	753.2	753.2	778.8
PBA	F	0.65	1.6	1	124.0	5.2	225.2	266.7	237.0
PBA	F	0.9	2.7	1	55.4	9.6	194.2	271.4	232.3
PBA	F	1.2	3.7	1	135.7	0.5	334.6	334.6	337.2
PBA	M	0.65	4.8	1	74.6	8.4	164.3	231.1	222.7
PBA	M	0.9	3.4	1	122.6	4.7	197.7	235.0	220.9
PBA	M	1.2	2.6	1	57.3	8.0	203.8	267.7	234.2

M – Male
F – Female

PART B: Treatment from PND 2 through mating and day 20 of gestation (a total treatment duration of 125-127 days)

Mortality: Deaths occurred, but these were not dose dependent (see sponsor's table). The deaths are not considered as treatment related.

Text Table 6: Mortality - Summary

	0 (control) g/kg/day		0.65 g/kg/day		0.9 g/kg/day		1.2 g/kg/day	
	Male	Female	Male	Female	Male	Female	Male	Female
Assigned to Study[a]	25	25	25	25	25	25	25	25
Unscheduled Sacrificed	-	-	-	-	1	-	-	1
Found Dead	2	1	3	2	1	1	1	1
Missing / Presumed cannibalized	-	-	-	-	-	-	-	-
Total Deaths	2	1	3	2	2	1	1	2
Replaced	-	-	-	-	-	-	-	-
Death due to confirmed intubation accidents	-	-	-	-	-	-	-	-

a. Number of pups administered HPN-100 on postnatal day 2 until sacrifice.

Clinical Signs: High-dose male rats had increased incidence of urine-stained abdominal fur.

Body Weights: Terminal body weights in the low, middle, and high dose males were 96.8%, 87.4% and 84.2% of the control group, respectively. Terminal body weights in the low, middle, and high dose females were 96.7%, 89.8% and 87.8% of the control group, respectively.

Feed Consumption: The treatment did not have clearly adverse effects on feed consumption.

Hematology: Small alterations of the hematological parameters were noted including slightly reduced platelet counts, red blood cells, hemoglobin, and hematocrit in treated males. The clinical significance of these changes are not clear.

Clinical Chemistry: Triglyceride levels were higher in the treatment groups (192, 190, and 180 mg/dl in males and 432, 463, 522 mg/dl in females) as compared to the controls (122 mg/dl in males and 206 mg/dl in females).

Sexual Maturation: Delayed vaginal patency was noted in the high dose group (PND 37) as compared to the control group (PND 35).

Motor Activity and Acoustic Startle Habituation: There were no treatment-related changes.

Learning and Memory: There were no treatment-related changes in the learning and memory tests including passive avoidance and water maze tests.

Mating and Fertility: The number of animals mating and the time to mating were not adversely affected by the treatment. The fertility index (number of rats that mated and were pregnant) was lower in the low, middle, and high dose groups (78, 75, and 70%) as compared to the control group (96%).

Caesarean-Sectioning and Litter Observations: The early and total resorptions per litter, and percent post-implantation loss were significantly increased in all treatment groups. The fetal weights for males and females were significantly decreased in all treatment groups. The number of live fetuses per litter was significantly reduced in the middle and high dose groups. Preimplantation loss was increased with dose, but this change was not statistically significant. The results are summarized in the tables below (taken from the study report).

TABLE B32 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY - F1 GENERATION FEMALE RATS - PART B

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)		0 (CONTROL)	0.65	0.9	1.2
RATS TESTED	N	24a	23a	24a	23a
PREGNANT	N(%)	23(95.8)	18(78.3)	18(75.0)	16(69.6)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 21 OF GESTATION	N	22b	17b	18	16
CORPORA LUTEA	MEAN±S.D.	16.2 ± 1.9	16.2 ± 2.6	14.5 ± 3.0	15.5 ± 4.2
IMPLANTATIONS	MEAN±S.D.	15.4 ± 1.9	15.2 ± 2.2	13.7 ± 3.2	13.2 ± 3.4
% PREIMPLANTATION LOSS	MEAN±S.D.	4.9 ± 6.5	5.6 ± 7.3	6.0 ± 7.4	13.0 ± 15.8
LITTER SIZES	MEAN±S.D.	15.0 ± 2.2	13.6 ± 2.4	12.0 ± 3.2**	11.1 ± 3.2**
LIVE FETUSES	N	331	231	215	177
	MEAN±S.D.	15.0 ± 2.2	13.6 ± 2.4	11.9 ± 3.3**	11.1 ± 3.2**
DEAD FETUSES	N	0	0	1	0
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.2	0.0 ± 0.0
RESORPTIONS	MEAN±S.D.	0.4 ± 0.6	1.6 ± 1.5**	1.7 ± 1.8**	2.2 ± 1.6**
EARLY RESORPTIONS	N	8	27	31	31
	MEAN±S.D.	0.4 ± 0.6	1.6 ± 1.5**	1.7 ± 1.8**	1.9 ± 1.4**
LATE RESORPTIONS	N	0	0	0	4
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.4*
% POSTIMPLANTATION LOSS	MEAN±S.D.	2.5 ± 4.0	10.3 ± 9.3*	13.6 ± 14.0**	15.9 ± 11.6**
DAMS WITH ANY RESORPTIONS	N(%)	7(31.8)	12(70.6)**	14(77.8)**	13(81.2)**
DAMS WITH ALL CONCEPTUSES DEAD OR RESORBED	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

% PREIMPLANTATION LOSS = [(NUMBER OF CORPORA LUTEA - NUMBER OF IMPLANTATIONS) / NUMBER OF CORPORA LUTEA] x 100
% POSTIMPLANTATION LOSS = [(NUMBER OF IMPLANTATIONS - NUMBER OF LIVE FETUSES) / NUMBER OF IMPLANTATIONS] x 100
a. Excludes values for rats the were found dead or sacrificed due to adverse clinical observations prior to cohabitation.
b. Excludes values for rats that did not have a confirmed mating date.
* Significantly different from the control group value (p≤0.05).
** Significantly different from the control group value (p≤0.01).

TABLE B33 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY - F2 GENERATION LITTERS - PART B

DOSAGE GROUP		I	II	III	IV
DOSAGE (G/KG/DAY)		0 (CONTROL)	0.65	0.9	1.2
LITTERS WITH ONE OR MORE LIVE FETUSES	N	23	18	18	16
INCLUDED IN ANALYSES	N	22a	17a	18	16
IMPLANTATIONS	MEAN±S.D.	15.4 ± 1.9	15.2 ± 2.2	13.7 ± 3.2	13.2 ± 3.4
LIVE FETUSES	N	331	231	215	177
	MEAN±S.D.	15.0 ± 2.2	13.6 ± 2.4	11.9 ± 3.3**	11.1 ± 3.2**
LIVE MALE FETUSES	N	158	109	105	87
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	47.8 ± 14.7	46.7 ± 16.6	50.7 ± 16.1	48.6 ± 15.8
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	5.36 ± 0.63	4.62 ± 0.46**	4.17 ± 0.40**	3.55 ± 0.48**
MALE FETUSES	MEAN±S.D.	5.54 ± 0.66	4.79 ± 0.49**	4.28 ± 0.38**	3.72 ± 0.50**
FEMALE FETUSES	MEAN±S.D.	5.19 ± 0.61	4.47 ± 0.50**	4.06 ± 0.43**	3.40 ± 0.44**
% DEAD OR RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	2.5 ± 4.0	10.3 ± 9.3*	13.6 ± 14.0**	15.9 ± 11.6**

a. Excludes values for rats that did not have a confirmed mating date.
* Significantly different from the control group value (p≤0.05).
** Significantly different from the control group value (p≤0.01).

Three fetuses in the middle dose group had gross external alterations. One had an umbilical hernia, one had an absent tail, and a dead fetus had exencephaly, absent pollex of both forepaws, absent fifth digit of the right forepaw, short right hindlimb, absence of all digits of both hindpaws, gastroschisis, and short trunk. In the high dose

group, seven fetuses from 3 litters had gross external alterations. Two of these fetuses had an umbilical hernia, three fetuses had a thread-like tail, one fetus had edema, and one fetus had a thread-like tail and no anal opening. No gross external alterations were observed in the control and low-dose groups.

Gross Pathology: There were no treatment-related changes.

Organ Weights: Absolute and relative weights of ovaries was reduced in all treatment groups. Decreased weight of the adrenals, brain, thymus, and spleen were noted mainly in the high-dose groups. The liver weight was generally higher in the treatment groups. The results were summarized in the sponsor's table below.

Text Table 7: Selected Organ Weights

Parameter	0 (Control) g/kg/day	0.65 g/kg/day	0.9 g/kg/day	1.2 g/kg/day
Brain				
Male	2.14	2.13 (99.5)	2.02* (94.4)	1.98** (92.5)
Female	1.99	1.92 (96.5)	1.91 (96.0)	1.87 (94.0)
Liver				
Male	22.24	24.54 (110.3)	22.54 (101.3)	21.67 (97.4)
% of TBW	3.850	4.243**	4.410**	4.514**
% of BrW	1041.9	1153.3	1120.7	1093.1
Female	16.21	19.90** (122.8)	19.13** (118.0)	19.43** (119.9)
% of TBW	3.570	4.532**	4.700**	4.878**
% of BrW	813.1	1037.0**	1002.1**	1042.3**
Kidneys Paired				
Male	4.09	4.42 (108.1)	4.04 (98.8)	3.82 (93.4)
% of TBW	0.717	0.768*	0.792**	0.798**
% of BrW	191.8	207.4	200.1	192.9
Female	2.24	2.50* (111.6)	2.48* (110.7)	2.49* (111.2)
% of TBW	0.494	0.569**	0.610**	0.626**
% of BrW	112.3	130.0**	130.0**	133.6**
Adrenals Paired				
Male	0.063	0.058 (92.1)	0.049** (77.8)	0.044** (69.8)
Female	0.073	0.070 (95.9)	0.069 (94.5)	0.060 (82.2)
Spleen				
Male	1.04	0.96 (92.3)	0.85* (81.7)	0.80** (76.9)
Female	0.76	0.76 (100.0)	0.78 (102.6)	0.70 (92.1)
Heart				
Male	1.78	1.87 (105.0)	1.76 (98.9)	1.76 (98.9)
% of TBW	0.310	0.327	0.345*	0.367**
% of BrW	83.4	87.9	87.5	88.5
Female	1.28	1.25 (97.6)	1.21 (94.5)	1.20 (93.8)
% of TBW	0.282	0.284	0.298	0.299
% of BrW	64.2	65.3	63.8	64.2
Ovaries Paired				
Female	0.163	0.129** (79.1)	0.127** (77.9)	0.116** (71.2)
% of TBW	0.036	0.030*	0.031*	0.029**
% of BrW	8.2	6.7**	6.6**	6.3**

* Significantly different from the 0 (Control) g/kg/day at $p \leq 0.05$.
** Significantly different from the 0 (Control) g/kg/day at $p \leq 0.01$.
(Percent of control)
TBW – Terminal Body Weight
BrW – Brain Weight

Histopathology: Histopathological findings similar to those observed in Part A (minimal to mild periductular mixed cellular infiltrates) were noted in all treatment groups in Part B. These changes were not identified in the control group.

10 Special Toxicology Studies

None.

11 Integrated Summary and Safety Evaluation

Glycerol phenylbutyrate (GPB) is a triglyceride containing three molecules of 4-phenylbutyric acid (PBA) linked to a glycerol backbone. Glycerol phenylbutyrate is hydrolyzed to glycerol and PBA following oral administration. PBA is then metabolized to phenylacetic acid (PAA), which is then conjugated with glutamine to form phenylacetylglutamine (PAGN). PAGN is utilized as an alternate means for metabolic disposal of nitrogen waste in patients with genetic defects in their urea cycle (urea cycle disorders or UCDs). The sodium salt of PBA (Buphenyl®) is approved for treatment of UCDs.

In the present NDA, the sponsor seeks market approval for Ravicti™ (glycerol phenylbutyrate) as adjunctive therapy for chronic management of adult and pediatric patients ≥ 6 years of age with urea cycle disorders involving deficiencies of the following enzymes: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) or arginase (ARG), as well as the mitochondrial transporter ornithine translocase (hyperornithinemia–hyperammonemia–homocitrullinuria [HHH] syndrome, also referred to as ornithine translocase deficiency). In support of this NDA, the following nonclinical studies were submitted: pharmacological studies, pharmacokinetic studies, oral acute toxicity studies in rats and monkeys, 14-day oral toxicity studies in mice, rats, and monkeys, 13-week oral toxicity studies in mice, rats, and monkeys, 26-week oral toxicity study in rats, 52-week oral toxicity study in monkeys, 26-week oral carcinogenicity study in Tg.rasH2 mice with a 28-day dose ranging study in CByB6F1 mice, 2-year oral carcinogenicity study in rats, Segment I mating and fertility study in rats, Segment II embryo-fetal developmental studies in rats and rabbits, Segment III pre- and post-natal developmental study in rats, oral toxicity study in neonatal rats, Ames test, *in vitro* chromosomal aberration test in human lymphocytes, and a rat micronucleus test. In addition, following mutagenicity studies were conducted with metabolites including PBA, PAA, PAGN, and phenylacetylglycine (PAG): Ames tests and *in vitro* chromosomal aberration tests in Chinese hamster ovary (CHO) cells or human lymphocytes.

In the conscious, unrestrained monkeys with telemetry monitoring, a single oral dose of GT4P significantly prolonged QT_c interval by ~25 ms at a dose of 4 g/kg but not at 1 g/kg. Slight shortening of the PR interval (8-14 ms) was also observed at 4 g/kg of GT4P in this study. The metabolites PBA at 894 µg/ml and PAA at 988 µg/ml inhibited

hERG current by ~36% and 54%, respectively, as compared to the vehicle control in HEK 293 cells transfected with hERG channels.

Following oral administration of GT4P, no parent compound was detected in the plasma in rats and monkeys. There were measurable levels of PBA and PAA in the plasma and urine in rats and monkeys, suggesting that GT4P is hydrolyzed to glycerol and PBA prior to absorption or distribution into the general circulation. PBA is then hydrolyzed to PAA through ß-oxidation. PAA is conjugated with glutamine to form phenylacetylglutamine (PAGN) or with glycine to form phenylacetylglycine (PAG). Both PAGN and PAG are eliminated in the urine.

In the single oral dose toxicity study in rats, GT4P was lethal at doses of 1.2 g/kg or higher. The no effect dose was identified at 0.65 g/kg. In the single oral dose toxicity study in monkeys, the minimal lethal dose was not identified.

In the 14-day oral dose-ranging toxicity study in mice, GT4P was given by oral gavage at 0, 0.65, 0.9, 1.2, and 2.0 g/kg/day for 14 days (5/sex/group). The high dose was lethal (4 males and 4 females died). The central nervous system was the target organ of toxicity based on the clinical signs including hypoactivity, impaired equilibrium, ptosis, and shallow or labored respiration. The no effect dose was not identified. The dose of 0.65 g/kg/day was tolerated.

In the 13-week oral toxicity study in mice, GT4P was given by oral gavage to mice at 0, 0.65, 0.9 and 1.2 g/kg/day for 90 days. The results indicated that there were no treatment-related deaths or clinical signs of toxicity. Treatment increased the liver weight and produced hepatocellular hypertrophy. The high dose of 1.2 g/kg/day was the no-observed-adverse-effect level (NOAEL).

In the 14-day oral toxicity study in rats, GT4P was administered by oral gavage for 14 days to rats at 0, 0.65, 0.9 and 1.2 g/kg/day. There were no deaths. The central nervous system was the target organ of toxicity based on the clinical signs including hypoactivity, impaired equilibrium, impaired muscle coordination and rigid muscle tone. A no effect dose was not identified. The dose of 0.65 g/kg/day was tolerated.

In the 13-week oral toxicity study in rats, GT4P was give by oral gavage at 0, 0.65, 0.9 and 1.2 g/kg/day for 91 days. There were no treatment-related deaths. Rigid muscle tone (all treatment groups) and hypoactivity (middle and high-dose groups) were observed during first few days of treatment. Decreased terminal body weight gain was noted in the low (11%), middle (21%), and high (37%) dose males, as compared to the control males. Body weight gain was not affected in the female groups. There were no treatment-related histopathologic findings. In conclusion, a no effect dose was not identified. The dose of 0.65 g/kg/day was the maximum tolerated dose for males based on the decrease in body weight gain. The dose of 1.2 g/kg/day was tolerated in females. The central nervous system was the target organ of toxicity based on the clinical signs.

In the 26-week oral toxicity study in rats, GT4P was given by oral gavage at 0, 0.65, 0.9 and 1.2 g/kg/day for 6 months. Treatment with GT4P reduced the terminal body weight gain by at least 10% or more in all treatment groups. Therefore, a NOAEL was not established. Central nervous system was a target organ of toxicity based on the clinical signs (hypoactivity and rigid muscle tone in the 0.9 and 1.2 g/kg/day groups). One high-dose male was found dead. This death was possibly treatment-related.

In the 14-day oral toxicity study in cynomolgus monkeys, GT4P was given at 0, 1, 5, and 10 g/kg/day (3/sex/group) via nasogastric intubation in the dose ranging phase. One middle dose male and one high dose female were sacrificed after the first dose due to clinical signs of toxicity including hunched posture, hypoactivity, recumbency, labored respiration, vomitus containing food and red discharge, discharge of bright yellow fluid from the anus, and cold to the touch. On Day 2, the high and middle doses were decreased to 5 g/kg/day and 2.5 g/kg/day, respectively. The two remaining high-dose females were sacrificed due to the clinical signs of toxicity. The dosing was discontinued on Day 3. Based on these results, the sponsor selected doses for GT4P at 0, 1, 2.5, and 3.5 g/kg/day for the main study. Dosing of the middle and high dose groups (2.5 and 3.5 g/kg/day) in the main study was terminated on Day 9 due to clinical signs of toxicity. The dose of 1 g/kg/day was tolerated through the end of the 14-day treatment period. A no effect dose was not identified. The central nervous system was the target organ of toxicity based on the clinical signs.

In the 13-week oral toxicity study in cynomolgus monkeys, GT4P was given by nasogastric intubation at 0, 0.75, 1.25 and 1.75 g/kg/day for 91 days. All animals survived to the scheduled termination. Tremors (continuous or intermittent) were observed in 1 middle-dose female and 2 high-dose females. The tremor was sometimes accompanied by hypoactivity, impaired muscle coordination, twitching, body pallor, and labored respiration. Decreased terminal body weight gain was noted in the middle (19%) and high (24%) dose males, and in the middle (13%) and high dose (20%) females, as compared to the control group. Pathological examination revealed small thymus (high dose males) and minimal to mild lymphoid depletion (all treatment male groups and the high dose females). Histopathologic examination also revealed centrilobular hepatocellular hypertrophy (all treatment groups) and mild fatty infiltration in the sternal bone marrow (all treatment male groups and the middle and high dose female groups). A no effect dose was not identified. The dose of 1.25 g/kg/day was close to or slightly higher than the maximum tolerated dose based on the reduction of body weight gain and clinical signs of toxicity. The central nervous system was the target organ of toxicity based on the clinical signs.

In the 52-week oral toxicity study in monkeys, GT4P was given by nasogastric intubation at 0.7, 1.1, and 1.5 g/kg/day for 52 weeks. Treatment with GT4P induced clinical signs of toxicity including hypoactivity, hunched posture, thinness, pallor and/or cool to touch, impaired equilibrium, and increased respiration rate in the high dose group. The terminal body weights were ~14%, 8%, and 22% lower in the low, middle, and high dose males, respectively, and 10% lower in the high dose females. Liver

weight (absolute and relative) was increased in all treatment groups at weeks 26 and 52, and this change was associated with hepatocellular hypertrophy.

GT4P was not genotoxic in the Ames test, the *in vitro* chromosomal aberration test, and the rat micronucleus test. The metabolite PBA was not genotoxic in the Ames, but significantly increased the proportion of cells with structural aberrations in the presence of S-9 after 4 hours treatment in an *in vitro* chromosome aberration test in Chinese hamster ovary (CHO) cells. However, the result was not reproducible in a repetition of this test in human lymphocytes. Other metabolites including PAA, PAGN, and PAG were not genotoxic in the Ames test or the *in vitro* chromosomal aberration test.

In the 26-week oral dose carcinogenicity study in Tg.rasH2 mice, mice were treated with HPN-100 (neat) at dose levels of 600 and 1000 mg/kg/day via oral gavage for 26 weeks. The dose levels were recommended by the Executive Carcinogenicity Assessment Committee, based on MTD and the minimum feasible dose. Two water control groups were included. The positive control animals received urethane at 1000 mg/kg via intraperitoneal injection on Days 1, 3 and 5. The toxicokinetic evaluation (exposure study) was conducted in hybrid CByB6F1 (nontransgenic) mice (5 mice/sex/group). HPN-100 was well tolerated at all dose levels (600 and 1000 mg/kg/day). The carcinogenicity study was conducted appropriately. The tumor incidences were within the historical control ranges from the testing laboratory. No statistically significant increase in tumors was observed in groups treated with HPN-100. Treatment with urethane (positive control) produced a high incidence of lung tumors and hemangiosarcoma in spleen. The FDA statistical review concluded that HPN-100 did not produce any significant increase in tumor incidence. The Executive Carcinogenicity Assessment Committee concluded that there were no drug-related neoplasms.

In the 24-month oral dose carcinogenicity study in Crl:CD(SD) rats, HPN-100 (neat) was administered via oral gavage at dose levels of 70, 210, and 650 mg/kg/day in males, and 100, 300, and 900 mg/kg/day in females for 2 years. The dose levels were recommended by the Executive Carcinogenicity Assessment Committee, based on MTD and/or lethality. Two control groups (water and corn oil) were included. The study was conducted appropriately. HPN-100 did not produce statistically significant changes in mortality. The terminal body weight was 7% and 11% lower in the high dose males and females, respectively, as compared to the water control group. The terminal body weight gain was 13% and 21% lower in the high dose males and females, respectively, as compared to the water control group. Treatment-related non-neoplastic changes included focal hypertrophy in the adrenal cortex, pancreatic acinar cell hyperplasia, follicular cell hyperplasia in the thyroid gland, cystic endometrial hyperplasia of the uterus, Zymbal's gland hyperplasia, basophilic foci in the liver, and retinal atrophy.

The Executive Carcinogenicity Assessment Committee concluded that HPN-100 increased the incidence of the following neoplasms in the 24-month rat study, as indicated by statistical significance in both the dose-response and pair-wise tests using the water control group, with exception of Zymbal's gland carcinoma in males: in males,

pancreatic acinar cell adenoma, carcinoma and combined adenoma or carcinoma at the high dose and Zymbal's gland carcinoma at the middle and high doses, and in females, pancreatic acinar cell adenoma, carcinoma and combined adenoma or carcinoma at the high dose, thyroid follicular cell adenoma, carcinoma and combined adenoma or carcinoma at the high dose, adrenal cortical combined adenoma or carcinoma at the high dose, uterine endometrial stromal polyp and combined polyp or sarcoma at the high dose, and Zymbal's gland carcinoma at the high dose. The increased incidence of Zymbal's gland carcinoma in males was considered to be drug-related, based on the very low incidence of this neoplasm in historical control data.

Statistically significant dose-response relationships were found for the following tumors, based on comparison to the water control group: acinar cell adenoma, carcinoma and combined adenoma or carcinoma in pancreas in both sexes, follicular cell adenoma in thyroid in both sexes, malignant schwannoma in skin in males, malignant lymphoma in males, adenoma and combined adenoma or carcinoma in adrenal cortex in females, hepatocellular adenoma in females, follicular cell carcinoma and combined adenoma or carcinoma in thyroid in females, polyp and combined polyp or sarcoma in uterus, and carcinoma in Zymbal's glands in females (see statistical review by Dr. Min Min). The FDA statistical review also found significant increases in the following tumors, based on pair-wise comparison to the water control group: acinar cell adenoma, carcinoma and combined adenoma or carcinoma in pancreas in high-dose groups for both sexes, follicular cell adenoma in thyroid in high-dose groups for both sexes, combined adenoma or carcinoma in adrenal cortex in high-dose females, follicular cell carcinoma and combined follicular cell adenoma or carcinoma in thyroid in high-dose females, polyp and combined polyp or sarcoma in uterus in high-dose females, and carcinoma in the Zymbal's glands in high-dose females.

In the fertility and general reproduction toxicity study in rats, male rats were treated with 0 (corn oil), 0.65, 0.9, and 1.2 g/kg/day HPN-100 once daily beginning 28 days before the first cohabitation (with females treated up to 15 days), and through the second cohabitation (with untreated females up to 14 days). Treatment of males continued through the day before sacrifice. Treated female rats were given HPN-100 at 0 (corn oil), 0.65, 0.9, and 1.2 g/kg/day once daily beginning 15 days before cohabitation through gestation day 7. The major finding in this study was a small but statistically significant increase in embryo-lethality in the high-dose group. Mating and fertility parameters were unaffected.

In the oral developmental Segment II toxicity study in rats, pregnant rats were treated with HPN-100 at oral doses of 0 (corn oil), 0.3, 0.65, and 0.9 g/kg/day during gestation days 7-17. The dose selection was justified based on the results of the dose-ranging study in pregnant rats (MQY00007). In the present study, the most common fetal effect was the presence of cervical ribs at the 7th cervical vertebra. This effect was dose-dependent. The litter incidence was statistically significant in the middle and high-dose groups, and fetal incidence was significant only in the high-dose group. Malformations were observed in the middle and high groups (3 and 2 fetuses, respectively), but were not statistically significant. Mild maternal toxicity was observed

in the middle and high dose groups, based on reduction in weight gain. Reduced motor activity and splayed limbs were also noted in the high dose group.

In the oral developmental Segment II toxicity study in rabbits, the pregnant rabbits were treated with HPN-100 given via stomach tube once daily on gestation days 7 through 19 at doses of 0 (corn oil), 0.15, 0.25, and 0.35 g/kg/day. The dose selection was justified based on the results of a dose range-finding study ((b) (4) MYQ00009) in pregnant NZW rabbits. In the present study, there were no signs of maternal toxicity and no adverse effects in fetuses.

In the oral pre- and post-natal reproduction toxicity study in rats, GT4P was given to pregnant rats by oral gavage at 0 (corn oil), 300, 600, and 900 mg/kg/day from DG7 through DG24 or day 20 of lactation. Treatment with 600 and 900 mg/kg/day reduced the body weight gain in pregnant rats (F0 generation). No treatment-related effects were observed in the learning ability, sexual maturation, mating and fertility, or pregnancies of the F1 generation.

In the oral toxicity study in neonatal rats, HPN-100 was given at 0.65, 0.9, and 1.2 g/kg/day (25/sex/group) by oral gavage from postnatal day (PND) 2 to 51 (Part A) or from PND 2 through mating and day 20 of gestation for a total of 125-127 days of treatment (Part B). No drug-related deaths occurred. In Part A, the major finding was periductal mixed cellular infiltrates in liver in all drug-treated animals, with no incidence in the control group. A reduction in neutrophils and lymphocytes occurred in the high-dose group. In Part B, terminal body weights were decreased by approximately 10-16% in the middle and high-dose groups. Triglyceride levels were increased by more than 2-fold in females in all treatment groups. Fertility index was decreased to 70-78% in all treatment group females, compared to 96% in the control group. Sperm count and morphology were not evaluated in this study. C-sections showed a dose-dependent increase in post-implantation loss (i.e. resorptions) and a dose-dependent reduction in fetal weight in all treatment groups. The number of live fetuses per litter was significantly reduced in the middle and high dose groups. Pre-implantation loss was increased with dose, but this change was not statistically significant.

The sponsor seeks market approval for glycerol phenylbutyrate (GPB) as adjunctive therapy for chronic management of adult and pediatric patients ≥ 6 years of age with urea cycle disorders (UCD). UCDs are characterized by hyperammonemia, encephalopathy, and respiratory alkalosis. Patients with UCDs are at high risk for neurologic deficits and death due to hyperammonemia. The current approved products in the U.S. include Buphenyl (oral sodium phenylbutyrate) for long-term therapy, and Ammonul (combination of sodium phenylacetate and sodium benzoate, intravenous) for acute hyperammonemia. GPB and sodium phenylbutyrate are metabolized to the same active metabolite (PAA), therefore both drugs share the same mechanism of action. GPB is an odorless and tasteless (b) (4) that will eliminate the sodium burden and relieve the pill burden of sodium phenylbutyrate. The major finding from the nonclinical program is the tumorigenicity in the 2-year carcinogenicity study in rats. GPB was not genotoxic in the standard genotoxicity test battery. The potential tumorigenic risk of

GPB is presumably shared by sodium phenylbutyrate, since the plasma metabolic profile for both drugs is expected to be very similar. Buphenyl was approved in 1996 and no cancer risk has been identified with the use of Buphenyl. UCDs are life threatening diseases, and sodium phenylbutyrate is the only approved drug for long-term therapy. Therefore, from a nonclinical standpoint, we conclude that the benefit from the treatment with glycerol phenylbutyrate outweighs the risk of the potential tumorigenicity, and thus recommend that this application be approved for the proposed indication. The sponsor should be asked to revise the label as recommended.

12 Appendix/Attachments

1. Executive CAC meeting minutes dated August 12, 2008

Executive CAC
Date of Meeting: August 12, 2008

Committee:
David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Adebayo Laniyonu, Ph.D., DMIHP, Alternate Member
Sushanta Chakder, Ph.D., DGP, Acting Supervisory Pharmacologist
Ke Zhang, Ph.D., DGP, Presenting Reviewer

Author of Draft: Ke Zhang, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

The committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogen bioassay, as this does not affect the sponsor's ability to initiate the bioassay. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2006).

IND # 73,480
Drug Name: Glyceryl Tri (4-phenylbutyrate) / GT4P / HPN-100
Sponsor: Hyperion Therapeutics
South San Francisco, CA

Background: GT4P is a triglyceride containing three molecules of 4-phenylbutyric acid (PBA) linked to a triglyceride backbone. GT4P is hydrolyzed to glycerol and PBA following oral administration. PBA is then metabolized to phenylacetate/phenylacetic acid (PAA). PAA is utilized as an alternate means for metabolic disposal of nitrogen waste in patients with genetic defects in their urea cycle. GT4P was not genotoxic in the Ames test, the in vitro chromosomal aberration test, and the rat micronucleus test.

In the current submission, the sponsor submitted study protocols for 2-year carcinogenicity studies with GT4P in mice and rats.

Mouse Carcinogenicity Study Protocol and Dose Selection:

For the 2-year carcinogenicity study in mice, the following dose levels are proposed by the sponsor: 300, 600, 1200 mg/kg/day for males and females. The dose selection was based on the results of a 13-week oral toxicity study and a 14-day dose ranging toxicity study in mice.

In 13-week oral toxicity study in mice ([(b) (4)]510008), GT4P was given by oral gavage to Crl:CD-1 mice at 0, 0.65, 0.90 and 1.20 g/kg/day in corn oil for 90 days. There were no treatment-related deaths or clinical signs of toxicity. The treatment increased the liver weight and produced hepatocellular hypertrophy. The high dose of 1.2g/kg/day is no-observed-adverse-effect level (NOAEL).

In the 14-day dose ranging toxicity study in mice ([(b) (4)]510007), GT4P was given to mice (5/sex/group) by oral gavage at 0, 0.65, 0.9, 1.2, and 2.0 g/kg/day for 14 days. The high dose of 2 g/kg/day was lethal (4 males and 4 females died).

Rat Carcinogenicity Study Protocol and Dose Selection:

For the 2-year carcinogenicity study in rats, following doses are proposed by the sponsor: 0, 225, 450, 900 mg/kg/day for males or 300, 600, 1200 mg/kg/day for females. The dose selection was based on the results of a 13-week oral toxicity study in rats.

In the 13-week oral toxicity study in rats, GT4P was given by oral gavage to Crl:CD(SD) rats at 0, 0.65, 0.90 and 1.20 g/kg/day in corn oil for 91 days. There were no treatment-related deaths. Rigid muscle tone (all treatment groups) and hypoactivity (mid and high dose groups) were observed during first few days of treatment. Decreased terminal body weight gain was noted in the low (11%), mid (21%), and high (37%) dose males as compared to the control. Body weight gain was not affected in the female groups. There were no treatment-related histopathologic findings. In conclusion, the dose of 0.65 g/kg/day was the maximum tolerated dose (MTD) for males based on the decrease of body weight gain. The dose of 1.20 g/kg/day was tolerated in females.

Doses up to 4.5 g/kg were tested in a single oral dose toxicity study in rats ([(b) (4)]-510001). In this study, one female was found dead at 1.5 g/kg and all females (3/3) were found dead at 2.3 g/kg. In a 14-day oral toxicity study in rats ([(b) (4)]-510002), there were no deaths at the high dose of 1.2 g/kg/day.

Executive CAC Recommendations and Conclusions:
Mouse:

The Committee recommended doses of 0 (vehicle), 100, 300, and 1000 mg/kg/day for both males and females based on lethality in the 14-day dose ranging toxicity study in mice. If the sponsor does not have historical data on the effects of the corn oil vehicle over 2 years, a water gavage control group should be included.

Rat:

The Committee recommended doses of 0 (vehicle), 70, 210, and 650 mg/kg/day for males based on an MTD (decreased body weight gain).

The Committee recommended doses of 0 (vehicle), 100, 300, and 900 mg/kg/day for females based on lethality in the single oral dose study in rats.

If the sponsor does not have historical data on the effects of the corn oil vehicle over 2 years, a water gavage control group should be included.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DGP
/Stark, DGP
/Chakder, DGP
/Zhang, DGP
/AJacobs, OND IO

2. Executive CAC meeting minutes dated February 16, 2010

Executive CAC
Date of Meeting: February 16, 2010

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D. OND IO, Member
David Joseph, DGP, Acting Team Leader
Ke Zhang, Ph.D., DGP, Presenting Reviewer

Author of Draft: Ke Zhang, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

The committee did not address the sponsor's proposed statistical evaluation for the 26-week carcinogenicity bioassay, as this does not affect the sponsor's ability to initiate the bioassay. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008) and the associated Study Data Specifications document.

IND # 73,480
Drug Name: Glyceryl Tri (4-phenylbutyrate) / GT4P / HPN-100
Sponsor: Hyperion Therapeutics
South San Francisco, CA

Background: GT4P is a triglyceride containing three molecules of 4-phenylbutyric acid (PBA) linked to a triglyceride backbone. GT4P is hydrolyzed to glycerol and PBA following oral administration. PBA is then metabolized to phenylacetate/phenylacetic acid (PAA). Conjugation of PAA with glutamine is utilized as an alternate means of metabolic disposal of nitrogen waste in patients with genetic defects in their urea cycle. GT4P was not genotoxic in the Ames test, the in vitro chromosomal aberration test, and the rat micronucleus test. In the current submission, the sponsor submitted a study protocol for a 26-week carcinogenicity study with GT4P in Tg.rasH2 mice.

Tg.rasH2 Mouse Carcinogenicity Study Protocol and Dose Selection

For the 26-week carcinogenicity study, the following dose levels are proposed: 600, 750, and 900 mg/kg/day for groups of 25 males and 600, 900, and 1200 mg/kg/day for groups of 25 females. The dose selection was based on the results of 5-day and 28-day dose ranging studies in CByB6F1 mice. The dose of 2000 mg/kg/day was lethal in both males and females in the dose ranging studies. The dose of 1000 mg/kg/day is estimated to be the maximum tolerated dose, since this dose is half of the lethal dose.

The Exec CAC previously recommended doses of 550 and 1000 mg/kg/day for a proposed 2-year carcinogenicity study of GT4P in CD-1 mice. Similarly, the dose of 2000 mg/kg/day was a lethal dose in both males and females in a 14-day dose ranging study in CD1 mice, and the dose of 1000 mg/kg/day was recommended as the high dose by the Exec CAC. The use of only two dose levels in the proposed 2-year study was recommended due to dosing limitations related to the minimum feasible dose and toxicity. Similar dosing limitations also apply to CByB6F1-Tg(HRAS)2Jic(+/-) mice. The dose of 600 mg/kg/day is the minimal feasible dose that can be given to mice over the entire course of the proposed study, based on the expected bodyweight at study initiation (approximately 20 g) and the minimum volume (10-11 µl) that can be dosed accurately.

Executive CAC Recommendations and Conclusions:

1. The Committee recommended doses of 0 (water), 600 (neat), and 1000 (neat) mg/kg/day, by oral gavage, based on the estimated maximum tolerated dose.

2. The corn oil control is not appropriate.

3. Peer review of the pathology data is preferred but not required.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DGP
/ Phillip, DGP
/Joseph, DGP
/Zhang, DGP
/ASeifried, OND IO

3. Executive CAC meeting minutes dated July 17, 2012

4 pages have been Withheld in Full immediately following this page as a duplicate copy of the "Executive CAC Meeting Minutes" dated July 17, 2012 which is located in the AdminCorres Section of the package

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KE ZHANG
11/28/2012

DAVID B JOSEPH
11/28/2012

I concur with Dr. Zhang's recommendations. Additional comments will be included in my Team Leader memo.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203284 **Applicant:** Hyperion Therapeutics **Stamp Date:** December 23, 2011

Drug Name: Ravicti **NDA/BLA Type:** 505 (b) 1

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			(b) (4) [redacted]
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	x		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	x		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			N/A
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes___

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Ke Zhang, Ph.D. — February 1, 2012
Reviewing Pharmacologist — Date

David Joseph, Ph.D. — February 1, 2012
Team Leader/Supervisor — Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KE ZHANG
02/02/2012

DAVID B JOSEPH
02/02/2012