# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 203284Orig1s000

# STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/BLA #:** | NDA 203-284 |
| **Supplement #:** | |
| **Drug Name:** | RAVICTI™ (glycerol phenylbutyrate; HPN-100); TID, in liquid solution, orally with meals |
| **Indication(s):** | Adjunctive therapy for chronic management of adults and pediatric patients ≥ 6 years of age with urea cycle disorders (UCDs) |
| **Applicant:** | Hyperion Therapeutics, Inc. |
| **Date(s):** | Stamp Date: December 23, 2011 |
| | PDUFA Goal date: January 23, 2013 |
| **Review Priority:** | Standard with Major Amendment (13 month review cycle) |
| **Biometrics Division:** | Division of Biometrics III |
| **Statistical Reviewer:** | Behrang Vali M.S. |
| **Concurring Reviewers:** | Mike Welch Ph.D. |
| **Medical Division:** | Division of Gastroenterology and Inborn Errors Products |
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**Keywords:** NDA review, Clinical Studies, Active Control/Non-Inferiority

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# 1 EXECUTIVE SUMMARY

There was a sufficient level of evidence to support an efficacy claim for RAVICTI™ (HPN-100), and the claims currently reflected within the applicant's submitted product label are supportable as shown in this NDA review. With further motivation under the current public health circumstances in which Urea Cycle Disorders are a rare, serious and life-threatening condition with a not fully met medical need, this reviewer supports the approval of HPN-100 for the treatment of adult and pediatric patients ≥ 6 years of age with this condition.

The efficacy of HPN-100 was principally demonstrated in the single study HPN-100-106. In this trial, HPN-100 was determined to be non-inferior to BUPHENYL® (sodium phenylbutyrate/NaPBA) with regard to the 24-hour area under the curve (AUC) for blood ammonia (i.e. $NH3_{24\text{-hour AUC}}$) on Study Days 14 and 28 which were when these drugs were expected to be at steady state. In addition, the overall correlation, calculated by pooling all patient data across both treatment groups, between urinary phenylacetylglutamine (i.e. $U\text{-}PAGN_{24\text{-hour Excr}}$) and $NH3_{24\text{-hour AUC}}$ was the only significant secondary endpoint determined through the pre-specified Hochberg's multiplicity adjustment procedure. This correlation was also shown to be positive within each individual treatment group thereby further supporting the comparability of the treatments themselves. Although pre-specified by the applicant through Hochberg's multiplicity adjustment procedure, the overall correlation endpoint was really exploratory in nature and was tested for possible future utilization of U-PAGN for dose selection and dose adjustment purposes. The correlation, whether overall or by individual treatment group, only indicates a possible linear association and does not confirm a treatment benefit. As such, the applicant never considered this endpoint for labeling purposes and hence the label does not reflect these correlation results.

There were no statistical issues that impacted the overall conclusions of trial HPN-100-106. The study's design was adjudicated as being adequate, and the applicant's corresponding analysis plan was deemed appropriate. Consequently, and in addition to the consensus regarding the clinical meaningfulness of the $NH3_{24\text{-hour AUC}}$ endpoint, results from trial HPN-100-106 are viewed positively as the formal basis for an efficacy claim to be reflected by the product's label. The apparent sustained efficacy profile during the extension study HPN-100-107 further supports the efficacy claim for HPN-100.

This reviewer recommends that careful consideration be made pertaining to the labeling of the HPN-100 dose in that the dose for a given patient, as described below in Section 3.2.1, was a function of the patient's NaPBA dose.

# 2 INTRODUCTION

## 2.1 Overview

As the regulatory agent on behalf of Ucyclyd Pharma, Inc., a wholly-owned subsidiary of Medicis Pharmaceutical Corporation, on December 23, 2011 Hyperion Therapeutics, Inc. submitted this New Drug Application (NDA) for RAVICTI™ (glycerol phenylbutyrate; HPN-100) pursuant to Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21, Part 314 of the Code of Federal Regulations. The active pharmaceutical ingredient in HPN-100 (to be orally administered as a liquid solution TID with meals) is glycerol phenylbutyrate. This is the first prescription product to have glycerol phenylbutyrate as its active pharmaceutical ingredient thereby making it a New Molecular Entity (NME). Effective on April 10, 2007, HPN-100 has officially undergone clinical development under IND 73,480 in patients with urea cycle disorders (UCDs), and has been developed specifically to establish safety and efficacy in a subpopulation of these patients. The official proposed indication for HPN-100 is as an adjuvant therapy for chronic management of adult and pediatric patients ≥ 6 years of age with UCDs involving deficiencies of the following enzymes; carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate (ASL) or arginase (ARG) as well as the mitochondrial transporter ornithine translocase (HHH deficiency).

The urea cycle is the major route for metabolism of waste nitrogen within the body. UCDs are inherited deficiencies of enzymes or transporters, e.g. those previously mentioned in the proposed indication, necessary for the synthesis of urea from ammonia. Hence the absence of these enzymes or transporters results in the accumulation of toxic levels of waste nitrogen, e.g. ammonia, in the blood and brain of all affected patients. Consequently these patients are highly sick and encephalopathic. Currently, there are FDA-approved treatment options for patients with UCDs e.g. BUPHENYL® (sodium phenylbutyrate/NaPBA) which acts as a nitrogen scavenger in the body. The mechanism of action of NaPBA is as follows. After absorption through oral administration, the sodium (Na) and the phenylbutyrate (PBA) break apart from each other. PBA then undergoes β-oxidation to become phenylacetate (PAA) which is the active metabolite utilized for nitrogen scavenging purposes. This is the reason NaPBA is considered a pro-drug of PAA. Each mole of PAA subsequently scavenges 2 moles of nitrogen (from existing ammonia in the blood) and is then conjugated with glutamine in the liver (and kidney) while ultimately being excreted in the form of urine as phenylacetylglutamine (PAGN). The urinary form of phenylacetylglutamine is referred to as U-PAGN. The utility of this mechanism of action is that the nitrogen content of the resulting U-PAGN in patients with UCDs is equivalent to that of urea in patients with a fully functioning urea cycle. Hence PBA (via PAA) provides an alternative pathway for nitrogen disposal in patients without a fully functioning urea cycle. The mechanism of action of HPN-100 is the same as that of NaPBA except that the initial step in the previously described process is slightly different. HPN-100 itself is an inactive compound; however upon absorption through oral administration, PBA is extracted from the compound which begins the same nitrogen scavenging process as previously described. For this reason, HPN-100 is considered a pre-pro-drug of PAA.

When administered at the recommended dose levels NaPBA has been shown from clinical experience to be safe and effective in improving long-term survival in patients with UCDs (i.e., reducing the incidence of deaths due to hyperammonemic encephalopathy). However, compliance with NaPBA is difficult due to a high pill burden (up to 40 pills or 40 mL of dissolved powder daily for patients taking 20 g of NaPBA), foul taste, unpleasant odor, and high sodium content (approximately 2,300 mg/day for patients taking 20 g). All of these factors render NaPBA very difficult to take, and compliance is suboptimal even for UCD patients with the most severe deficiency states, whose alternative is life-threatening hyperammonemia. Consequently UCDs remains as a rare, serious and life threatening condition with a not fully met medical need. HPN-100 is an alternative therapy to NaPBA in patients with UCDs as it is expected to provide similar nitrogen-scavenging ability while eliminating the current issues of bad taste, odor, sodium content, and pill burden.

Hyperion Therapeutics, Inc. obtained Fast Track designation from the Agency on October 4, 2010. The review cycle established by the Division of Gastroenterology and Inborn Error Products (DGIEP) was a standard 10 month cycle; however this was later amended to being a 13 month review cycle. The application also qualified for Orphan Exception under Section 736(a)(1)(E) of the Federal Food, Drug and Cosmetic Act, and Hyperion Therapeutics, Inc. did obtain *Orphan Designation* from the Office or Orphan Products Development (OOPD) on July 27, 2009.

The clinical efficacy and safety of HPN-100 has been principally evaluated through one study: a Phase 3, multicenter, randomized, double-blind, double-dummy, placebo controlled, cross-over non-inferiority study (HPN-100-006) which serves as the lone adequate and well controlled study of this clinical development program as per 21 CFR 314.126. The design of this study was agreed to by DGIEP in the context of a Special Protocol Assessment (SPA) with the agreement letter sent to Hyperion Therapeutics, Inc. on June 30, 2009.

Table 1 below presents information on this lone relevant clinical trial contained in the submission.

**Table 1**
**Summary Information for Relevant Clinical Trials**

| Type of Study; Phase | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Regimen; Route | Number of Dosed Patients | Patient Diagnosis | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Efficacy and Safety; Phase 3 | HPN-100-006 | To assess the non-inferiority of HPN-100 to NaPBA by evaluating blood ammonia levels in adult patients with UCDs from OTC, CPS, and ASS who were being treated with NaPBA for control of their UCD | Multicenter, randomized, double-blind, double-dummy, placebo controlled, cross-over, non-inferiority | Treatment Arm A: NaPBA and HPN-100 placebo followed by HPN-100 and NaPBA placebo,<br><br>Treatment Arm B: HPN-100 and NaPBA placebo followed by NaPBA and HPN-100 placebo;<br><br>TID orally with meals;<br><br>HPN-100 in liquid solution, NaPBA in tablet or powder form | Total: 45 | UCD Patients | 4 weeks (2 weeks each treatment arm) | Complete; Full |

Source: Reviewer's Table.

## 2.2 Data Sources

This NDA was submitted electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). Its content, including the electronic data sets and labeling information, has been stored in the electronic document room (EDR) at this path location: \\Cdsesub1\evsprod\NDA203284. Sequences 0000, 0007, and 0009 contain all the contents relevant for this review.

For study HPN-100-106, the applicant's clinical study report (CSR), clinical datasets and analysis datasets were reviewed. The clinical datasets were compliant to the CDISC/SDTM v.3.1.2 implementation guide standard; however, a non-standardized legacy approach for modeling the corresponding analysis data was implemented. This approach was, however, somewhat homologous in nature to the CDISC/ADaM v.1.0 implementation guide standard. Adequate data definition files, both in Define.XML and Define.PDF format, and software code, in .SAS format, were also submitted for the study.

# 3 STATISTICAL EVALUATION

The statistical evaluation section is written solely for trial HPN-100-006.

## 3.1 Data and Analysis Quality

This study utilized Electronic Data Capture (EDC), and the submitted data quality and integrity appeared to be adequate. There were no issues in reproducing the primary analysis dataset (along with the numerical results presented within the CSR), in particular the primary endpoint, from the original data source. It was possible to verify the randomized treatment assignments, and the applicant submitted documentation of data quality control/assurance procedures within Section 9.6 of their ICH E3 compliant CSR. The blinding/unblinding procedures were well documented within the protocol and in Section 9.4.6 of their ICH E3 compliant CSR. The applicant's statistical analysis plan (SAP) was finalized on September 23, 2010. The SAP was submitted, and all relevant analysis decisions were made before unblinding. Database hard-lock was on September 30, 2010 with unblinding one week later on October 7, 2010.

## 3.2 Evaluation of Efficacy

### 3.2.1 Study Design and Endpoints

As stated previously, the design of this study was agreed to by DGIEP in the context of a SPA with the agreement letter sent to Hyperion Therapeutics, Inc. on June 30, 2009. Consequently, the finalized protocol for this study was signed off on June 30, 2009. The study was initiated on October 12, 2009, and it was completed on September 9, 2010.

This Phase 3 efficacy and safety study serves as the clinical development program's adequate and well-controlled study which makes it the basis for an efficacy claim to be reflected by the product label. This was a 4-week, multicenter (with a total of 19 clinical sites), randomized, double-blind, double-dummy, placebo controlled, cross-over, non-inferiority trial whose primary objective was to assess the non-inferiority of HPN-100 to NaPBA by evaluating blood ammonia levels in adult patients with UCDs (with deficiencies of CPS, OTC, or ASS) who were being treated with NaPBA for control of their UCD. Patients must have had controlled ammonia levels (<100 μmol/L and without signs and symptoms of hyperammonemia) and be on a stable dose of NaPBA for at least one week prior to randomization.

After study eligibility was confirmed, patients were randomly assigned, in a blinded fashion, (on a 1:1 ratio, in accordance with a computer-generated central randomization schedule) to receive either treatment sequence presented in Table 2 below. This was a double blinded study. The patients, investigators, study personnel, including the site pharmacist, were all blinded to the study drug assignment.

**Table 2**
**Randomization to Treatment in HPN-100-006**

| Treatment Arm | Period 1 (2 weeks) | Period 2 (2 weeks) |
|---|---|---|
| A | NaPBA + HPN-100 placebo | HPN-100 + NaPBA placebo |
| B | HPN-100 + NaPBA placebo | NaPBA + HPN-100 placebo |

Source: Reviewer's Table.

It is to be noted that all patients who were randomized into and completed this study were later given the opportunity to roll over into a 12-month, multicenter, open-label, un-controlled extension study (trial HPN-100-007) which assesses the long term efficacy and safety of HPN-100.

HPN-100 is a colorless to pale yellow, odorless, nearly tasteless (b) (4) orally via mouth, gastrostomy or nasogastric tube. NaPBA tablets were the preferred formulation for administration of NaPBA, and every reasonable effort was made to convert medically eligible adult patients who may have been on NaPBA powder to tablets at least one week prior to study randomization. However, patients who could not comply with taking NaPBA tablets (e.g., had difficulty swallowing tablets) were able to receive NaPBA powder upon consultation with the applicant and documentation of the reason the patient was not able to take NaPBA tablets. Upon approval by the applicant, a supply of NaPBA powder was provided for that patient throughout the study duration. No patient was allowed to switch from NaPBA tablet to NaPBA powder, or vice versa, while the study was ongoing. NaPBA tablets were orally administered while oral, nasogastric, or gastrostomy tube administration was utilized for NaPBA powder. The motivation for the double-dummy design was due to the fact that NaPBA was in tablet or powder form while HPN-100 was a liquid. HPN-100 and NaPBA (regardless of formulation) have short half-lives, and, consequently, were administered TID with meals. The short half-lives of these treatments were also the reason why a wash-out period was not instituted in the cross-over design.

At the screening visit, the investigator determined the trial dose of NaPBA for each patient. Because the dose of NaPBA was chosen based on the severity of the enzyme deficiency, on the content of the patient's diet, and on the intake of amino acids or other supplements, the dose of NaPBA did vary among study patients. And because a patient's HPN-100 dose was dependent on their NaPBA dose, the HPN-100 dose also varied among study patients. The 100% HPN-100 dose-equivalent to the 100% NaPBA dose was calculated as follows:

$$\text{Total daily NaPBA dose (g)} \times 0.95/1.1 = \text{Total daily HPN-100 dose (mL)}$$

This equivalent HPN-100 total daily dose, which was derived to match the corresponding NaPBA total daily dose, was administered to ensure consistent metabolic control for each patient. The total daily dose of NaPBA (g) and HPN-100 (mL) divided by three was the dose to be taken during each meal. No adjustment to the NaPBA or HPN-100 dose (or schedule) was allowed during the study.

The following prohibited medications were not to be used during the study:

- Drugs known to cause hyperammonemia, such as valproate
- Drugs known to increase protein catabolism, such as corticosteroids
- Drugs known to significantly affect renal clearance, such as probenecid
- Drugs known to lower blood ammonia, including sodium benzoate

In addition, patients also followed a stable diet throughout the study as prescribed by the investigator and dietician. All patients were to adhere to the low-protein diet and amino acid supplements prescribed for them. The diet chosen for each individual depended on age and residual enzyme activity and should not have been altered for this study.

The primary study objective was to establish the non-inferiority of HPN-100 to NaPBA as assessed by venous ammonia. Blood samples were collected for assessment of venous ammonia levels, and at each designated time point indicated by the schedule of assessments; 2 mL of venous blood was drawn and processed by the laboratory at the investigator site per the facility standard operating procedures. This is consequently a local laboratory study (not a central laboratory study). There were different in vitro diagnostic methods administered at each site which measured plasma ammonia concentration. Two general types of methods were employed across the trial; an indirect, colorimetric method and a direct, enzymatic method. In addition, each laboratory used a slightly different normal reference range. Patients were ultimately admitted to the research unit for 24 hours of venous ammonia, PK blood and urine sampling (including an overnight stay) at the end of each treatment period by which time the study drug would have reached steady state.

The following primary and secondary endpoints were pre-specified by the applicant.

Primary Endpoint: The primary endpoint was the 24-hour area under the curve for blood ammonia ($NH3_{24\text{-hour AUC}}$) on Days 14 and 28 are when the drugs were expected to be at steady state. The AUC was calculated, using the trapezoidal rule, on a sequence of ammonia level concentrations obtained at pre-dose, and 2, 4, 8, 12, 16, 20, and 24 hours post-dose on Days 14 and 28.

Secondary Endpoints:

- Overall correlation between 24-hour urinary PAGN excretion (i.e. $U\text{-}PAGN_{24\text{-hour Excr}}$) and venous ammonia $AUC_{0\text{-}24}$ (i.e. $NH3_{24\text{-hour AUC}}$) observed on steady state. The overall correlation pertains to pooling all patient data across both treatment groups.
- Maximum venous ammonia values (i.e. $C_{max}$) observed on steady state NaPBA versus HPN-100.
- Rate (percentage) of ammonia values above upper limit of normal (ULN) observed on steady state NaPBA versus HPN-100.
- Number and severity of symptomatic hyperammonemic crises.
- PK parameters including $C_{max}$ for major metabolites of NaPBA and HPN-100 (including plasma PAA, PBA, PAGN and $U\text{-}PAGN_{24\text{-hour Excr}}$).
- Rate of adverse events in each treatment group.

A sample size of 44 evaluable patients will have provided 90% power to demonstrate that the ratio of the means of $NH3_{24\text{-hour AUC}}$ between HPN-100 and NaPBA did not exceed 1.25. This assumed a one-sided α of 0.025, a standard deviation of the within-patient differences (natural log scale) of 0.225 and an expected ratio of the group means of 1.

Statistical non-inferiority is shown if the upper limit of the two-sided 95% CI for the ratio of the treatment means ($\mu_{HPN\text{-}100}$ / $\mu_{NaPBA}$) is less than or equal to 1.25 Although $NH3_{24\text{-hour AUC}}$ is a pharmacodynamic endpoint, the upper margin of 1.25 was based on standard bioequivalence rules (i.e. the 95% CI for the ratio of mean AUCs being within 0.80 and 1.25) and deemed appropriate by the clinical and pharmacology teams. It is to be noted that meeting the 0.80 lower limit was not made a requirement because it was not clinically relevant. The aforementioned ratio would be allowed to go as low as possible with a lower ratio being deemed as more clinically meaningful/effective. Once non-inferiority is established, the first three secondary endpoints, i.e. the key secondary endpoints, are evaluated using Hochberg's multiplicity adjustment procedure in order to control the overall type I error.

Statistical significance of the following key secondary efficacy endpoints were to be evaluated using
Hochberg's procedure:

- S1. Overall correlation between $U\text{-}PAGN_{24\text{-hour Excr}}$ and $NH3_{24\text{-hour AUC}}$ at steady state i.e. $H_0$: $\rho=0$ vs. $H_1$: $\rho\neq0$
- S2. Maximum venous ammonia values (i.e. $C_{max}$) observed on steady state NaPBA versus HPN-100 i.e. $H_0$: $\mu_1=\mu_2$ vs. $H_1$: $\mu_1\neq\mu_2$
- S3. Rate (percentage) of ammonia values above upper limit of normal (ULN) observed on steady state NaPBA versus HPN-100 i.e. $H_0$: $\mu_1=\mu_2$ vs. $H_1$: $\mu_1\neq\mu_2$

Under Hochberg's procedure, the resulting three p-values, each corresponding to one of the three aforementioned key secondary endpoints, were to be ordered from highest to lowest. If the largest p-value is less than or equal to α (i.e. 0.05), then the null hypotheses for all three key secondary endpoints were to be rejected. If, however, this largest p-value is greater than 0.05, then the two other endpoints were to be assessed at α/2 (i.e. 0.025). If the largest remaining p-value is less than or equal to 0.025, then the null hypotheses of the two remaining endpoints were to be rejected. If, however, this largest remaining p-value is greater than 0.025, then the sole remaining endpoint was to be assessed at α/3 (i.e. 0.0167). If the p-value for this third endpoint is less than or equal to 0.0167, then the corresponding null hypothesis was to be rejected.

*Reviewer Comments*:
*The primary endpoint and non-inferiority margin were deemed by the review team as clinically meaningful, and the estimated sample size was validated and confirmed as appropriate. Overall, the design of study HPN-100-006 was deemed adequate. It would have been ideal if this study utilized a central laboratory. However this was not possible because clinical studies with very sick patients, such as those with UCDs, require laboratory assessment results to be reviewed as soon as possible for the overall welfare of the patient. There typically would not be enough time to send laboratory vials to a central laboratory for analysis, and to wait for these results to be sent back to the clinical sites for investigator review and potential subsequent action.*

*Consequently, local laboratories were utilized at the clinical sites themselves. The resulting drawback, of course, pertains to having the aforementioned two different laboratory assay methods (i.e. indirect and direct) in addition to having slightly different normal reference ranges across these clinical sites. The potential impact of the two different laboratory assay methods was assessed by an exploratory subgroup analysis (see results in Table 5 below in Section 3.2.4). To combat the slightly different normal reference ranges, the measured ammonia values themselves were normalized to a standard laboratory reference range before conducting the primary efficacy analyses. The method of normalizing these values is presented below in Section 3.2.2.2. Although pre-specified by the applicant through Hochberg's multiplicity adjustment procedure, the overall correlation endpoint was really exploratory in nature and tested for possible future utilization of U-PAGN for dose selection and dose adjustment purposes. The correlation, whether overall or by individual treatment group, only indicates a possible linear association and does not confirm a treatment benefit. As such, the applicant never considered this endpoint for labeling purposes and hence the label does not reflect these correlation results.*

### 3.2.2 Statistical Methodologies

#### 3.2.2.1 Analysis Sets

The primary analysis set, i.e. the analysis set used for all primary and key secondary endpoint analyses, was the Intent-to-Treat (ITT) analysis set which includes all randomized patients who receive at least one dose of either study drug (HPN-100 or NaPBA). In this analysis set, patients were included in the treatment group, based on period, within the treatment sequence that they were randomized to receive regardless of actual treatment sequence received.

All efficacy analyses were confirmed by utilizing the Per-Protocol (PP) analysis set which includes all patients in the ITT set who received both study medications (HPN-100 and NaPBA) and met all of the following criteria:

- Completed the study
- Actually received the treatment sequence that they were randomized to receive
- Had a calculable NH3 AUC for both treatment periods
- Had at least 4 ammonia samples one of which must be at either the 8 or 12 hour post-dose time point on Days 14 and 28
- On Days 14 and 28, time zero (i.e. pre-dose) ammonia sample drawn not more than 60 minutes after drug dosing and breakfast, and the 24 hour post-dose ammonia sample drawn not more than 60 minutes after drug dosing and breakfast
- Had been compliant with study medication ≥80% on Days 14 and 28
- Had not used sodium benzoate on either Day 14 or Day 28

In this analysis set, patients were included in the treatment group, based on period, within the treatment sequence that they actually received.

All analyses were re-conducted, for sensitivity analysis purposes, utilizing an All-Randomized analysis set which includes all patients who were randomized into the study. In this analysis set, patients were included in the treatment group, based on period, within the treatment sequence that they were randomized to receive regardless of actual treatment sequence received.

For further sensitivity analysis purposes, all analyses were re-conducted utilizing the Modified Intent-to-Treat (mITT) analysis set which includes all patients in the ITT set who had a calculable NH3 AUC for both treatment periods and had at least 4 ammonia samples one of which must be at either the 8 or 12 hour post-dose time point on Days 14 and 28. In this analysis set, patients were included in the treatment group, based on period, within the treatment sequence that they were randomized to receive regardless of actual treatment sequence received.

*Reviewer Comment*:
*The utilization of the applicant defined ITT and PP analysis sets is acceptable per ICH E9.*

### 3.2.2.2 Primary Endpoint Analysis

The ammonia level data were the data that support the primary efficacy analysis. As previously explained, these data were obtained from different laboratories, and each laboratory used a slightly different normal reference range. To account for these different normal reference ranges, the ammonia level data was normalized to a standard laboratory reference range before conducting the primary efficacy analyses.

Two units were used for the ammonia data, µmol/L and µg/dL. All ammonia data was first converted to SI Units (i.e. µmol/L) before the normalization and subsequent calculation of the AUC using the trapezoidal rule. The conversion formula is µg/dL × 0.5872 = µmol/L.

The normalization was then subsequently done by applying the scale normalization approach, using the following formula:

$$s = x \times (U_s / U_x),$$

where s is the normalized laboratory value, x is the original laboratory value, $U_x$ is the upper limit of the normal reference range from the original laboratory, and $U_s$ is the upper limit of the established normal reference range for the standard laboratory.

The primary endpoint was the 24-hour area under the curve for blood ammonia ($NH3_{24\text{-hour AUC}}$) on Days 14 and 28. $NH3_{24\text{-hour AUC}}$ was to be summarized by treatment group. An analysis of variance (ANOVA) model for the natural log-transformed $NH3_{24\text{-hour AUC}}$ was to be constructed with factors for treatment, sequence, patient nested in sequence (as a random effect), and period. A two-sided 95% Confidence Interval (CI) for the difference between HPN-100 and NaPBA means (HPN-100 minus NaPBA) on the natural log scale was to be constructed using the least square means from the ANOVA model. The sample difference along with the lower and upper CI values was subsequently exponentiated to express the results on the original scale. If the upper bound of the 95% CI on the original scale was less than or equal to 1.25, then non-inferiority was to be concluded.

For sensitivity analysis purposes, the primary analysis was conducted on the original, non-normalized, ammonia data. And, as previously stated, the potential impact of the two different laboratory assay methods (i.e. indirect and direct) was assessed by an exploratory subgroup analysis which does not impact the study's overall Type 1 error.

### 3.2.2.3 Key Secondary Endpoint Analyses

For the key secondary endpoint analyses, as previously stated, the Hochberg multiplicity adjustment procedure was employed in order to control the overall type I error rate due to multiple comparisons. All statistical comparisons for inequality between the treatment groups was performed using a two-sided α of 0.05 and two-sided 95% CIs.

The correlation between U-$PAGN_{24\text{-hour Excr}}$ and $NH3_{24\text{-hour AUC}}$ at steady state was summarized and the correlation (i.e. the Spearman rank-order correlation) was tested using the Hotelling-Pabst test. Data was presented by treatment group and overall. It is to be noted that the overall correlation pertains to pooling all patient data across both treatment groups. One would expect a positive/direct correlation as greater urinary PAGN output is related, stoichiometrically, to greater waste nitrogen excretion. Hence, at steady state, the greater the venous ammonia concentration, the more urinary PAGN would be outputted. Similarly, the smaller the venous ammonia concentration, the less urinary PAGN would be outputted. This hypothesized relationship, if significant and clinically meaningful, would subsequently enable the utilization of urinary PAGN for dose selection and dose adjustment purposes.

The maximum steady state venous ammonia level (i.e. blood ammonia 24-Hour $C_{max}$) observed on Days 14 and 28 was summarized by treatment sequence and overall. The treatment group comparison was made using a paired t-test.

For each time point, and over all time points, on Day 14 and Day 28, the number and percentage of patient samples with ammonia values above the ULN was summarized by treatment group. In addition, for each patient, the percentage of all their samples, from all time points on Day 14 and Day 28, with ammonia values above the ULN (i.e. the number of values above the ULN divided by the total number of evaluable samples) was summarized by treatment group, and the treatment groups were subsequently compared using a two-sample t-test.

For sensitivity analysis purposes, all the aforementioned analyses were conducted on the original, non-normalized, ammonia data.

*Reviewer Comment*:
*There is an issue with the independence assumption for the data points used to calculate the overall correlation between U-$PAGN_{24\text{-hour Excr}}$ and $NH3_{24\text{-hour AUC}}$. Because a patient contributes two different sets of data (one set while receiving HPN-100 and the other while receiving NaPBA), the independence assumption made for these data, which is necessary for statistical testing, may be compromised. Hence the results pertaining to the overall correlation should be interpreted with caution. Again, as previously stated, this really won't be an issue as this endpoint is not labeled by the applicant. There are no issues for calculated correlations and corresponding statistical testing for the individual treatment groups themselves.*

### 3.2.2.4 Handling of Dropouts/Missing Data

Multiple imputation methods were to be utilized by the sponsor to handle any missing data which was assumed to be missing at random. The primary approach utilized a strategy which

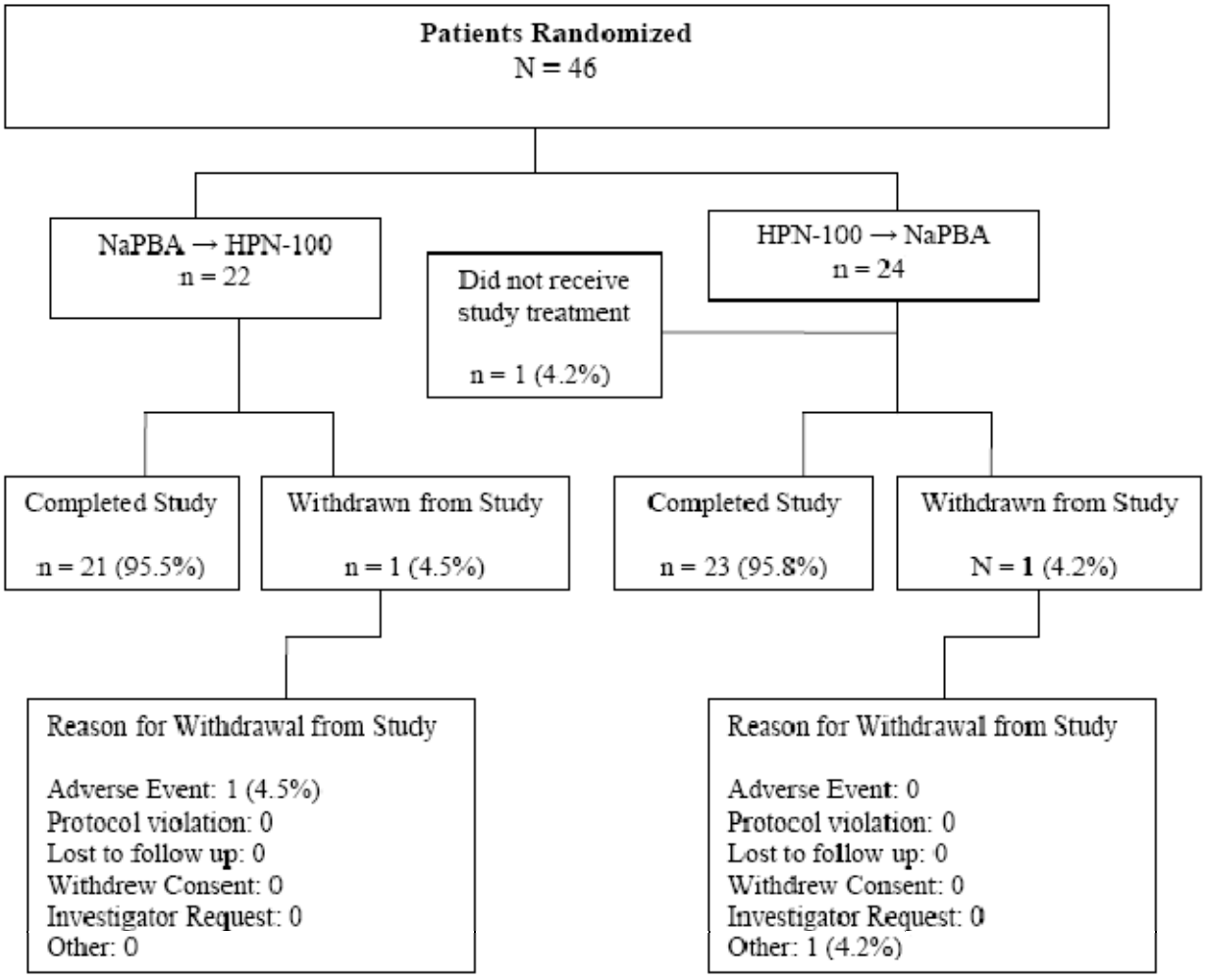
imputed a no-change-from-baseline/screening venous ammonia concentration for missing Day 14 and Day 28 data.

*Reviewer Comment*:
*As will be seen in Section 3.2.3 and 3.2.4 below, there were only two patients who dropped out of this study hence missing data did not impact the study results.*

### 3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The disposition information for all randomized patients is presented in Figure 1 and Table 3 below. It is to be noted that Figure 1 is presented by actual treatment sequence while Table 3 is presented by randomized treatment sequence. Patient 02-601, while successfully completing the study, was randomized to treatment sequence NaPBA → HPN-100, with notation X → Y meaning treatment X is followed by treatment Y, but mistakenly received treatment sequence HPN-100 → NaPBA.

**Figure 1**
**Disposition**




Source: HPN-100-106 CSR - Figure 1 on pg. 50.

**Table 3**
**Disposition – n (%)**
**(All Randomized)**

| | NaPBA → HPN-100 (N = 23) | HPN-100 → NaPBA (N = 23) | Total (N = 46) |
|---|---|---|---|
| Randomized | 23 (100%) | 23 (100%) | 46 (100%) |
| Randomized and Dosed i.e. ITT | 23 (100%) | 22 (95.6%) | 45 (97.8%) |
| Modified Intent-to-Treat (mITT) | 22 (95.6%) | 21 (91.3%) | 43 (93.5%) |
| Per-Protocol (PP) | 21 (91.3%) | 21 (91.3%) | 42 (91.3%) |
| Completed Study | 22 (95.6%) | 22 (95.6%) | 44 (95.7%) |
| Completed 1st Period of Treatment | 22 (95.6%) | 22 (95.6%) | 44 (95.7%) |
| Completed 2nd Period of Treatment | 22 (95.6%) | 22 (95.6%) | 44 (95.7%) |
| Discontinued Study Early | 1 (4.3%) | 1 (4.3%) | 2 (4.3%) |
| Adverse Event | 1 (4.3%) | 0 | 1 (2.2%) |
| Protocol Violation | 0 | 0 | 0 |
| Lost to follow-up | 0 | 0 | 0 |
| Withdrew Consent | 0 | 0 | 0 |
| Investigator Request | 0 | 0 | 0 |
| Other | 0 | 1 (4.3%) | 1 (2.2%) |

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each treatment sequence or overall.

The demographics and baseline characteristics for all randomized patients is presented in Table 4 below. Table 4 is presented by randomized treatment sequence.

**Table 4**
**Demographic and Baseline Characteristics**
**(All Randomized)**

| | NaPBA → HPN-100 (N = 23) | HPN-100 → NaPBA (N = 23) | Total (N = 46) |
|---|---|---|---|
| Age (years) | | | |
| n | 23 | 23 | 46 |
| Mean (SD) | 36.9 (14.78) | 28.5 (10.53) | 32.7 (13.38) |
| Median | 32.0 | 24.0 | 28.5 |
| Min, Max | 18, 75 | 18, 55 | 18, 75 |
| Age Group – n (%) | | | |
| ≥ 65 | 1 (4.3%) | 0 | 1 (2.2%) |
| < 65 | 22 (95.6%) | 23 (100%) | 45 (97.8%) |
| Gender – n (%) | | | |
| Female | 16 (69.6%) | 15 (65.2%) | 31 (67.4%) |
| Male | 7 (30.4%) | 8 (34.8%) | 15 (32.6%) |
| Race – n (%) | | | |
| White/Caucasian | 18 (78.3%) | 18 (78.3%) | 36 (78.3%) |
| Black or African American | 0 | 3 (13.0%) | 3 (6.5%) |
| Asian | 0 | 1 (4.3%) | 1 (2.2%) |
| American Indian or Alaska Native | 1 (4.3%) | 1 (4.3%) | 2 (4.3%) |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| Hispanic or Latino | 3 (13.0%) | 0 | 3 (6.5%) |
| Other | 1 (4.3%) | 0 | 1 (2.2%) |
| Prescribed NaPBA Daily Dose (g) [1] | | | |
| n | 23 | 22 | 45 |
| Mean (SD) | 14.1 (5.76) | 14.2 (7.19) | 14.4 (6.42) |
| Median | 15.0 | 14.3 | 15.0 |
| Min, Max | 2, 24 | 3, 36 | 2, 36 |
| Prescribed HPN-100 Daily Dose (mL) | | | |
| n | 23 | 22 | 45 |
| Mean (SD) | 12.2 (4.98) | 12.4 (6.13) | 12.3 (5.51) |
| Median | 13.0 | 12.5 | 13.0 |
| Min, Max | 1, 21 | 3, 31 | 1, 31 |

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each treatment sequence or overall.
[1]: Of the 44 patients who completed the study, 37 actually took NaPBA tablets while 7 took NaPBA powder.

*Reviewer Comments*:
*There is no significant imbalance between the treatment sequences regarding the presented demographic and baseline characteristics. It is to be noted that this patient sample consisted primarily of Caucasians between the ages of 18 and 65.*

### 3.2.4 Results and Conclusions

The results displayed in this section correspond to the endpoint order previously specified in Section 3.2.1 above.

**Table 5**
**Analysis of $NH3_{24\text{-hour AUC}}$ by Treatment Group**
**(ITT)**

| $NH3_{24\text{-hour AUC}}$ [(µmol/L) × hours] Statistic | Study Treatment HPN-100 (N = 45) | NaPBA (N=45) | Difference Between HPN-100 and NaPBA |
|---|---|---|---|
| *Overall* | | | |
| Log-Transformed Scale | | | |
| n | 44 | 44 | 44 |
| Mean (SD) | 6.5 (0.66) | 6.6 (0.67) | -0.10 (0.42) |
| Median | 6.5 | 6.5 | -0.05 |
| Min, Max | 5, 8 | 6, 8 | -1, 1 |
| Least Squares Mean [1] | 6.5 | 6.6 | -0.10 |
| 95% CI [1] | | | [-0.225, 0.033] |
| Original Scale | | | |
| Ratio of Geometric Means [2] | | | 0.91 |
| 95% CI [2] | | | [0.799, 1.034] |
| *Indirect (Colorimetric) Assay Method* | | | |
| Log-Transformed Scale | | | |
| n | 27 | 27 | 27 |
| Mean (SD) | 6.3 (0.52) | 6.3 (0.40) | -0.05 (0.40) |
| Median | 6.2 | 6.4 | 0.01 |
| Min, Max | 5, 7 | 6, 7 | -1, 1 |
| Least Squares Mean [1] | 6.3 | 6.3 | -0.05 |
| 95% CI [1] | | | [-0.219, 0.112] |
| Original Scale | | | |
| Ratio of Geometric Means [2] | | | 0.95 |
| 95% CI [2] | | | [0.803, 1.118] |
| *Direct (Enzymatic) Assay Method* | | | |
| Log-Transformed Scale | | | |
| n | 17 | 17 | 17 |
| Mean (SD) | 7.0 (0.65) | 7.1 (0.70) | -0.17 (0.46) |
| Median | 7.0 | 7.1 | -0.10 |
| Min, Max | 6, 8 | 6, 8 | -1, 1 |
| Least Squares Mean [1] | 7.0 | 7.1 | -0.14 |
| 95% CI [1] | | | [-0.388, 0.111] |
| Original Scale | | | |
| Ratio of Geometric Means [2] | | | 0.87 |
| 95% CI [2] | | | [0.678, 1.117] |

Source: Reviewer's Table.
[1]: ANOVA for the natural log-transformed $NH3_{24\text{-hour AUC}}$ with factors for treatment, sequence, patient nested in sequence (as a random effect), and period.
[2]: Results on original scale were obtained by exponentiating the corresponding log-transformed results.

*Reviewer Comments*:
*Overall, it can be seen that the upper 95% CI value on the original scale (i.e. 1.034) is less than 1.25 and hence non-inferiority can be concluded. The exploratory subgroup analysis results based on the two different laboratory assay methods (i.e. indirect and direct) is consistent with the overall results. This exploratory finding suggests that the laboratory assay methods did not influence the overall results. These analyses were all re-conducted utilizing the PP, All-Randomized, and mITT analysis sets with no changes to the conclusions. In addition, all of these analyses were conducted using the original, non-normalized ammonia data with no changes to the conclusions. From the 46 patients who were originally randomized, there were only 2 total dropouts hence missing data was not an issue in this trial, and it was determined that there was no treatment-by-period interaction. Adjusting the overall analysis by site would have been ideal, but there were too many sites (19 in total) relative to the total number of patients randomized (i.e. 46). The sparseness of the site adjusted data precluded this approach. It is still important to note, however, that no one site influenced/drove these study results.*

**Table 6**
**Correlation of U-PAGN$_{24\text{-hour Excr}}$ and NH3$_{24\text{-hour AUC}}$ by Treatment Group and Overall (ITT)**

| | Study Treatment | | |
|---|---|---|---|
| | HPN-100 (N = 45) | NaPBA (N=45) | Overall (N=45) |
| Correlation [1] of NH3$_{24\text{-hour AUC}}$ [(µmol/L) × hours] with U-PAGN$_{24\text{-hour Excr}}$ (µg) | 0.219 | 0.437 | 0.322 |
| p-value [2] | 0.153 | 0.003 | 0.002 |

Source: Reviewer's Table.
Note: Patients in the overall column contribute two different sets of data: one set while receiving HPN-100 and the other while receiving NaPBA.
[1]: Correlation obtained using the Spearman rank-order correlation.
[2]: Based on the Hotelling-Pabst test.

*Reviewer Comments*:
*As previously stated in Section 3.2.2.3, one would expect a positive correlation between NH3$_{24\text{-hour AUC}}$ and U-PAGN$_{24\text{-hour Excr}}$ as greater urinary PAGN output is related, stoichiometrically, to greater waste nitrogen excretion. It can be seen that the correlation was indeed positive overall and in each individual treatment group. It's reassuring that these results are consistent between the treatment groups thereby further supporting the comparability of the treatments. The positive correlation was strongest in the NaPBA group, and hence the data in this treatment group provided the greatest influence for the overall result. The p-value corresponding to the overall correlation was 0.002. The interpretation of this result, with respect to Hochberg's procedure, is presented in the Reviewer Summary Comments which appear at the end of this Results and Conclusions section. These analyses were all re-conducted utilizing the PP, All-Randomized, and mITT analysis sets with no changes to the conclusions. In addition, all of these analyses were conducted using the original, non-normalized ammonia data with no changes to the conclusions.*

**Table 7**
**Summary of Blood Ammonia 24-Hour $C_{max}$ (µmol/L) by Treatment Sequence and Overall (ITT)**

| Study Sequence | Visit | n | Mean | SD | Median | Min | Max | p-value [1] |
|---|---|---|---|---|---|---|---|---|
| NaPBA → HPN-100 | Day 14 | 22 | 59.6 | 64.94 | 41.5 | 14 | 293 | |
| | Day 28 | 22 | 55.9 | 48.76 | 52.4 | 12 | 245 | |
| | Difference [2] | 22 | -3.7 | 31.72 | -0.2 | -107 | 43 | |
| HPN-100 → NaPBA | Day 14 | 22 | 65.9 | 44.08 | 50.7 | 19 | 167 | |
| | Day 28 | 22 | 82.0 | 68.06 | 58.2 | 19 | 303 | |
| | Difference [2] | 22 | 16.1 | 52.11 | 10.4 | -85 | 163 | |
| Overall | Day 14 | 44 | 62.8 | 54.94 | 43.7 | 14 | 293 | |
| | Day 28 | 44 | 69.0 | 59.98 | 55.8 | 12 | 303 | |
| | Difference [2] | 44 | 6.2 | 43.79 | 4.7 | -107 | 163 | |
| Overall | HPN-100 Visit [3] | 44 | 60.9 | 46.21 | 50.7 | 12 | 245 | |
| | NaPBA Visit [3] | 44 | 70.8 | 66.71 | 46.0 | 14 | 303 | |
| | Difference [4] | 44 | -9.9 | 43.09 | -3.6 | -163 | 185 | 0.135 |

Source: Reviewer's Table.
[1]: The treatment comparison is based on a paired t-test.
[2]: Change from Day 14 to Day 28.
[3]: HPN-100 Visit and NaPBA Visit are steady state Day 14 and Day 28 visits, based on randomized treatment sequence.
[4]: Change from HPN-100 Visit to NaPBA Visit.

*Reviewer Comments*:
*The p-value corresponding to the paired t-test was 0.135. The interpretation of this result, with respect to Hochberg's procedure, is presented in the Reviewer Summary Comments which appear at the end of this Results and Conclusions section. These analyses were all re-conducted utilizing the PP, All-Randomized, and mITT analysis sets with no changes to the conclusions. In addition, all of these analyses were conducted using the original, non-normalized ammonia data with no changes to the conclusions.*

**Table 8**
**Summary of Ammonia Levels above ULN by Treatment Group**
**(ITT)**

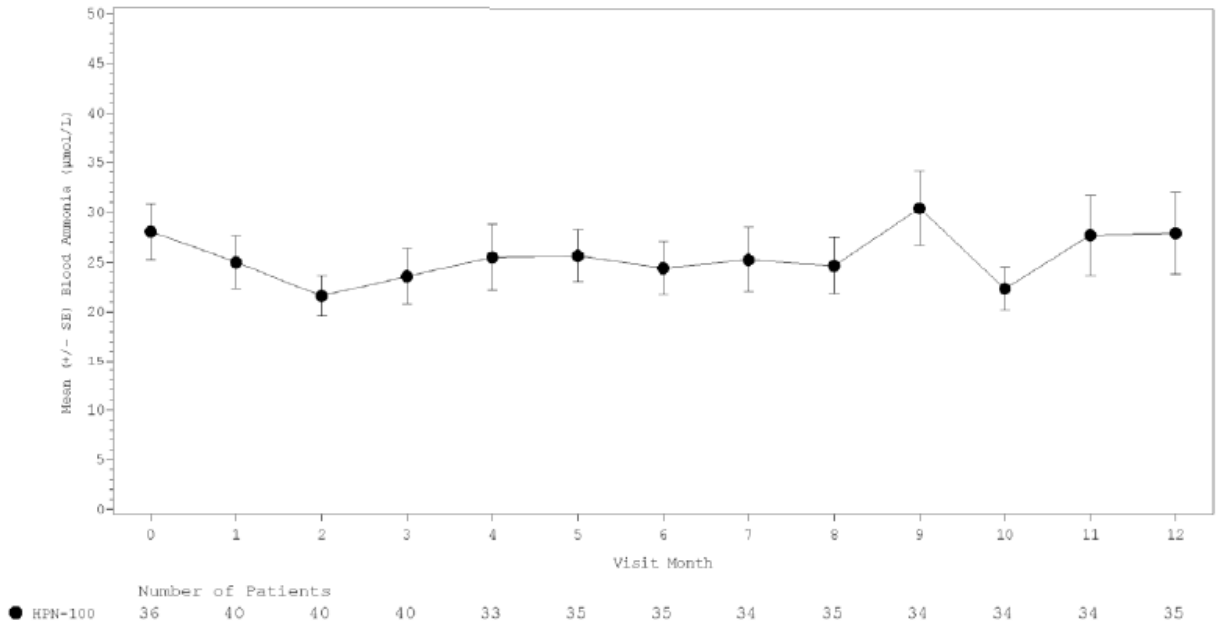
| | Study Treatment | | |
|---|---|---|---|
| | HPN-100 (N = 45) | NaPBA (N=45) | p-value [1] |
| Number (%) of samples with ammonia value above ULN [2] | | | |
| Pre-dose | 13 / 44 (29.5%) | 15 / 44 (34.1%) | |
| 2-hour post-dose | 20 / 43 (46.5%) | 13 / 42 (31.0%) | |
| 4-hour post-dose | 22 / 43 (51.2%) | 20 / 44 (45.5%) | |
| 8-hour post-dose | 17 / 43 (39.5%) | 18 / 42 (42.9%) | |
| 12-hour post-dose | 15 / 42 (35.7%) | 13 / 43 (30.2%) | |
| 16-hour post-dose | 11 / 41 (26.8%) | 17 / 42 (40.5%) | |
| 20-hour post-dose | 12 / 44 (27.3%) | 14 / 44 (31.8%) | |
| 24-hour post-dose | 12 / 43 (27.9%) | 15 / 44 (34.1%) | |
| All timepoints | 122 / 343 (35.6%) | 125 / 345 (36.2%) | |
| Percentage of samples above ULN [3] | | | 0.905 |
| n | 44 | 44 | |
| Mean (SD) | 35.5 (36.80) | 36.4 (36.12) | |
| Median | 25.0 | 25.0 | |
| Min, Max | 0, 100 | 0, 100 | |

Source: Reviewer's Table.
[1]: The treatment comparison is based on a two-sample t-test.
[2]: Numerator is the number of samples above the ULN at the specified timepoint. The denominator is the total number of ammonia values at the corresponding time point.
[3]: Percentage of samples above ULN is calculated for each subject using data from all time points on Day 14 and Day 28.

*Reviewer Comments*:
*The p-value corresponding to the two-sample t-test was 0.905. The interpretation of this result, with respect to Hochberg's procedure, is given in the Reviewer Summary Comments which appear at the end of this Results and Conclusions section. These analyses were all re-conducted utilizing the PP, All-Randomized, and mITT analysis sets with no changes to the conclusions. In addition, all of these analyses were conducted using the original, non-normalized ammonia data with no changes to the conclusions.*

As stated previously in section 3.2.1, all patients participating in study HPN-100-106 were eligible to roll over into the long term efficacy and safety trial HPN-100-107. It turned out that of the 46 patients randomized into the HPN-100-006 study, 40 participated in HPN-100-107, and Figure 2 below displays the long term venous ammonia across this entire 12 month open-label study for these 40 patients.

**Figure 2**
**Mean (± SE) Blood Ammonia by Monthly Visit – HPN-100-106/HPN-100-107**
**(HPN-100-106 ITT patients rolling over into HPN-100-107)**




Source: Response to Information Request (Sequence 0009 on 23Aug2012) - Figure AH3.1.1 on pg. 161.

*Reviewer Comments*:
*As can be seen from Figure 2, monthly venous ammonia concentration stayed relatively flat, and below 35 µmol/L (considered the ULN), during further HPN-100 treatment exposure thereby suggesting a stable long-term efficacy profile. Using the original, non-normalized ammonia data resulted in no changes to the conclusions.*

*Reviewer Summary Comments including interpretation of key secondary endpoint results*:
*It was determined that HPN-100 was non-inferior to NaPBA based on the primary analysis of $NH3_{24\text{-hour AUC}}$. With respect to Hochberg's procedure, the p-values corresponding to the three key secondary endpoint analyses are ordered from highest to lowest as follow: 0.905 (corresponding to percentage of ammonia values above ULN while on steady state), 0.135 (corresponding to $C_{max}$ of ammonia values observed on steady state), and 0.002 (corresponding to the overall correlation between U-$PAGN_{24\text{-hour Excr}}$ and $NH3_{24\text{-hour AUC}}$ observed on steady state). The Hochberg procedure, as described previously in Section 3.2.1, subsequently commences. Starting with the largest p-value, 0.905, we see that it is greater than 0.05 hence we fail to reject that corresponding hypothesis test. Moving on to the next largest p-value, 0.135, we see that it is greater than 0.025 hence we fail to reject that corresponding hypothesis test as well. Finally moving on to the smallest p-value, 0.002, we see that it is less than 0.0167 hence we can reject that corresponding hypothesis test. Consequently, the overall correlation between U-$PAGN_{24\text{-hour Excr}}$ and $NH3_{24\text{-hour AUC}}$ observed on steady state is the only significant secondary endpoint. As explained previously, it was reassuring that this correlation was positive, including those within each individual treatment group, and that the results were consistent between the treatment groups thereby further supporting the comparability of the treatments themselves. But*

*also as explained previously, although pre-specified by the applicant through Hochberg's multiplicity adjustment procedure, the overall correlation endpoint was really exploratory in nature and tested for possible future utilization of U-PAGN for dose selection and dose adjustment purposes. The correlation, whether overall or by individual treatment group, only indicates a possible linear association and does not confirm a treatment benefit. It is not a measure of efficacy nor is significant positive correlation necessarily informative regarding level of efficacy. As such, the applicant never considered this endpoint for labeling purposes and hence the label does not reflect these correlation results.*

*It is also to be noted that no patient took prohibited medications, and that almost all patients were fully compliant to the study treatments and diet restrictions. Hence regarding contribution to the overall level of evidence, the results within trial HPN-100-106 are viewed positively as the formal basis for an efficacy claim to be reflected by the product's label. The only consideration that needs to be made pertains to how the HPN-100 dose will be officially labeled in that a given patient's dose, as previously described in Section 3.2.1, was a function of that patient's stable NaPBA dose.*

### 3.3 Evaluation of Safety

During the entire HPN-100 development program, there were a cumulative total of zero deaths in patients administered HPN-100. In addition, there were only a limited number of treatment-emergent serious adverse events (e.g. hyperammonemia). Please see Section 7 of the clinical review for full details regarding the safety profile of HPN-100.

### 3.4 Benefit-Risk Assessment

Based on the clinical review, the risk-benefit tradeoff favors the approval of HPN-100. Please see Section 1 of the clinical review for full details.

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, Age, and Geographic Region

In study HPN-100-106, the majority of randomized patients (i.e. 76.1%) were Caucasian and between the ages of 18 and 65. In addition, all of the patients participating in this trial were from North America (mostly the United States). Hence race, age, and geographic region analyses would not be informative. Due to this lack of representation, extrapolation of these study results to patients who are not Caucasian or not between 18 and 65 years old or not from North America should be made with caution.

Efficacy was assessed by gender, and it was found that the results were fairly consistent across the female and male subgroups. It is to be noted that for the male subgroup, the upper bound of the 95% CI, 1.284, was slightly larger than 1.25. This, however, may be attributable to the small number of males, 14, in this study.

**Table 9**
**Gender Subgroup Analysis of $NH3_{24\text{-hour AUC}}$ by Treatment Group (ITT)**

| $NH3_{24\text{-hour AUC}}$ [(µmol/L) × hours] Statistic | Study Treatment HPN-100 (N = 45) | Study Treatment NaPBA (N=45) | Difference Between HPN-100 and NaPBA |
|---|---|---|---|
| *Female* | | | |
| Log-Transformed Scale | | | |
| n | 31 | 31 | 31 |
| Mean (SD) | 6.4 (0.63) | 6.5 (0.59) | -0.1 (0.41) |
| Median | 6.3 | 6.5 | -0.1 |
| Min, Max | 5, 8 | 6, 8 | -1, 1 |
| Least Squares Mean [1] | 6.4 | 6.5 | -0.1 |
| 95% CI [1] | | | [-0.280, 0.029] |
| Original Scale | | | |
| Ratio of Geometric Means [2] | | | 0.88 |
| 95% CI [2] | | | [0.756, 1.029] |
| *Male* | | | |
| Log-Transformed Scale | | | |
| n | 14 | 14 | 14 |
| Mean (SD) | 6.9 (0.61) | 6.9 (0.75) | -0.03 (0.46) |
| Median | 7.0 | 6.9 | -0.03 |
| Min, Max | 6, 8 | 6, 8 | -1, 1 |
| Least Squares Mean [1] | 6.9 | 6.9 | -0.01 |
| 95% CI [1] | | | [-0.269, 0.250] |
| Original Scale | | | |
| Ratio of Geometric Means [2] | | | 0.99 |
| 95% CI [2] | | | [0.764, 1.284] |

Source: Reviewer's Table.
[1]: ANOVA for the natural log-transformed $NH3_{24\text{-hour AUC}}$ with factors for treatment, sequence, patient nested in sequence (as a random effect), and period.
[2]: Results on original scale were obtained by exponentiating the corresponding log-transformed results.

## 4.2 Other Special/Subgroup Populations

There were no other special/subgroup populations of interest.

# 5 SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues

There were no statistical issues that impacted the overall conclusions of trial HPN-100-106. The study's design was adjudicated as being adequate, and the applicant's corresponding analysis plan was deemed appropriate.

## 5.2 Collective Evidence

The efficacy of HPN-100 was principally demonstrated in trial HPN-100-106. In this trial, HPN-100 was determined to be non-inferior to NaPBA based on $NH3_{24\text{-hour AUC}}$ on Study Days 14 and 28. In addition, the overall correlation, calculated by pooling all patient data across both treatment groups, between U-$PAGN_{24\text{-hour Excr}}$ and $NH3_{24\text{-hour AUC}}$ observed on steady state was the only significant key secondary endpoint determined through the pre-specified Hochberg's multiplicity adjustment procedure. As explained previously, it was reassuring that this correlation was positive and that the results were consistent between the individual treatment groups thereby supporting the comparability of the treatments themselves.

Based on a sustained efficacy profile shown during extension study HPN-100-107 and with consensus regarding the clinical meaningfulness of the $NH3_{24\text{-hour AUC}}$ endpoint, there appears to be a sufficient level of evidence to support an efficacy claim for HPN-100. Hence, regarding contribution to overall level of evidence, the HPN-100-106 trial results are viewed positively as the formal basis for an efficacy claim to be reflected by the product's label.

## 5.3 Conclusions and Recommendations

As previously mentioned, there was a sufficient level of evidence to support an efficacy claim for HPN-100, and the claims currently reflected within the applicant's submitted product label were verified during this NDA review. With further motivation under the current public health circumstances in which Urea Cycle Disorders are a rare, serious and life-threatening condition with a not fully met medical need, this reviewer supports the approval of HPN-100 for the treatment of adult and pediatric patients $\geq$ 6 years of age with this condition.

## 5.4 Labeling Recommendations

Although pre-specified by the applicant through Hochberg's multiplicity adjustment procedure, the overall correlation endpoint was really exploratory in nature and was tested for possible future utilization of U-PAGN for dose selection and dose adjustment purposes. The correlation, whether overall or by individual treatment group, only indicates a possible linear association and does not confirm a treatment benefit. As such, the applicant never considered this endpoint for

labeling purposes and hence the label should not reflect these correlation results. The reviewer concurs with the applicant's labeling consideration.

This reviewer recommends that careful consideration be made pertaining to the official labeling of the HPN-100 dose in that the dose for a given patient, as previously described in Section 3.2.1, was a function of the patient's stable NaPBA dose. Currently, the label reflects that the total daily HPN-100 dose is not to exceed 17.5 mL.

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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.**

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/s/

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BEHRANG VALI
01/18/2013

MICHAEL E WELCH
01/18/2013
Concur with review.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

# Statistical Review and Evaluation

## CARCINOGENICITY STUDIES

| | |
|---|---|
| **IND/NDA Number:** | NDA 203-284 |
| **Drug Name:** | HPN-100 |
| **Applicant:** | Sponosor: Hyperion Therapeutics, Inc. 601 Gateway Bld., Suite 200 South San Francisco, CA 94080 |
| | Test Facility: Rats: (b) (4) Transgenic mice: (b) (4) |
| **Documents Reviewed:** | Electronic data submitted on February 16, 2012 |
| **Review Priority:** | Standard |
| **Biometrics Division:** | Division of Biometrics -6 |
| **Statistical Reviewer:** | Min Min, Ph.D. |
| **Concurring Reviewer:** | Karl Lin, Ph.D. |
| **Medical Division:** | Division of Gastroenterology and Inborn Errors Products |
| **Reviewing Pharmacologist:** | Ke Zhang, Ph.D. |
| **Project Manager:** | |
| **Keywords:** | Carcinogenicity, Dose response |

## Table of Contents

## 1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in Tg.rasH2 mice. The purpose of rat study was to assess the carcinogenic potential of HPN100, Glyceryl Tri (4-Phenylbutyrate), a triglyceride that, when metabolized, is used as a means for metabolic disposal of nitrogen waste in patients with nitrogen retention states, when administered orally via gavage to rats (65/sex/group) for up to 24 months. Rats (65/sex/group) were gavaged once daily at a dose level of 70, 210, or 650 mg/kg/day for males and 100, 300, and 900 mg/kg/day for females, respectively. Concurrent control groups (Groups 1 and 2) received deionized water and corn oil, respectively, on a comparable regimen. The dose volumes were 0.59, 0.59, 0.06, 0.19, and 0.59 mL/kg for males and 0.82, 0.82, 0.09, 0.27, and 0.82 mL/kg for females in Groups 1, 2, 3, 4, and 5, respectively. Toxicology group males were dosed for a minimum of 728 consecutive days. Due to increased mortality rates, toxicology group females were dosed for a minimum of 702 consecutive days. The purpose of mice study was to assess the carcinogenic potential of HPN-100 [(glyceryltri-(4-phenylbutyrate)] following once daily repeated oral administration (gavage) for 26 weeks (182-183 dosing days) in male and female hemizygous Tg.rasH2 mice (Main Study). In addition, the study included groups of CByB6F1 Hybrid mice (Tg.ras nontransgenic littermates) to confirm exposure of metabolites of HPN-100 following approximately 184 days of oral (gavage) exposure to HPN-100 (Exposure Study). In the Main Study, there were four groups of 25 transgenic mice per sex: two vehicle control groups which were administered sterile water by oral gavage (Groups 1 and 2) and two test article treatment groups (Groups 3 and 4) were administered the test article (HPN-100) at dose levels of 600 and 1000 mg/kg/day via oral gavage, respectively. The positive control group (Group 5) consisted of 16 male and 15 female transgenic mice that were treated with urethane at 1000 mg/kg via intraperitoneal injection on Days 1, 3 and 5 for a total of 3 injections. Results of this review have been discussed with the reviewing pharmacologist Dr. Zhang.

## 2. Rat Study

Two separate experiments were conducted, one in males and one in females. Male and female Crl:SD(CD) rats were assigned to 5 groups (65/sex/group) and received two controls (control Group 1 vehicle was deionized water (prepared on-site) and control Group 2 vehicle was corn oil), or at a dose level of 70, 210, or 650 mg/kg/day for males and 100, 300, and 900 mg/kg/day for females, respectively. The dose volumes were 0.59, 0.59, 0.06, 0.19, and 0.59 mL/kg for males and 0.82, 0.82, 0.09, 0.27, and 0.82 mL/kg for females in Groups 1, 2, 3, 4, and 5, respectively. The following table contains the information about the study design:

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 |

For toxicology assessment, all animals were observed twice daily for mortality or moribundity. Clinical observations were recorded daily and detailed physical examinations and palpable masses were recorded approximately weekly. Body weights and food consumption were recorded at least weekly through study week

12 and biweekly thereafter. Moribund animals were euthanized by carbon dioxide inhalation and complete necropsies were performed. All animals found dead were examined microscopically as soon as possible to ensure that tissues were not lost due to autolysis. A complete necropsy was conducted on all toxicology group animals. Animals were euthanized by carbon dioxide inhalation followed by exsanguination. The necropsies included, but were not limited to, examination of the external surface, all orifices, and the cranial, thoracic, abdominal and pelvic cavities including viscera.

The following tissues and organs were collected and placed in 10% neutral-buffered formalin (except as noted):

- Adrenals (2)
- Aorta
- Bone with marrow
  - Femur
  - Sternum
- Bone marrow smear[a]
- Brain
  - Cerebrum level 1
  - Cerebrum level 2
  - Cerebellum with medulla/pons
- Cervix
- Clitoral glands (2)
- Epididymides (2)[b]
- Eyes with optic nerve (2)[c]
- Gastrointestinal tract
  - Esophagus
  - Stomach
  - Duodenum
  - Jejunum
  - Ileum
  - Cecum
  - Colon
  - Rectum
- Harderian glands (2)
- Heart
- Kidneys (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
- Peripheral nerve (sciatic)
- Pituitary
- Preputial glands (2)
- Prostate
- Salivary glands (mandibular [2])
- 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 with vagina
- Zymbal's glands (2)
- All gross lesions including masses (when possible)

[a] = Bone marrow smears were obtained at 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] = Oviducts and parathyroids examined if in plane of section and in all cases when a gross lesion is present.
[e] = For females; a corresponding section of skin was taken from the same anatomic area for males

## 2.1. Sponsor's analyses

### 2.1.1. Survival analysis

The statistical analyses for mortality data were performed for each sex separately. Kaplan-Meier estimates (Kaplan and Meier, 1958) of group survival rates were calculated, by sex, and presented graphically. The generalized Wilcoxon test (Gehan, 1965) for survival was used to compare the homogeneity of survival rates across the groups at the 0.05 significance level. If the survival rates were significantly different, the generalized Wilcoxon test (Gehan, 1965) was used to make pair-wise comparisons of each test article-treated group with each of the control groups. A log-rank dose-response trend test of survival rates was also performed including the control groups and active treatment groups. The trend test and pair-wise comparisons were conducted with each control group individually. The 2 control groups were also compared using the generalized Wilcoxon test. Survival times in which the status of the animal's death was classified as an accidental death, planned interim euthanasia, or early terminal euthanasia were considered censored values (survival times for which the death event did not occur) for the purpose of the Kaplan-Meier estimates (Kaplan and Meier, 1958) and survival rate analyses.

**Sponsor's findings**: There were no statistically significant survival findings among males or females.

**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)<br>0.0882 (T) |
| | p-value (2) | | | NT | NT | NT | 0.9881 (O)<br>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)<br>0.4921 (T) |
| | p-value (2) | | | NT | NT | NT | 0.6399 (O)<br>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**

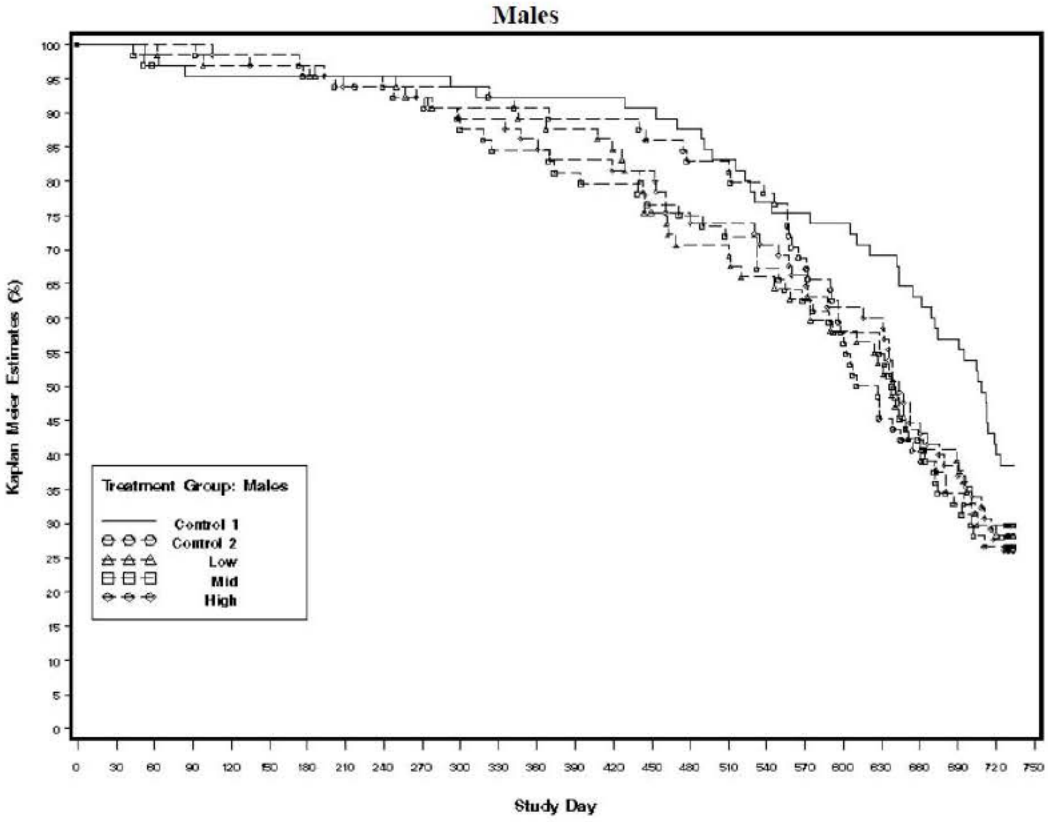


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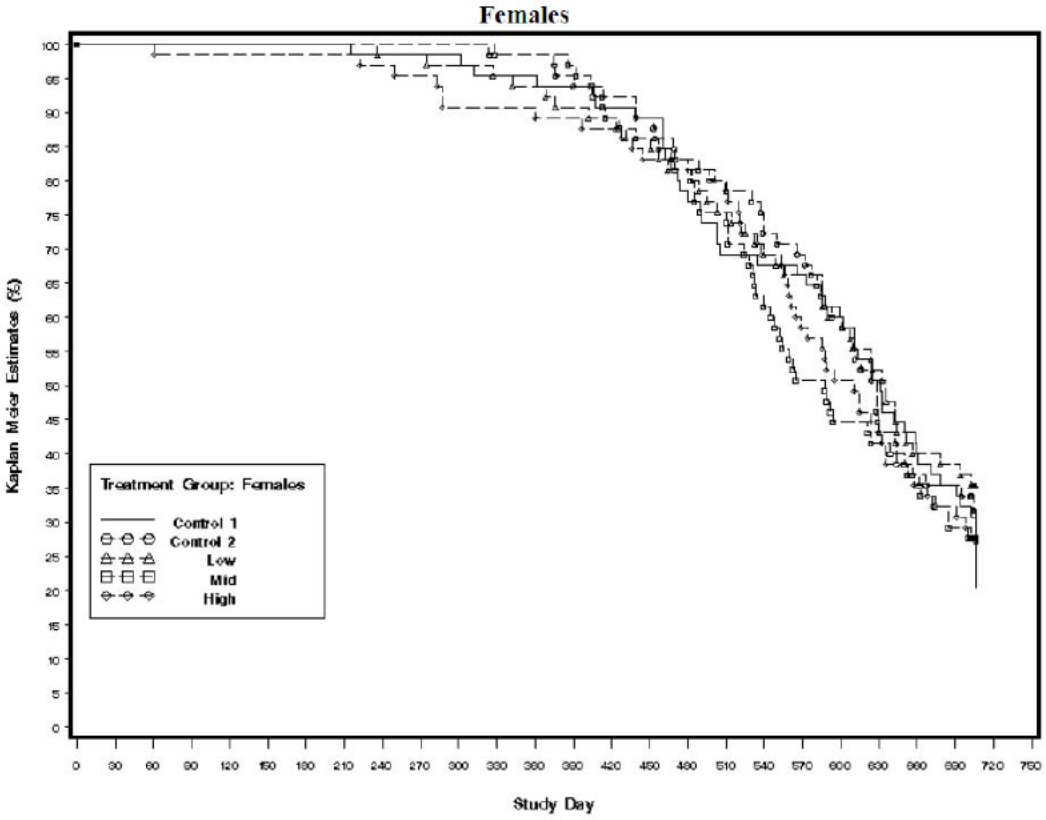
**Figure 5.1.4 Kaplan-Meier Estimates of Survival: Females**






### 2.1.2. Tumor data analysis

The principal statistical method used to evaluate tumor incidence and to guide interpretation of possible oncogenic effects was linear trend analysis by the method of Peto (Peto *et al.*, 1980). The mortality-prevalence method of Peto was performed without continuity correction, incorporating the context (incidental or fatal) in which tumors were observed. The following fixed intervals were used for incidental tumor analyses: study weeks 0-52, 53-78, 79-92, 93-end of study, and the scheduled terminal euthanasia. Tumors classified as mortality-independent, such as, but not limited to, those of the mammary gland and skin, were analyzed with Peto's mortality-independent methods incorporating the day of detection. Each diagnosed tumor type was analyzed separately and, at the discretion of the Study Director, analysis of combined tumor types was performed as described by McConnell (1986). For males and females, benign adenoma, acinar cell and malignant carcinoma, acinar cell in the pancreas; benign adenoma and malignant carcinoma in the adrenal cortex; benign adenoma, follicular cell and malignant carcinoma, follicular cell in the thyroid; and benign adenoma, hepatocellular and malignant carcinoma, hepatocellular in the liver were combined for statistical analysis.

For organs in which an exhaustive examination of animals was planned (all animals in all dose groups), the incidence of each tumor type was analyzed with a one-sided trend test using dose coefficients. In addition, pair-wise comparisons with the control groups were conducted for each active treatment group. All

comparisons were conducted for each control group individually. In addition, a 2-sided comparison of control Group 1 vs. control Group 2 was conducted for all tumors.
An exact permutation test was conducted for analyses with low tumor incidence. (Low tumor incidence is defined as one in which the marginal incidence rate within a defined interval was 4 or less). Statistical significance was determined according to the following guidelines: trend tests were conducted at the 0.005 and 0.025 significance levels for common and rare tumors, respectively (Lin, 1995; Lin, 1997; Lin and Rahman, 1998[a]; Lin and Rahman, 1998[b]). Pair-wise comparisons with the control groups were conducted at the 0.01 and 0.05 significance levels for common and rare tumors, respectively (Haseman, 1983). Common tumors were defined as those with a spontaneous rate of 1% or more in the concurrent control group and/or the (b) (4) historical control database; rare tumors were defined as those with a spontaneous rate of less than 1% in the concurrent control group and/or the (b) (4) historical control database. Test article-related neoplastic findings were noted in the mid- and/or high-dose group males and/or females. These findings included adrenal cortical carcinomas in the adrenal cortex, acinar cell adenomas and carcinomas in the pancreas, follicular cell adenomas and carcinomas in the thyroid gland, benign endometrial stromal polyps of the uterus, Zymbal's gland carcinomas, and malignant schwannomas in the cervix. In the event of a negative study (no statistically significant tumor findings), an assessment of the validity of the study design will be made through an evaluation of the group survival rates.

**Sponsor's findings**: In conclusion, daily oral (gavage) administration of HPN-100 to male and female Crl:SD(CD) rats at dosage levels of 70/100, 210/300, and 650/900 mg/kg/day, respectively, for up to 24 months was associated with test-article related neoplasms which included pancreatic acinar cell adenomas and/or carcinomas in males administered 210 and 650 mg/kg/day and in females administered 300 and 900 mg/kg/day, respectively; adrenal cortical carcinomas in males administered ≥ 210 mg/kg/day and adrenal cortical adenomas in females administered 900 mg/kg/day; thyroid follicular cell adenomas in males administered 650 mg/kg/day and thyroid follicular adenomas and carcinomas in females administered 900 mg/kg/day; Zymbal's gland carcinomas in males administered ≥ 210 mg/kg/day and in females administered 900 mg/kg/day; benign endometrial stromal polyps in females administered 900 mg/kg/day; and malignant schwannomas in the cervix of females administered 300 mg/kg/day.

**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

## 2.2. Reviewer's analyses

To verify sponsor's analyses and to perform the additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. There are three sets of analysis included: water control with three treated groups, corn-oil control with three treated groups and the combined controls with three treated groups. Data used in this reviewer's analyses were provided by the sponsor electronically.

### 2.2.1. Survival analysis

The survival distributions of animals in all four treatment groups (three treated groups and the water control, corn-oil control and the combined water-corn-oil control group, respectively.) and five groups including two controls were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested using the Cox test (Cox, 1972). The inter-current mortality data are given in Tables 1A and 1B in the appendix for five groups (including two controls) in males and females, respectively. The

Kaplan-Meier curves for survival rate are given in Figures 1A and 1B with five groups including two control groups in the appendix for males and females, respectively. Results for the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A1, 2A2, 2A3, 2B1, 2B2 and 2B3 for three sets groupings (water control, corn-oil control, combined water and corn-oil control with three treated groups) in the appendix for males and females, respectively.

**Reviewer's findings**: The test results showed no statistically significant dose-response relationship and statistically significant difference in mortality in either sex when compared with water control, corn-oil control and the combined control, respectively. In addition, the test results showed no statistically significant difference in mortality when compared between water control and corn-oil control in males and females. There were some differences between reviewer's and sponsor's survival rates and the differences may be caused by the different dates of starting the terminal killing.

### 2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships and pair-wise comparisons of the water control group, corn-oil control group and the combined water-corn-oil control group with each of the treated groups were performed using the Poly-k method described in the paper of Bailer and Portier (1988), and Bieler and Williams (1993). One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. For short term study of 26 weeks no such suggestion is available, in the mouse tumor data analysis we chose k=3 here. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A1, 3A2, 3A3, 3B1, 3B2 and 3B3 for three sets of groupings (water control, corn-oil control and combined water-corn-oil control with three treated groups) in the appendix for males and females, respectively.

As suggested by the reviewing pharmacologist Dr. Zhang, this reviewer did the analysis of the combinations of all organ/tumors as the following:

**Rat:**
Hemangiosarcomas, Hemangiomas, Hemangiomas+Hemangiosarcomas from all sites;
Adenoma and Carcinoma from Adrenal Cortex or Pituitary;
Hepatocellular adenoma + carcinoma from Liver; Cholangioma + Cholangiocarcinoma from Liver;
Adenoma + Adenocarcinoma from Mammary gland;
Benign and Malignant pheochromocytoma from Adrenal Medulla;
Benign and Malignant Thecoma from Ovaries;
Acinar cell adenoma and carcinoma from Pancreas; Islet cell adenoma and carcinoma from Pancreas;
Fibroma and Fibrosarcoma from Skin; Squamous cell papiloma and carcinoma from Skin; Sebaceous cell adenoma + carcinoma from Skin;
Benign and Malignant Hibernoma from Soft tissue;
Hemangioma and Hemangiosarcoma from Systemic tumors; Lymphomas from Systemic tumors;
Benign and Malignant Thymoma from Thymus;
C-cell adenoma and carcinoma from Thyroid gland; Follicular cell adenoma and carcinoma from Thyroid gland; Polyp + Sarcoma from Uterus;

**Mouse:**
Hemangioma, Hemangiosarcoma and combined hemangioma and hemangiosarcoma from all sites;
Adenoma and carcinoma from lung;

**Multiple testing adjustment**: Adjustment for the multiple dose response relationship testing was done using

the criteria developed by Lin and Rahman (1998). The criteria recommend the use of a significance level $\alpha$=0.025 for rare tumors and $\alpha$=0.005 for common tumors for a submission with two species for 2-year rodent studies, and a significance level $\alpha$=0.05 for rare tumors and $\alpha$=0.01 for common tumors for a submission with only one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the spontaneous tumor rate is less than 1%. The adjustment for multiple pair-wise comparisons was done using the criteria developed by Haseman (1983) that recommends the use of a significance level $\alpha$=0.05 for rare tumors and $\alpha$=0.01 for common tumors, in order to keep the false-positive rate at the nominal level of approximately 10%. It should be noted that the recommended test levels by Lin and Rahman for the adjustment of multiple testing were originally based on the result of a simulation and an empirical study using the Peto method for dose response relationship analysis. However, some later simulation results by Rahman and Lin (2008) indicate that the criteria apply equally well to the analysis using the poly-3 test.
For 2-year rat study plus 26-week transgenic mouse, a new level of significance was proposed as below:

| Test type | Rare tumor | Common tumor |
|---|---|---|
| Trend test | 0.05 | 0.01 |
| High dose vs. control | 0.10 | 0.025 |
| Trend test and<br>high vs. control | 0.05<br>0.10 | 0.01<br>0.05 |

**Reviewer's findings**: Following tumor types showed p-values less than or equal to 0.05 either tests for dose response relationship and/or pair-wise comparisons between control and each of individual treated groups. In the following table, p-values in red show significant findings based on old rule and adding p-values in blue together show the significant findings based on the above proposed levels of significance.

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

| = | | | 0 mg Water Cont N=65 | 70 mg Low N=65 | 210 mg Med N=65 | 650 mg High N=65 | P_Value Dos Resp | P_Value C vs. L | P_Value C vs. M | P_Value 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 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Corn-oil 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 | 0 | 1 | 4 | 5 | 0.017 | 0.494 | 0.055 | 0.029 |
| | ADRENAL_CORTEX | ADENOMA+CARCINOMA | 1 | 3 | 5 | 6 | 0.047 | 0.298 | 0.089 | 0.054 |
| | PANCREAS | #B ADENOMA, ACINAR C | 1 | 0 | 3 | 8 | 0.001 | 1.000 | 0.308 | 0.016 |
| | | #M CARCINOMA, ACINAR | 0 | 0 | 0 | 6 | 0.000 | . | . | 0.015 |
| | | ACINAR_CELL_ADENOMA+ CARCINOMA | 1 | 0 | 3 | 14 | 0.000 | 1.000 | 0.308 | 0.000 |
| | SOFT TISSUE- TH | #M HIBERNOMA, MALIGN | 1 | 0 | 1 | 5 | 0.010 | 1.000 | 0.741 | 0.118 |
| | SOFT_TISSUE_TH | HIBERNOMAS | 2 | 1 | 1 | 5 | 0.048 | 0.865 | 0.865 | 0.236 |
| | SOFT_TISSUE | HIBERNOMAS | 2 | 1 | 1 | 6 | 0.019 | 0.865 | 0.865 | 0.148 |
| | SYSTEMIC TUMORS | #M SARCOMA, HISTIOCY | 1 | 2 | 2 | 5 | 0.047 | 0.481 | 0.481 | 0.112 |
| | THYROID GLANDS | #B ADENOMA, FOLLICUL | 1 | 3 | 3 | 6 | 0.038 | 0.289 | 0.298 | 0.058 |

| | | | 0 mg | 70 mg | 210 mg | 650 mg | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Combined Cont | Low | Med | High | P_Value | P_Value | P_Value | P_Value |
| | Organ Name | Tumor Name | N=130 | 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 | 0.007 | 0.518 | 0.030 | 0.012 |
| | ADRENAL_CORTEX | ADENOMA+CARCINOMA | 3 | 3 | 5 | 6 | 0.021 | 0.271 | 0.056 | 0.028 |
| | EYES/OPTIC N. | #M MELANOMA, AMELANO | 0 | 0 | 0 | 2 | 0.039 | . | . | 0.099 |
| | LIVER | #M CARCINOMA, HEPATO | 3 | 6 | 1 | 0 | 0.954 | 0.028 | 0.771 | 1.000 |
| | PANCREAS | #B ADENOMA, ACINAR C | 2 | 0 | 3 | 8 | 0.000 | 1.000 | 0.176 | 0.002 |
| | | #M CARCINOMA, ACINAR | 0 | 0 | 0 | 6 | 0.000 | . | . | 0.001 |
| | | ACINAR_CELL_ADENOMA+ CARCINOMA | 2 | 0 | 3 | 14 | 0.000 | 1.000 | 0.176 | 0.000 |
| | SOFT TISSUE- TH | #M HIBERNOMA, MALIGN | 4 | 0 | 1 | 5 | 0.030 | 1.000 | 0.840 | 0.129 |
| | SOFT_TISSUE_TH | HIBERNOMAS | 5 | 1 | 1 | 5 | 0.072 | 0.888 | 0.888 | 0.190 |
| | SYSTEMIC TUMORS | #M SARCOMA, HISTIOCY | 3 | 2 | 2 | 5 | 0.039 | 0.483 | 0.483 | 0.074 |
| | THYROID GLANDS | #B ADENOMA, FOLLICUL | 1 | 3 | 3 | 6 | 0.006 | 0.084 | 0.088 | 0.004 |
| | | FOLLICULAR_CELL ADENOMA+CARCINOMA | 5 | 4 | 4 | 7 | 0.034 | 0.289 | 0.289 | 0.046 |
| | ZYMBAL'S GLANDS | #M CARCINOMA | 2 | 2 | 5 | 5 | 0.024 | 0.366 | 0.029 | 0.034 |

| | Organ Name | Tumor Name | 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 | 0 | 1 | 1 | 4 | 0.013 | 0.506 | 0.488 | 0.055 |
| | | HEPATOCELLULAR 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 |

| | Organ Name | Tumor Name | 0 mg Corn-oil 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 |
| | ADRENAL_CORTEX | ADENOMA+CARCINOMA | 3 | 3 | 3 | 10 | 0.004 | 0.662 | 0.616 | 0.028 |
| | ADRENAL_MEDULLA | PHEOCHROMOCYTOMA_B+M | 1 | 0 | 2 | 5 | 0.008 | 1.000 | 0.473 | 0.091 |
| | CERVIX | #M SCHWANNOMA, MALIG | 0 | 1 | 8 | 1 | 0.414 | 0.500 | 0.002 | 0.482 |
| | LIVER | #B ADENOMA, HEPATOCE | 0 | 1 | 1 | 4 | 0.013 | 0.500 | 0.482 | 0.053 |
| | | HEPATOCELLULAR ADENOMA+CARCINOMA | 0 | 1 | 3 | 4 | 0.026 | 0.500 | 0.108 | 0.053 |
| | MAMMARY GLAND | #B FIBROADENOMA | 23 | 36 | 32 | 20 | 0.910 | 0.010 | 0.031 | 0.640 |
| | OVARIES | #B GRANULOSA CELL TU | 0 | 1 | 0 | 3 | 0.032 | 0.500 | . | 0.112 |
| | PANCREAS | #B ADENOMA, ACINAR C | 0 | 0 | 0 | 6 | 0.000 | . | . | 0.012 |
| | | #M CARCINOMA, ACINAR | 0 | 0 | 2 | 6 | 0.001 | . | 1.000 | 0.011 |
| | | ACINAR_CELL_ADENOMA+ CARCINOMA | 0 | 0 | 2 | 12 | 0.000 | . | 0.230 | 0.000 |
| | SOFT TISSUE- TH | #B HIBERNOMA, BENIGN | 0 | 0 | 1 | 3 | 0.018 | . | 0.482 | 0.116 |
| | SOFT_TISSUE | HIBERNOMAS | 0 | 1 | 2 | 5 | 0.007 | 0.506 | 0.236 | 0.029 |
| | THYROID GLANDS | #B ADENOMA, FOLLICUL | 1 | 1 | 2 | 9 | 0.000 | 0.753 | 0.473 | 0.006 |
| | | #M CARCINOMA, FOLLIC | 1 | 2 | 2 | 5 | 0.031 | 0.500 | 0.473 | 0.086 |
| | THYROID_GLANDS | FOLLICULAR_CELL ADENOMA+CARCINOMA | 2 | 3 | 4 | 14 | 0.000 | 0.511 | 0.305 | 0.001 |
| | UTERUS | #B POLYP, ENDOMETRIA | 1 | 5 | 4 | 12 | 0.001 | 0.096 | 0.152 | 0.001 |
| | | POLYP+SARCOMA | 1 | 5 | 4 | 13 | 0.000 | 0.096 | 0.152 | 0.000 |
| | ZYMBAL'S GLANDS | #M CARCINOMA | 1 | 1 | 2 | 5 | 0.018 | 0.753 | 0.473 | 0.091 |

| | Organ Name | Tumor Name | Combined | 0 mg Cont | 100 mg Low | 300 mg Med | 900 mg High | P_Value Dos Resp | P_Value C vs. L | P_Value C vs. M | P_Value C vs. H |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | N=130 | N=65 | N=65 | N=65 | | | | | |
| Female | ADRENAL CORTEX | #B ADENOMA | 2 | 2 | 1 | 7 | | 0.002 | 0.416 | 0.686 | 0.006 |
| | ADRENAL MEDULLA | #M PHEOCHROMOCYTOMA, | 0 | 0 | 0 | 2 | | 0.037 | . | . | 0.103 |
| | ADRENAL_CORTEX | ADENOMA+CARCINOMA | 4 | 3 | 3 | 10 | | 0.001 | 0.441 | 0.393 | 0.002 |
| | ADRENAL_MEDULLA | PHEOCHROMOCYTOMA_B+M | 2 | 0 | 2 | 5 | | 0.006 | 1.000 | 0.380 | 0.036 |
| | CERVIX | #M SCHWANNOMA, MALIG | 2 | 1 | 8 | 1 | | 0.362 | 0.704 | 0.002 | 0.683 |
| | LIVER | #B ADENOMA, HEPATOCE | 0 | 1 | 1 | 4 | | 0.004 | 0.333 | 0.318 | 0.010 |
| | | HEPATOCELLULAR ADENOMA+CARCINOMA | 0 | 1 | 3 | 4 | | 0.008 | 0.333 | 0.031 | 0.010 |
| | MAMMARY GLAND | #B FIBROADENOMA | 53 | 36 | 32 | 20 | | 0.906 | 0.024 | 0.072 | 0.859 |
| | OVARIES | #B GRANULOSA CELL TU | 0 | 1 | 0 | 3 | | 0.013 | 0.333 | . | 0.032 |
| | | #B THECOMA, BENIGN | 0 | 0 | 0 | 2 | | 0.036 | . | . | 0.099 |
| | PANCREAS | #B ADENOMA, ACINAR C | 0 | 0 | 0 | 6 | | 0.000 | . | . | 0.001 |
| | | #M CARCINOMA, ACINAR | 0 | 0 | 2 | 6 | | 0.000 | . | 0.099 | 0.001 |
| | | ACINAR_CELL_ADENOMA+ CARCINOMA | 0 | 0 | 2 | 12 | | 0.000 | . | 0.099 | 0.000 |
| | SOFT TISSUE- TH | #B HIBERNOMA, BENIGN | 1 | 0 | 1 | 3 | | 0.027 | 1.000 | 0.536 | 0.103 |
| | SOFT_TISSUE | HIBERNOMAS | 1 | 1 | 2 | 5 | | 0.005 | 0.564 | 0.244 | 0.017 |
| | SYSTEMIC TUMORS | #M SARCOMA, HISTIOCY | 0 | 0 | 0 | 2 | | 0.037 | . | . | 0.103 |
| | THYROID GLANDS | #B ADENOMA, FOLLICUL | 1 | 1 | 2 | 9 | | 0.000 | 0.557 | 0.237 | 0.000 |
| | | #M CARCINOMA, FOLLIC | 1 | 2 | 2 | 5 | | 0.007 | 0.258 | 0.237 | 0.012 |
| | THYROID_GLANDS | FOLLICULAR_CELL ADENOMA+CARCINOMA | 2 | 3 | 4 | 14 | | 0.000 | 0.214 | 0.081 | 0.000 |
| | UTERUS | #B POLYP, ENDOMETRIA | 3 | 5 | 4 | 12 | | 0.000 | 0.079 | 0.141 | 0.000 |
| | | POLYP+SARCOMA | 3 | 5 | 4 | 13 | | 0.000 | 0.079 | 0.141 | 0.000 |
| | VAGINA | #M SCHWANNOMA, MALIG | 0 | 0 | 0 | 2 | | 0.037 | . | . | 0.103 |
| | ZYMBAL'S GLANDS | #M CARCINOMA | 1 | 1 | 2 | 5 | | 0.004 | 0.557 | 0.237 | 0.013 |

For tumor analysis including water control and three treated groups:

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, the positive dose-response relationships in the incidence of Acinar cell adenoma, carcinoma and combined adenoma and

carcinoma from Pancreas and Follicular cell adenoma from Thyroid glands in both males and females, malignant schwannoma from skin and malignant lymphoma from systemic tumors in males, adenoma and combined adenoma and carcinoma from Adrenal cortex, Hepatocellular adenoma from Liver, Follicular cell carcinoma and combined adenoma and carcinoma from thyroid glands, polyp and combined polyp and sarcoma from Uterus and carcinoma from Zymbal's glands in females were considered to be statistically significant.

Also based on the criteria of Haseman, the pair-wise comparison of acinar cell adenoma, carcinoma and combined adenoma and carcinoma from pancreas and follicular cell adenoma from thyroid glands between the high dose group and water control were considered to be statistically significant in both females and males for increased tumor incidence.
In females only, the pair-wise comparison of combined adenoma and carcinoma in adrenal cortex, follicular cell carcinoma and combined follicular cell adenoma and carcinoma in thyroid glands, polyp in uterus and combined polyp and sarcoma in uterus and carcinoma in zymbal's glands between the high dose group and water control were considered to be statistically significant in females for increased tumor incidence.

For tumor analysis including corn-oil control and three treated groups:

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, the positive dose-response relationships in the incidence of Acinar cell adenoma, carcinoma and combined adenoma and carcinoma from pancreas in both males and females, adenoma, combined adenoma and carcinoma in adrenal cortex, hepatocellular adenoma in liver, combined hibernomas in all soft tissues, benign hibernoma in soft tissue-TH, follicular cell adenoma and combined adenoma and carcinoma in thyroid glands, polyp and combined polyp and sarcoma from Uterus in females and carcinoma from adrenal cortex in males were considered to be statistically significant.

Also based on the criteria of Haseman, the pair-wise comparisons of acinar cell carcinoma and combined adenoma and carcinoma from pancreas between the high dose group and corn-oil control were considered to be statistically significant in both females and males for increased tumor incidence.

In males only, the pair-wise comparison of carcinoma in adrenal cortex between the high dose group and the corn-oil control was considered to be statistically significant for increased tumor incidence.

In females only, the pair-wise comparison of follicular cell adenoma and combined follicular cell adenoma and carcinoma in thyroid glands, acinar cell adenoma in pancreas, poly in uterus and combined polyp and sarcoma in uterus between the high dose group and corn-oil control were considered to be statistically significant for increased tumor incidence. In addition, the pair-wise comparison of malignant schwannoma in cervix between medium dose group and corn-oil control was considered to be statistically significant for increase tumor incidence.

For tumor analysis including combined controls and three treated groups:

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, the positive dose-response relationships in the incidence of Acinar cell adenoma, carcinoma and combined adenoma and carcinoma from Pancreas in both males and females, adenoma and combined adenoma and carcinoma from Adrenal cortex, Hepatocellular adenoma and combined adenoma and carcinoma from Liver, granulose cell tumor from Ovaries, Follicular cell adenoma and combined adenoma and carcinoma from Thyroid glands,

polyp and combined polyp and sarcoma from Uterus and carcinoma from Zymbal's glands in females were considered to be statistically significant.

Also based on the criteria of Haseman, the pair-wise comparison of acinar cell adenoma, carcinoma and combined adenoma and carcinoma from pancreas and follicular cell adenoma from thyroid glands between the high dose group and the combined controls were considered to be statistically significant in both females and males for increased tumor incidence.
In females only, the pair-wise comparison of adenoma and combined adenoma and carcinoma in adrenal cortex, hepatocellular adenoma and combined hepatocellular adenoma and carcinoma in liver, granulose cell tumor in ovaries, combined follicular cell adenoma and carcinoma in thyroid gland, poly in uterus and combined polyp and sarcoma in uterus between the high dose group and the combined controls were considered to be statistically significant for increased tumor incidence. In addition, the pair-wise comparison of malignant schwannoma in cervix and combined hepatocellular adenoma and carcinoma in liver between medium dose group and the combined controls was considered to be statistically significant for increase tumor incidence.

### 3. Mouse Study

The objective of this study was to determine if there was an increased incidence of tumors in hemizygous Tg.rasH2 mice after administration of HPN-100 via oral gavage for 26 weeks. In the Main Study, there were four groups of 25 transgenic mice per sex: two vehicle control groups which were administered sterile water by oral gavage (Groups 1 and 2) and two test article treatment groups (Groups 3 and 4) were administered the test article (HPN-100) at dose levels of 600 and 1000 mg/kg/day via oral gavage, respectively. The positive control group (Group 5) consisted of 16 male and 15 female transgenic mice that were treated with urethane at 1000 mg/kg via intraperitoneal injection on Days 1, 3 and 5 for a total of 3 injections. The Exposure Study included 5 hybrid CByB6F1 (nontransgenic) mice per sex and dose in Groups 1 - 4 which were treated with either vehicle or test article in the same manner as the Main Study mice. Toxicity assessment was based on mortality, clinical signs, body weight, and body weight gain and food consumption.
Carcinogenicity was based on complete necropsies, organ weights and microscopic evaluations of selected tissues. Main Study animals that are found dead or moribund on test will be subject to gross necropsy (as per Section 8.5) as soon as possible after being found, but within 8 hours. Carcasses will be refrigerated until necropsied. Moribund animals will be sacrificed immediately by $CO_2$ overdose and necropsied. Tissues (as described in Section 8.5) will be preserved (including preservation of any macroscopic findings) for possible histology evaluation. A portion of the tail from each animal will be taken prior to necropsy and frozen in liquid nitrogen and stored at -60°C for possible future evaluation of the genotype. Organs will not be weighed at necropsy for interim deaths or moribund sacrificed animals. Unscheduled necropsies will be supervised by gross necropsy supervisor or pathologist whenever possible. Exposure study animals that die on test (found dead or moribund sacrifice) will not receive a full necropsy, but will only be evaluated by necropsy for evidence of gavage error.
As a result of the increased sensitivity of the Tg.rasH2 mice to carcinogenicity, it is expected that treatment with the positive control article will result in lethal tumors signs associated with target organ toxicity/carcinogenicity. Furthermore, Positive Control animals may be sacrificed as a group once those signs are evident in the majority of animals so as to avoid the loss of valuable tissues for histopathologic evaluation due to death and tissue autolysis.

The summary table of the study design given the following table:

**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<br>- | 5<br>- |
| 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.

## 3.1. Sponsor's analyses

### 3.1.1. Survival analysis

Survival data from the mouse study were analyzed by the sponsor using the same statistical methodologies that were used to analyze the survival data from the rat study.

**Sponsor's findings**: No significant dose related increased mortality was observed in either sex following

treatment with HPN-100 as compared to controls. All other mice survived until terminal sacrifice on Day 183 or 184. None of the deaths are considered to be related to treatment with the test article.

## 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 Positive Control | - | - | 1/25 | - | - | SPINE |
| Various Days 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 Between Day 43 and Day 114 | Positive Control 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

### 3.1.2. Tumor data analysis

Tumor data from the mouse study were also analyzed by the sponsor using the same statistical methodologies that were used to analyze the tumor data from the rat study.

**Sponsor's findings**: There were no test article-related gross necropsy findings. The incidence of single or multiple adenomas, carcinomas and that of combined incidence of all pulmonary tumors in the test article treated mice was comparable to the vehicle control and fell within the historical control range established at the testing laboratory. When the incidence of pulmonary tumors was compared between the vehicle and test article treated mice of both sexes there were no statistically significant differences either for incidence or for trend. This was also true for the incidence of splenic hemangiosarcomas in the test article treated groups compared to the vehicle control mice which also fell within the historical control range established at the testing laboratory. The combined incidence of all hemangiomas and hemangiosarcomas in multiple organs including spleen in vehicle as well as test article treated dose groups of both sexes also fell within the historical range established at the testing laboratory. And again, when the incidence of multiple organ hemangiomas and hemangiosarcomas including spleen was compared between the vehicle control and test article treated mice of both sexes, there were no statistically significant differences either for incidence or for trend. There were a variety of non-pulmonary, non-vascular neoplastic lesions (tumors) observed sporadically in other organs in this study as well as non-neoplastic lesions but all were background/spontaneous, incidental and/or their incidence was comparable across the dose groups. None of the neoplastic or non-neoplastic lesions observed in this study were considered to be test article related**.**
In conclusion, male and female Tg.rasH2 mice treated with HPN-100 by oral administration at 600 and 1000 mg/kg/day dose levels for up to 26 weeks showed no increased incidence of tumors in either sex as compared to water treated control animals. In contrast, the positive control Tg.rasH2 mice when treated with urethane showed the expected findings, tumors in lung and spleen and increased mortality. The summary of tumor analysis given in the following four tables (copied from sponsor's report):

**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

**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

**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

**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

### 3.2. Reviewer's analyses

To verify sponsor's analyses and to perform the additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Since there are five groups with three controls (two water controls and one positive control), the reviewing pharmacologist suggested to do three sets of analyses: Goups 1, 3, 4; Goups 2, 3, 4 and Groups combined water controls 1 and 2, 3, 4 (refer to the study design table on page 19).

#### 3.2.1. Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for all five groups of males and females, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for all the seven groups of males and females, respectively. Results for the tests for dose response relationship and homogeneity of survivals, are given in Tables 5A1, 5A2, 5A3, 5B1, 5B2 and 5B3 in the appendix for three sets of groupings in males and females, respectively.

**Reviewer's findings**: The test results showed no statistically significant dose-response relationship and statistically significant difference in mortality in either sex when compared with the combined water controls, water control 1 and water control 2, respectively. In addition, the test results showed no statistically significant difference in mortality when compared between the water control 1 and the water control 2 groups in males and females. There were some differences between reviewer's and sponsor's survival rates and the differences may be caused by the different dates of starting the terminal killing.

### 3.2.2. Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and pair-wise comparisons of the control group and treated groups are given in Table 6A1, 6A2, 6A3 and 6B1, 6B2, 6B3 in the appendix for three sets of groupings in males and females, respectively.

**Reviewer's findings**: It has been proposed that the 0.05 level of significance should be used in the test for positive trend and pair-wise comparisons for tumor increase in transgenic mouse studies. Based on the proposed significance level, none of the incidence of any tested tumor types in either sex was considered to have statistically significant positive dose relationship. Also based on the same proposed level of significance, none of the pair-wise comparisons of treated groups with the water control1, water control 2 and combined water controls was considered to be statistically significant in either sex for increased tumor incidence in the treated group.

## 4. Evaluation of validity of the designs of the mouse studies

### 4.1. Mouse Study

As having been noted, the tumor data analyses from mouse study showed no statistically significant dose-response relationship in any tested single tumor type. The criteria for determining if the high dose is close to MTD for 2-year rodent study may not be applied to transgenic mouse studies. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered by the pharm-tox reviewers.

## 5. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in Tg.rasH2 mice. The purpose of rat study was to assess the carcinogenic potential of HPN100, Glyceryl Tri (4-Phenylbutyrate), a triglyceride that, when metabolized, is used as a means for metabolic disposal of nitrogen waste in patients with nitrogen retention states, when administered orally via gavage to rats (65/sex/group) for up to 24 months. The purpose of mice study was to assess the carcinogenic potential of HPN-100 [(glyceryltri-(4-phenylbutyrate)] following once daily repeated oral administration (gavage) for 26 weeks (182-183 dosing days) in male and female hemizygous Tg.rasH2 mice (Main Study).

**Rat Study:** Two separate experiments were conducted, one in males and one in females. Male and female Crl:SD(CD) rats were assigned to 5 groups (65/sex/group) and received two controls (control Group 1 vehicle was deionized water (prepared on-site) and control Group 2 vehicle was corn oil), or at a dose level of 70, 210, or 650 mg/kg/day for males and 100, 300, and 900 mg/kg/day for females, respectively. The dose volumes were 0.59, 0.59, 0.06, 0.19, and 0.59 mL/kg for males and 0.82, 0.82, 0.09, 0.27, and 0.82 mL/kg for females in Groups 1, 2, 3, 4, and 5, respectively. The test results showed no statistically significant dose-response relationship and statistically significant difference in mortality in either sex when compared with the water control, corn-oil control and the combined control, respectively. In addition, the test results showed no statistically significant difference in mortality when compared between water control and corn-oil control in males and females. The following shows tumor analysis based on water and corn-oil controls, respectively:

For tumor analysis including water control and three treated groups:

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, the positive dose-response relationships in the incidence of Acinar cell adenoma, carcinoma and combined adenoma and

carcinoma from Pancreas and Follicular cell adenoma from Thyroid glands in both males and females, malignant schwannoma from skin and malignant lymphoma from systemic tumors in males, adenoma and combined adenoma and carcinoma from Adrenal cortex, Hepatocellular adenoma from Liver, Follicular cell carcinoma and combined adenoma and carcinoma from thyroid glands, polyp and combined polyp and sarcoma from Uterus and carcinoma from Zymbal's glands in females were considered to be statistically significant.

Also based on the criteria of Haseman, the pair-wise comparison of acinar cell adenoma, carcinoma and combined adenoma and carcinoma from pancreas and follicular cell adenoma from thyroid glands between the high dose group and water control were considered to be statistically significant in both females and males for increased tumor incidence.
In females only, the pair-wise comparison of combined adenoma and carcinoma in adrenal cortex, follicular cell carcinoma and combined follicular cell adenoma and carcinoma in thyroid glands, poly in uterus and combined polyp and sarcoma in uterus and carcinoma in zymbal's glands between the high dose group and water control were considered to be statistically significant in females for increased tumor incidence.

For tumor analysis including corn-oil control and three treated groups:

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, the positive dose-response relationships in the incidence of Acinar cell adenoma, carcinoma and combined adenoma and carcinoma from pancreas in both males and females, adenoma, combined adenoma and carcinoma in adrenal cortex, hepatocellular adenoma in liver, combined hibrtnomas in all soft tissues, benign hibernoma in soft tissue-TH, follicular cell adenoma and combined adenoma and carcinoma in thyroid glands, polyp and combined polyp and sarcoma from Uterus in females and carcinoma from adrenal cortex in males were considered to be statistically significant.

Also based on the criteria of Haseman, the pair-wise comparisons of acinar cell carcinoma and combined adenoma and carcinoma from pancreas between the high dose group and corn-oil control were considered to be statistically significant in both females and males for increased tumor incidence.

In males only, the pair-wise comparison of carcinoma in adrenal cortex between the high dose group and the corn-oil control was considered to be statistically significant for increased tumor incidence.

In females only, the pair-wise comparison of follicular cell adenoma and combined follicular cell adenoma and carcinoma in thyroid glands, acinar cell adenoma in pancreas, poly in uterus and combined polyp and sarcoma in uterus between the high dose group and corn-oil control were considered to be statistically significant for increased tumor incidence. In addition, the pair-wise comparison of malignant schwannoma in cervix between medium dose group and corn-oil control was considered to be statistically significant for increase tumor incidence.

**Mouse Study:** The objective of this study was to determine if there was an increased incidence of tumors in hemizygous Tg.rasH2 mice after administration of HPN-100 via oral gavage for 26 weeks. In the Main Study, there were four groups of 25 transgenic mice per sex: two vehicle control groups which were administered sterile water by oral gavage (Groups 1 and 2) and two test article treatment groups (Groups 3 and 4) were administered the test article (HPN-100) at dose levels of 600 and 1000 mg/kg/day via oral gavage, respectively. The positive control group (Group 5) consisted of 16 male and 15 female transgenic mice that were treated with urethane at 1000 mg/kg via intraperitoneal injection on Days 1, 3 and 5 for a total of 3 injections. The Exposure Study included 5 hybrid CByB6F1 (nontransgenic) mice per sex and dose in Groups

1 - 4 which were treated with either vehicle or test article in the same manner as the Main Study mice. The test results showed no statistically significant dose-response relationship and statistically significant difference in mortality in either sex when compared with the combined water controls, water control 1 and water control 2, respectively. In addition, the test results showed no statistically significant difference in mortality when compared between the water control 1 and the water control 2 groups in males and females. Tests showed no statistically significant positive dose response relationship and no the statistically significant difference in pair-wise comparisons in tumor incidence when compared to the control group in both females and males for all three sets of analysis (groups 1, 3, 4; groups 2, 3, 4; groups combined water controls, 3, 4). As having been noted, the tumor data analyses from mouse study showed no statistically significant dose-response relationship in any tested single tumor type. The criteria for determining if the high dose is close to MTD for 2-year rodent study may not be applied to transgenic mouse studies. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered by pharm-tox reviewers.

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## 6. Appendix

### Table 1A: Intercurrent Mortality Rate
### Male Rats

| Week | WATER CONTROL1 NO.OF DEATH | PERCENT | CORN-OIL CONTROL NO.OF DEATH | PERCENT | 75mg NO.OF DEATH | PERCENT | 210mg NO.OF DEATH | PERCENT | 650mG NO.OF DEATH | PERCENT |
|---|---|---|---|---|---|---|---|---|---|---|
| 0-52 | 5 | 7.7% | 7 | 10.8% | 7 | 10.8% | 11 | 16.9% | 10 | 15.4% |
| 53-78 | 11 | 24.6% | 9 | 24.6% | 17 | 36.9% | 11 | 33.9% | 9 | 29.2% |
| 79-92 | 7 | 35.4% | 21 | 35.4% | 11 | 53.9% | 14 | 55.4% | 14 | 50.8% |
| 93-103 | 16 | 60.0% | 11 | 60.0% | 12 | 72.3% | 10 | 70.8% | 14 | 72.3% |
| Term. Sac. | 26 | 100.0% | 17 | 100.0% | 18 | 100.0% | 19 | 100.0% | 18 | 100.0% |

### Table 1B: Intercurrent Mortality Rate
### Female Rats

| Week | WATER CONTROL NO.OF DEATH | PERCENT | CORN-OIL CONTROL NO.OF DEATH | PERCENT | 100mg NO.OF DEATH | PERCENT | 300mg NO.OF DEATH | PERCENT | 900mG NO.OF DEATH | PERCENT |
|---|---|---|---|---|---|---|---|---|---|---|
| 0-52 | 4 | 6.2% | 1 | 1.5% | 4 | 6.2% | 1 | 1.5% | 7 | 10.8% |
| 53-78 | 17 | 32.3% | 17 | 27.7% | 16 | 30.8% | 25 | 40.0% | 13 | 30.8% |
| 79-92 | 15 | 55.4% | 22 | 61.5% | 17 | 56.9% | 13 | 60.0% | 20 | 61.5% |
| 93-103 | 8 | 67.7% | 3 | 66.2% | 4 | 63.1% | 8 | 72.3% | 6 | 70.8% |
| Term. Sac. | 21 | 100.0% | 22 | 100.0% | 24 | 100.0% | 18 | 100.0% | 19 | 100.0% |

**Table 2A1: Intercurrent Mortality Comparison**
**Male Rats (Water Control)**

| Test | P-Value (across four groups) | P-Value (water control vs low) | P-Value (water control vs medium) | P-Value (water control vs high) |
|---|---|---|---|---|
| Dose Response | 0.3169 | 0.1280 | 0.1279 | 0.6777 |
| Homogeneity | 0.2058 | 0.0658 | 0.0789 | 0.6825 |

**Table 2A2: Intercurrent Mortality Comparison**
**Male Rats (Corn-oil Control)**

| Test | P-Value (across four groups) | P-Value (corn-oil control vs low) | P-Value (corn-oil control vs medium) | P-Value (corn-oil control vs high) |
|---|---|---|---|---|
| Dose Response | 0.8949 | 0.8962 | 0.9378 | 0.8427 |
| Homogeneity | 0.9998 | 0.9718 | 0.9613 | 0.9145 |

**Table 2A3: Intercurrent Mortality Comparison**
**Male Rats (Combined Controls)**

| Test | P-Value (across four groups) | P-Value (combined control vs low) | P-Value (control vs medium) | P-Value (control vs high) |
|---|---|---|---|---|
| Dose Response | 0.4974 | 0.3965 | 0.3818 | 0.4115 |
| Homogeneity | 0.6000 | 0.2787 | 0.3080 | 0.3030 |

**Table 2B1: Intercurrent Mortality Comparison**
**Female Rats (Water Control)**

| Test | P-Value (across four groups) | P-Value (water control vs low) | P-Value (water control vs medium) | P-Value (water control vs high) |
|---|---|---|---|---|
| Dose Response | 0.5707 | 0.7661 | 0.5525 | 0.6777 |
| Homogeneity | 0.7370 | 0.6207 | 0.6056 | 0.6825 |

**Table 2B2: Intercurrent Mortality Comparison**
**Female Rats (Corn-oil Control)**

| Test | P-Value (across four groups) | P-Value (corn-oil control vs low) | P-Value (corn-oil control vs medium) | P-Value (corn-oil control vs high) |
|---|---|---|---|---|
| Dose Response | 0.5707 | 0.7661 | 0.5525 | 0.6777 |
| Homogeneity | 0.7370 | 0.6207 | 0.6056 | 0.6825 |

**Table 2B3: Intercurrent Mortality Comparison**
**Female Rats (Combined Controls)**

| Test | P-Value (across four groups) | P-Value (combined controls vs low) | P-Value (control vs medium) | P-Value (control vs high) |
|---|---|---|---|---|
| Dose Response | 0.4890 | 0.7803 | 0.4169 | 0.5693 |
| Homogeneity | 0.6930 | 0.6233 | 0.4463 | 0.5552 |

**Table 3A1: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons**
**Male Rats (Water Control)**

| Organ Name | Tumor Name | 0 mg Cont N=65 | 70 mg Low N=65 | 210 mg Med N=65 | 650 mg High N=65 | P_Value Dos Resp | P_Value C vs. L | P_Value C vs. M | P_Value C vs. H |
|---|---|---|---|---|---|---|---|---|---|
| ADRENAL CORTEX | #B ADENOMA | 1 | 2 | 1 | 1 | 0.572 | 0.431 | 0.699 | 0.712 |
| | #M CARCINOMA | 1 | 1 | 4 | 5 | 0.027 | 0.699 | 0.122 | 0.070 |
| ADRENAL MEDULLA | #B PHEOCHROMOCYTOMA, COMPLEX | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #B PHEOCHROMOCYTOMA, | 3 | 3 | 3 | 3 | 0.450 | 0.571 | 0.571 | 0.584 |
| | #M PHEOCHROMOCYTOMA, | 1 | 1 | 2 | 2 | 0.243 | 0.699 | 0.422 | 0.441 |
| | PHEOCHROMOCYTOMA_B+M | 5 | 4 | 5 | 5 | 0.396 | 0.658 | 0.509 | 0.542 |
| ADRENAL_CORTEX | ADENOMA+CARCINOMA | 2 | 3 | 5 | 6 | 0.060 | 0.413 | 0.141 | 0.088 |
| BONE | #M OSTEOSARCOMA | 0 | 0 | 1 | 0 | 0.479 | . | 0.448 | . |
| BRAIN | #B GRANULAR CELL TUM | 1 | 4 | 0 | 1 | 0.766 | 0.122 | 1.000 | 0.712 |
| | #B SCHWANNOMA, BENIG | 0 | 1 | 0 | 0 | 0.714 | 0.455 | . | . |
| | #M ASTROCYTOMA, MALI | 0 | 2 | 2 | 3 | 0.087 | 0.209 | 0.204 | 0.098 |
| DUODENUM | #M LEIOMYOSARCOMA | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.461 |
| EYES/OPTIC N. | #M MELANOMA, AMELANO | 0 | 0 | 0 | 2 | 0.059 | . | . | 0.209 |
| HARDERIAN GLAND | #M CARCINOMA, SQUAMO | 0 | 0 | 1 | 0 | 0.479 | . | 0.448 | . |
| HEART | #M MESOTHELIOMA, ATR | 0 | 1 | 0 | 0 | 0.713 | 0.448 | . | . |
| KIDNEYS | #B LIPOMA | 0 | 0 | 2 | 0 | 0.485 | . | 0.198 | . |
| | #B ONCOCYTOMA | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.461 |
| | #M OSTEOSARCOMA | 0 | 0 | 1 | 0 | 0.479 | . | 0.448 | . |
| LIVER | #B ADENOMA, HEPATOCE | 0 | 1 | 3 | 1 | 0.358 | 0.455 | 0.086 | 0.461 |
| | #B CHOLANGIOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #M CARCINOMA, HEPATO | 1 | 6 | 1 | 0 | 0.964 | 0.035 | 0.699 | 1.000 |
| LUNGS | #M CARCINOMA, BRONCH | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.461 |
| PANCREAS | #B ADENOMA, ACINAR C | 1 | 0 | 3 | 8 | 0.000 | 1.000 | 0.243 | 0.008 |
| | #B ADENOMA, ISLET CE | 3 | 3 | 2 | 0 | 0.963 | 0.547 | 0.740 | 1.000 |
| | #M CARCINOMA, ACINAR | 0 | 0 | 0 | 6 | 0.000 | . | . | 0.008 |
| | #M CARCINOMA, ISLET | 4 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | ACINAR_CELL_ADENOMA+ | 1 | 0 | 3 | 14 | 0.000 | 1.000 | 0.243 | 0.000 |
| | ISLET_CELL_ADENOMA+C | 7 | 3 | 2 | 0 | 0.998 | 0.901 | 0.963 | 1.000 |
| PARATHYROIDS | #B ADENOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |

**Table 3A1 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Water Control)**

| Organ Name | Tumor Name | 0 mg Cont N=65 | 70 mg Low N=65 | 210 mg Med N=65 | 650 mg High N=65 | P_Value Dos Resp | P_Value C vs. L | P_Value C vs. M | P_Value C vs. H |
|---|---|---|---|---|---|---|---|---|---|
| PITUITARY | #B ADENOMA, PARS DIS | 43 | 34 | 27 | 24 | 0.996 | 0.859 | 0.979 | 0.998 |
| | #B ADENOMA, PARS INT | 0 | 1 | 0 | 0 | 0.713 | 0.448 | . | . |
| | #M CARCINOMA, PARS D | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.461 |
| | PARS_DISTALIS+INTERM | 43 | 35 | 27 | 25 | 0.994 | 0.803 | 0.979 | 0.997 |
| PREPUTIAL GLAND | #B ADENOMA | 0 | 1 | 0 | 0 | 0.713 | 0.448 | . | . |
| PROSTATE | #M ADENOCARCINOMA | 0 | 2 | 0 | 0 | 0.783 | 0.204 | . | . |
| | #M LEIOMYOSARCOMA | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.461 |
| SEMINAL VESICLE | #M ADENOCARCINOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| SKELETAL MUSCLE | #M SARCOMA, UNDIFFER | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #M SCHWANNOMA, MALIG | 2 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| SKIN | #B ADENOMA, SEBACEOU | 0 | 1 | 2 | 1 | 0.303 | 0.448 | 0.198 | 0.461 |
| | #B FIBROMA | 3 | 4 | 5 | 3 | 0.531 | 0.398 | 0.247 | 0.584 |
| | #B KERATOACANTHOMA, | 2 | 7 | 4 | 6 | 0.187 | 0.052 | 0.245 | 0.095 |
| | #B LIPOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #B NEURAL CREST TUMO | 0 | 0 | 1 | 0 | 0.479 | . | 0.448 | . |
| | #B PAPILLOMA, SQUAMO | 0 | 2 | 1 | 1 | 0.387 | 0.198 | 0.448 | 0.461 |
| | #B TRICHOEPITHELIOMA | 0 | 1 | 0 | 0 | 0.713 | 0.448 | . | . |
| | #M CARCINOMA, BASAL | 0 | 1 | 1 | 2 | 0.106 | 0.448 | 0.448 | 0.209 |
| | #M CARCINOMA, SQUAMO | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #M FIBROSARCOMA | 2 | 1 | 1 | 2 | 0.369 | 0.832 | 0.832 | 0.622 |
| | #M MYXOSARCOMA | 1 | 0 | 0 | 1 | 0.430 | 1.000 | 1.000 | 0.706 |
| | #M OSTEOSARCOMA | 1 | 1 | 0 | 1 | 0.512 | 0.699 | 1.000 | 0.712 |
| | #M SCHWANNOMA, MALIG | 0 | 0 | 1 | 3 | 0.018 | . | 0.448 | 0.102 |
| | FIBROMA+FIBROSARCOMA | 5 | 5 | 6 | 5 | 0.433 | 0.495 | 0.340 | 0.512 |
| | SQUAMOUS_CELL_PAPILO | 1 | 2 | 1 | 1 | 0.575 | 0.422 | 0.699 | 0.712 |
| SOFT TISSUE- AB | #B HIBERNOMA, BENIGN | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.461 |
| SOFT TISSUE- TH | #B HIBERNOMA, BENIGN | 0 | 1 | 0 | 0 | 0.713 | 0.448 | . | . |
| | #M HIBERNOMA, MALIGN | 3 | 0 | 1 | 5 | 0.045 | 1.000 | 0.909 | 0.298 |
| SOFT_TISSUE_TH | HIBERNOMAS | 3 | 1 | 1 | 5 | 0.074 | 0.909 | 0.909 | 0.298 |
| SOFT_TISSUE | HIBERNOMAS | 3 | 1 | 1 | 6 | 0.032 | 0.909 | 0.909 | 0.192 |
| STOMACH, GLAN | #M LEIOMYOSARCOMA | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.461 |
| STOMACH, NON | #M CARCINOMA, SQUAMO | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.461 |
| SYSTEMIC TUMORS | #M FIBROUS HISTIOCYT | 2 | 0 | 0 | 2 | 0.250 | 1.000 | 1.000 | 0.622 |
| | #M HEMANGIOSARCOMA | 1 | 0 | 1 | 0 | 0.727 | 1.000 | 0.693 | 1.000 |
| | #M LYMPHOMA, MALIGNA | 0 | 0 | 1 | 3 | 0.018 | . | 0.448 | 0.102 |

**Table 3A1 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Water Control)**

| Organ Name | Tumor Name | 0 mg Cont N=65 | 70 mg Low N=65 | 210 mg Med N=65 | 650 mg High N=65 | P_Value Dos Resp | P_Value C vs. L | P_Value C vs. M | P_Value C vs. H |
|---|---|---|---|---|---|---|---|---|---|
| SYSTEMIC TUMORS | #M MESOTHELIOMA, MAL | 1 | 0 | 1 | 0 | 0.730 | 1.000 | 0.699 | 1.000 |
| | #M SARCOMA, HISTIOCY | 2 | 2 | 2 | 5 | 0.072 | 0.610 | 0.610 | 0.174 |
| SYSTEMIC_TUMORS | HAEMANGIOSARCOMA+HAE | 1 | 0 | 1 | 0 | 0.727 | 1.000 | 0.693 | 1.000 |
| TAIL | #B KERATOACANTHOMA, | 1 | 0 | 0 | 1 | 0.432 | 1.000 | 1.000 | 0.712 |
| | #B NEURAL CREST TUMO | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| TESTES | #B INTERSTITIAL CELL | 1 | 1 | 3 | 2 | 0.269 | 0.699 | 0.234 | 0.441 |
| THYMUS | #B THYMOMA, BENIGN | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.461 |
| | #M CARCINOMA, SQUAMO | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.461 |
| | #M THYMOMA, MALIGNAN | 0 | 0 | 1 | 0 | 0.479 | . | 0.448 | . |
| | THYMOMA_B+M | 0 | 0 | 1 | 1 | 0.175 | . | 0.448 | 0.461 |
| THYROID GLANDS | #B ADENOMA, C-CELL | 5 | 3 | 7 | 3 | 0.666 | 0.799 | 0.241 | 0.819 |
| | #B ADENOMA, FOLLICUL | 0 | 3 | 3 | 6 | 0.014 | 0.086 | 0.090 | 0.008 |
| | #M CARCINOMA, C-CELL | 3 | 0 | 0 | 1 | 0.694 | 1.000 | 1.000 | 0.920 |
| | #M CARCINOMA, FOLLIC | 2 | 1 | 1 | 1 | 0.648 | 0.837 | 0.837 | 0.848 |
| THYROID_GLANDS | C_CELL_ADENOMA+CARCI | 8 | 3 | 7 | 4 | 0.727 | 0.946 | 0.531 | 0.899 |
| | FOLLICULAR_CELL_ADEN | 2 | 4 | 4 | 7 | 0.041 | 0.256 | 0.256 | 0.052 |
| TONGUE | #M CARCINOMA, SQUAMO | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.461 |
| ZYMBAL'S GLANDS | #M CARCINOMA | 1 | 2 | 5 | 5 | 0.054 | 0.431 | 0.065 | 0.074 |

**Table 3A2: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons**
**Male Rats (Corn-oil Control)**

| Organ Name | Tumor Name | 0 mg Cont N=65 | 70 mg Low N=65 | 210 mg Med N=65 | 650 mg High N=65 | P_Value Dos Resp | P_Value C vs. L | P_Value C vs. M | P_Value C vs. H |
|---|---|---|---|---|---|---|---|---|---|
| ADRENAL CORTEX | #B ADENOMA | 1 | 2 | 1 | 1 | 0.613 | 0.491 | 0.741 | 0.753 |
| | #M CARCINOMA | 0 | 1 | 4 | 5 | 0.017 | 0.494 | 0.055 | 0.029 |
| ADRENAL MEDULLA | #B PHEOCHROMOCYTOMA, | 6 | 3 | 3 | 3 | 0.775 | 0.917 | 0.917 | 0.923 |
| | #M PHEOCHROMOCYTOMA, | 1 | 1 | 2 | 2 | 0.274 | 0.741 | 0.481 | 0.500 |
| | PHEOCHROMOCYTOMA_B+M | 7 | 4 | 5 | 5 | 0.628 | 0.887 | 0.801 | 0.825 |
| ADRENAL_CORTEX | ADENOMA+CARCINOMA | 1 | 3 | 5 | 6 | 0.047 | 0.298 | 0.089 | 0.054 |
| ALL_SITES | HAEMANGIOMAS | 1 | 1 | 0 | 1 | 0.541 | 0.741 | 1.000 | 0.753 |
| AORTA | #M HIBERNOMA, MALIGN | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| BONE | #M OSTEOSARCOMA | 0 | 0 | 1 | 0 | 0.503 | . | 0.494 | . |
| BRAIN | #B GRANULAR CELL TUM | 1 | 4 | 0 | 1 | 0.799 | 0.172 | 1.000 | 0.759 |
| | #B SCHWANNOMA, BENIG | 0 | 1 | 0 | 0 | 0.750 | 0.500 | . | . |
| | #M ASTROCYTOMA, MALI | 2 | 2 | 2 | 3 | 0.307 | 0.692 | 0.683 | 0.512 |
| DUODENUM | #M LEIOMYOSARCOMA | 0 | 0 | 0 | 1 | 0.258 | . | . | 0.506 |
| EYES/OPTIC N. | #M MELANOMA, AMELANO | 0 | 0 | 0 | 2 | 0.065 | . | . | 0.253 |
| HARDERIAN GLAND | #M CARCINOMA, SQUAMO | 0 | 0 | 1 | 0 | 0.503 | . | 0.494 | . |
| HEART | #M MESOTHELIOMA, ATR | 0 | 1 | 0 | 0 | 0.748 | 0.494 | . | . |
| KIDNEYS | #B ADENOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #B LIPOMA | 0 | 0 | 2 | 0 | 0.509 | . | 0.241 | . |
| | #B ONCOCYTOMA | 0 | 0 | 0 | 1 | 0.258 | . | . | 0.506 |
| | #M OSTEOSARCOMA | 0 | 0 | 1 | 0 | 0.503 | . | 0.494 | . |
| LIVER | #B ADENOMA, HEPATOCE | 1 | 1 | 3 | 1 | 0.530 | 0.747 | 0.289 | 0.753 |
| | #M CARCINOMA, HEPATO | 2 | 6 | 1 | 0 | 0.988 | 0.132 | 0.870 | 1.000 |
| LUNGS | #M CARCINOMA, BRONCH | 0 | 0 | 0 | 1 | 0.258 | . | . | 0.506 |
| PANCREAS | #B ADENOMA, ACINAR C | 1 | 0 | 3 | 8 | 0.001 | 1.000 | 0.308 | 0.016 |
| | #B ADENOMA, ISLET CE | 4 | 3 | 2 | 0 | 0.988 | 0.763 | 0.888 | 1.000 |
| | #M CARCINOMA, ACINAR | 0 | 0 | 0 | 6 | 0.000 | . | . | 0.015 |
| | #M CARCINOMA, ISLET | 2 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | ACINAR_CELL_ADENOMA+ | 1 | 0 | 3 | 14 | 0.000 | 1.000 | 0.308 | 0.000 |
| | ISLET_CELL_ADENOMA+C | 6 | 3 | 2 | 0 | 0.998 | 0.911 | 0.967 | 1.000 |

**Table 3A2 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Corn-oil Control)**

| Organ Name | Tumor Name | 0 mg Cont N=65 | 70 mg Low N=65 | 210 mg Med N=65 | 650 mg High N=65 | P_Value Dos Resp | P_Value C vs. L | P_Value C vs. M | P_Value C vs. H |
|---|---|---|---|---|---|---|---|---|---|
| PARATHYROIDS | #B ADENOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| PITUITARY | #B ADENOMA, PARS DIS | 40 | 34 | 27 | 24 | 0.995 | 0.819 | 0.969 | 0.997 |
| | #B ADENOMA, PARS INT | 0 | 1 | 0 | 0 | 0.748 | 0.494 | . | . |
| | #M CARCINOMA, PARS D | 1 | 0 | 0 | 1 | 0.450 | 1.000 | 1.000 | 0.759 |
| | PARS_DISTALIS+INTERM | 41 | 35 | 27 | 25 | 0.994 | 0.820 | 0.981 | 0.997 |
| PREPUTIAL GLAND | #B ADENOMA | 0 | 1 | 0 | 0 | 0.748 | 0.494 | . | . |
| PROSTATE | #M ADENOCARCINOMA | 0 | 2 | 0 | 0 | 0.813 | 0.247 | . | . |
| | #M LEIOMYOSARCOMA | 0 | 0 | 0 | 1 | 0.258 | . | . | 0.506 |
| SKIN | #B ADENOMA, SEBACEOU | 0 | 1 | 2 | 1 | 0.335 | 0.494 | 0.241 | 0.506 |
| | #B FIBROMA | 1 | 4 | 5 | 3 | 0.400 | 0.179 | 0.095 | 0.317 |
| | #B KERATOACANTHOMA, | 5 | 7 | 4 | 6 | 0.460 | 0.378 | 0.720 | 0.500 |
| | #B NEURAL CREST TUMO | 0 | 0 | 1 | 0 | 0.503 | . | 0.494 | . |
| | #B PAPILLOMA, SQUAMO | 0 | 2 | 1 | 1 | 0.428 | 0.241 | 0.494 | 0.506 |
| | #B TRICHOEPITHELIOMA | 0 | 1 | 0 | 0 | 0.748 | 0.494 | . | . |
| | #M CARCINOMA, BASAL | 0 | 1 | 1 | 2 | 0.125 | 0.494 | 0.494 | 0.253 |
| | #M FIBROSARCOMA | 0 | 1 | 1 | 2 | 0.125 | 0.494 | 0.494 | 0.253 |
| | #M MYXOSARCOMA | 2 | 0 | 0 | 1 | 0.591 | 1.000 | 1.000 | 0.880 |
| | #M OSTEOSARCOMA | 1 | 1 | 0 | 1 | 0.545 | 0.747 | 1.000 | 0.759 |
| | #M SCHWANNOMA, MALIG | 2 | 0 | 1 | 3 | 0.152 | 1.000 | 0.870 | 0.523 |
| | FIBROMA+FIBROSARCOMA | 1 | 5 | 6 | 5 | 0.199 | 0.100 | 0.050 | 0.106 |
| | SQUAMOUS_CELL_PAPILO | 0 | 2 | 1 | 1 | 0.428 | 0.241 | 0.494 | 0.506 |
| SOFT TISSUE, OR | #M OSTEOSARCOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| SOFT TISSUE- AB | #B HIBERNOMA, BENIGN | 0 | 0 | 0 | 1 | 0.258 | . | . | 0.506 |
| SOFT TISSUE- TH | #B HIBERNOMA, BENIGN | 1 | 1 | 0 | 0 | 0.936 | 0.741 | 1.000 | 1.000 |
| | #M HIBERNOMA, MALIGN | 1 | 0 | 1 | 5 | 0.010 | 1.000 | 0.741 | 0.118 |
| SOFT_TISSUE_TH | HIBERNOMAS | 2 | 1 | 1 | 5 | 0.048 | 0.865 | 0.865 | 0.236 |
| SOFT_TISSUE | HIBERNOMAS | 2 | 1 | 1 | 6 | 0.019 | 0.865 | 0.865 | 0.148 |
| STOMACH, GLAN | #M LEIOMYOSARCOMA | 0 | 0 | 0 | 1 | 0.258 | . | . | 0.506 |
| STOMACH, NON | #M CARCINOMA, SQUAMO | 0 | 0 | 0 | 1 | 0.258 | . | . | 0.506 |
| SYSTEMIC TUMORS | #B HEMANGIOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #B MESOTHELIOMA, BEN | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #M FIBROUS HISTIOCYT | 0 | 0 | 0 | 2 | 0.065 | . | . | 0.253 |
| | #M HEMANGIOSARCOMA | 0 | 0 | 1 | 0 | 0.503 | . | 0.494 | . |
| | #M LYMPHOMA, MALIGNA | 2 | 0 | 1 | 3 | 0.152 | 1.000 | 0.870 | 0.523 |
| | #M MESOTHELIOMA, MAL | 0 | 0 | 1 | 0 | 0.503 | . | 0.494 | . |

**Table 3A2 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Corn-oil Control)**

| Organ Name | Tumor Name | 0 mg Cont N=65 | 70 mg Low N=65 | 210 mg Med N=65 | 650 mg High N=65 | P_Value Dos Resp | P_Value C vs. L | P_Value C vs. M | P_Value C vs. H |
|---|---|---|---|---|---|---|---|---|---|
| SYSTEMIC TUMORS | #M SARCOMA, HISTIOCY | 1 | 2 | 2 | 5 | 0.047 | 0.481 | 0.481 | 0.112 |
| SYSTEMIC_TUMORS | HAEMANGIOSARCOMA+HAE | 1 | 0 | 1 | 0 | 0.755 | 1.000 | 0.747 | 1.000 |
| TAIL | #B KERATOACANTHOMA, | 0 | 0 | 0 | 1 | 0.258 | . | . | 0.506 |
| TESTES | #B INTERSTITIAL CELL | 2 | 1 | 3 | 2 | 0.435 | 0.875 | 0.488 | 0.702 |
| | #B SEMINOMA, BENIGN | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| THYMUS | #B THYMOMA, BENIGN | 0 | 0 | 0 | 1 | 0.258 | . | . | 0.506 |
| | #M CARCINOMA, SQUAMO | 0 | 0 | 0 | 1 | 0.258 | . | . | 0.506 |
| | #M THYMOMA, MALIGNAN | 0 | 0 | 1 | 0 | 0.503 | . | 0.494 | . |
| | THYMOMA_B+M | 0 | 0 | 1 | 1 | 0.193 | . | 0.494 | 0.506 |
| THYROID GLANDS | #B ADENOMA, C-CELL | 7 | 3 | 7 | 3 | 0.837 | 0.943 | 0.536 | 0.952 |
| | #B ADENOMA, FOLLICUL | 1 | 3 | 3 | 6 | 0.038 | 0.289 | 0.298 | 0.058 |
| | #M CARCINOMA, C-CELL | 0 | 0 | 0 | 1 | 0.258 | . | . | 0.506 |
| | #M CARCINOMA, FOLLIC | 2 | 1 | 1 | 1 | 0.682 | 0.870 | 0.870 | 0.880 |
| THYROID_GLANDS | C_CELL_ADENOMA+CARCI | 7 | 3 | 7 | 4 | 0.715 | 0.943 | 0.536 | 0.895 |
| | FOLLICULAR_CELL_ADEN | 3 | 4 | 4 | 7 | 0.091 | 0.486 | 0.486 | 0.166 |
| TONGUE | #M CARCINOMA, SQUAMO | 0 | 0 | 0 | 1 | 0.258 | . | . | 0.506 |
| URINARY BLADDER | #B PAPILLOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| ZYMBAL'S GLANDS | #M CARCINOMA | 1 | 2 | 5 | 5 | 0.071 | 0.491 | 0.095 | 0.106 |

**Table 3A3: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons**
**Male Rats (Combined Controls)**

| Organ Name | Tumor Name | 0 mg Cont N=65 | 70 mg Low N=65 | 210 mg Med N=65 | 650 mg High N=65 | P_Value Dos Resp | P_Value C vs. L | P_Value C vs. M | P_Value C vs. H |
|---|---|---|---|---|---|---|---|---|---|
| ADRENAL CORTEX | #B ADENOMA | 2 | 2 | 1 | 1 | 0.528 | 0.366 | 0.667 | 0.683 |
| | #M CARCINOMA | 1 | 1 | 4 | 5 | 0.007 | 0.518 | 0.030 | 0.012 |
| ADRENAL MEDULLA | #B PHEOCHROMOCYTOMA, COMPLEX | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #B PHEOCHROMOCYTOMA, | 9 | 3 | 3 | 3 | 0.665 | 0.778 | 0.778 | 0.790 |
| | #M PHEOCHROMOCYTOMA, | 2 | 1 | 2 | 2 | 0.210 | 0.667 | 0.356 | 0.375 |
| | PHEOCHROMOCYTOMA_B+M | 12 | 4 | 5 | 5 | 0.543 | 0.792 | 0.656 | 0.686 |
| ADRENAL_CORTEX | ADENOMA+CARCINOMA | 3 | 3 | 5 | 6 | 0.021 | 0.271 | 0.056 | 0.028 |
| ALL_SITES | HAEMANGIOMAS | 1 | 1 | 0 | 1 | 0.376 | 0.518 | 1.000 | 0.533 |
| AORTA | #M HIBERNOMA, MALIGN | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| BONE | #M OSTEOSARCOMA | 0 | 0 | 1 | 0 | 0.387 | . | 0.307 | . |
| BRAIN | #B GRANULAR CELL TUM | 2 | 4 | 0 | 1 | 0.707 | 0.071 | 1.000 | 0.686 |
| | #B SCHWANNOMA, BENIG | 0 | 1 | 0 | 0 | 0.577 | 0.313 | . | . |
| | #M ASTROCYTOMA, MALI | 2 | 2 | 2 | 3 | 0.123 | 0.375 | 0.366 | 0.187 |
| DUODENUM | #M LEIOMYOSARCOMA | 0 | 0 | 0 | 1 | 0.198 | . | . | 0.318 |
| EYES/OPTIC N. | #M MELANOMA, AMELANO | 0 | 0 | 0 | 2 | 0.039 | . | . | 0.099 |
| HARDERIAN GLAND | #M CARCINOMA, SQUAMO | 0 | 0 | 1 | 0 | 0.387 | . | 0.307 | . |
| HEART | #M MESOTHELIOMA, ATR | 0 | 1 | 0 | 0 | 0.575 | 0.307 | . | . |
| KIDNEYS | #B ADENOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #B LIPOMA | 0 | 0 | 2 | 0 | 0.392 | . | 0.093 | . |
| | #B ONCOCYTOMA | 0 | 0 | 0 | 1 | 0.198 | . | . | 0.318 |
| | #M OSTEOSARCOMA | 0 | 0 | 1 | 0 | 0.387 | . | 0.307 | . |
| LIVER | #B ADENOMA, HEPATOCE | 1 | 1 | 3 | 1 | 0.336 | 0.526 | 0.084 | 0.533 |
| | #B CHOLANGIOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #M CARCINOMA, HEPATO | 3 | 6 | 1 | 0 | 0.954 | 0.028 | 0.771 | 1.000 |
| LUNGS | #M CARCINOMA, BRONCH | 0 | 0 | 0 | 1 | 0.198 | . | . | 0.318 |
| PANCREAS | #B ADENOMA, ACINAR C | 2 | 0 | 3 | 8 | 0.000 | 1.000 | 0.176 | 0.002 |
| | #B ADENOMA, ISLET CE | 7 | 3 | 2 | 0 | 0.982 | 0.631 | 0.818 | 1.000 |
| | #M CARCINOMA, ACINAR | 0 | 0 | 0 | 6 | 0.000 | . | . | 0.001 |
| | #M CARCINOMA, ISLET | 6 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | ACINAR_CELL_ADENOMA+ | 2 | 0 | 3 | 14 | 0.000 | 1.000 | 0.176 | 0.000 |

**Table 3A3 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons**
**Male Rats (Combined Controls)**

| Organ Name | Tumor Name | 0 mg Cont N=65 | 70 mg Low N=65 | 210 mg Med N=65 | 650 mg High N=65 | P_Value Dos Resp | P_Value C vs. L | P_Value C vs. M | P_Value C vs. H |
|---|---|---|---|---|---|---|---|---|---|
| PANCREAS | ISLET_CELL_ADENOMA+C | 13 | 3 | 2 | 0 | 0.999 | 0.915 | 0.972 | 1.000 |
| PARATHYROIDS | #B ADENOMA | 2 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| PITUITARY | #B ADENOMA, PARS DIS | 83 | 34 | 27 | 24 | 0.999 | 0.862 | 0.985 | 0.999 |
| | #B ADENOMA, PARS INT | 0 | 1 | 0 | 0 | 0.575 | 0.307 | . | . |
| | #M CARCINOMA, PARS D | 1 | 0 | 0 | 1 | 0.358 | 1.000 | 1.000 | 0.536 |
| | PARS_DISTALIS+INTERM | 84 | 35 | 27 | 25 | 0.998 | 0.832 | 0.990 | 0.999 |
| PREPUTIAL GLAND | #B ADENOMA | 0 | 1 | 0 | 0 | 0.575 | 0.307 | . | . |
| PROSTATE | #M ADENOCARCINOMA | 0 | 2 | 0 | 0 | 0.659 | 0.096 | . | . |
| | #M LEIOMYOSARCOMA | 0 | 0 | 0 | 1 | 0.198 | . | . | 0.318 |
| SEMINAL VESICLE | #M ADENOCARCINOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| SKELETAL MUSCLE | #M SARCOMA, UNDIFFER | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #M SCHWANNOMA, MALIG | 2 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| SKIN | #B ADENOMA, SEBACEOU | 0 | 1 | 2 | 1 | 0.197 | 0.307 | 0.093 | 0.318 |
| | #B FIBROMA | 4 | 4 | 5 | 3 | 0.333 | 0.206 | 0.097 | 0.387 |
| | #B KERATOACANTHOMA, | 7 | 7 | 4 | 6 | 0.217 | 0.109 | 0.438 | 0.194 |
| | #B LIPOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #B NEURAL CREST TUMO | 0 | 0 | 1 | 0 | 0.387 | . | 0.307 | . |
| | #B PAPILLOMA, SQUAMO | 0 | 2 | 1 | 1 | 0.249 | 0.093 | 0.307 | 0.318 |
| | #B TRICHOEPITHELIOMA | 0 | 1 | 0 | 0 | 0.575 | 0.307 | . | . |
| | #M CARCINOMA, BASAL | 0 | 1 | 1 | 2 | 0.050 | 0.307 | 0.307 | 0.099 |
| | #M CARCINOMA, SQUAMO | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #M FIBROSARCOMA | 2 | 1 | 1 | 2 | 0.220 | 0.667 | 0.667 | 0.375 |
| | #M MYXOSARCOMA | 3 | 0 | 0 | 1 | 0.593 | 1.000 | 1.000 | 0.785 |
| | #M OSTEOSARCOMA | 2 | 1 | 0 | 1 | 0.530 | 0.671 | 1.000 | 0.686 |
| | #M SCHWANNOMA, MALIG | 2 | 0 | 1 | 3 | 0.065 | 1.000 | 0.667 | 0.195 |
| | FIBROMA+FIBROSARCOMA | 6 | 5 | 6 | 5 | 0.208 | 0.224 | 0.114 | 0.237 |
| | SQUAMOUS_CELL_PAPILO | 1 | 2 | 1 | 1 | 0.395 | 0.223 | 0.522 | 0.536 |
| SOFT TISSUE, OR | #M OSTEOSARCOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| SOFT TISSUE- AB | #B HIBERNOMA, BENIGN | 0 | 0 | 0 | 1 | 0.198 | . | . | 0.318 |
| SOFT TISSUE- TH | #B HIBERNOMA, BENIGN | 1 | 1 | 0 | 0 | 0.818 | 0.518 | 1.000 | 1.000 |
| | #M HIBERNOMA, MALIGN | 4 | 0 | 1 | 5 | 0.030 | 1.000 | 0.840 | 0.129 |
| SOFT_TISSUE_TH | HIBERNOMAS | 5 | 1 | 1 | 5 | 0.072 | 0.888 | 0.888 | 0.190 |
| SOFT_TISSUE | HIBERNOMAS | 5 | 1 | 1 | 6 | 0.0292 | 0.882 | 0.882 | 0.102 |

**Table 3A3 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Combined Controls)**

| Organ Name | Tumor Name | 0 mg Cont N=65 | 70 mg Low N=65 | 210 mg Med N=65 | 650 mg High N=65 | P_Value Dos Resp | P_Value C vs. L | P_Value C vs. M | P_Value C vs. H |
|---|---|---|---|---|---|---|---|---|---|
| STOMACH, GLAN | #M LEIOMYOSARCOMA | 0 | 0 | 0 | 1 | 0.198 | . | . | 0.318 |
| STOMACH, NON | #M CARCINOMA, SQUAMO | 0 | 0 | 0 | 1 | 0.198 | . | . | 0.318 |
| SYSTEMIC TUMORS | #B HEMANGIOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #B MESOTHELIOMA, BEN | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #M FIBROUS HISTIOCYT | 2 | 0 | 0 | 2 | 0.175 | 1.000 | 1.000 | 0.375 |
| | #M HEMANGIOSARCOMA | 1 | 0 | 1 | 0 | 0.622 | 1.000 | 0.518 | 1.000 |
| | #M LYMPHOMA, MALIGNA | 2 | 0 | 1 | 3 | 0.065 | 1.000 | 0.667 | 0.195 |
| | #M MESOTHELIOMA, MAL | 1 | 0 | 1 | 0 | 0.622 | 1.000 | 0.518 | 1.000 |
| | #M SARCOMA, HISTIOCY | 3 | 2 | 2 | 5 | 0.039 | 0.483 | 0.483 | 0.074 |
| SYSTEMIC_TUMORS | HAEMANGIOSARCOMA+HAE | 2 | 0 | 1 | 0 | 0.775 | 1.000 | 0.667 | 1.000 |
| TAIL | #B KERATOACANTHOMA, | 1 | 0 | 0 | 1 | 0.358 | 1.000 | 1.000 | 0.536 |
| | #B NEURAL CREST TUMO | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| TESTES | #B INTERSTITIAL CELL | 3 | 1 | 3 | 2 | 0.307 | 0.774 | 0.265 | 0.510 |
| | #B SEMINOMA, BENIGN | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| THYMUS | #B THYMOMA, BENIGN | 0 | 0 | 0 | 1 | 0.198 | . | . | 0.318 |
| | #M CARCINOMA, SQUAMO | 0 | 0 | 0 | 1 | 0.198 | . | . | 0.318 |
| | #M THYMOMA, MALIGNAN | 0 | 0 | 1 | 0 | 0.387 | . | 0.307 | . |
| | THYMOMA_B+M | 0 | 0 | 1 | 1 | 0.114 | . | 0.307 | 0.318 |
| THYROID GLANDS | #B ADENOMA, C-CELL | 12 | 3 | 7 | 3 | 0.773 | 0.893 | 0.317 | 0.908 |
| | #B ADENOMA, FOLLICUL | 1 | 3 | 3 | 6 | 0.006 | 0.084 | 0.088 | 0.004 |
| | #M CARCINOMA, C-CELL | 3 | 0 | 0 | 1 | 0.593 | 1.000 | 1.000 | 0.785 |
| | #M CARCINOMA, FOLLIC | 4 | 1 | 1 | 1 | 0.704 | 0.843 | 0.843 | 0.855 |
| THYROID_GLANDS | C_CELL_ADENOMA+CARCI | 15 | 3 | 7 | 4 | 0.777 | 0.955 | 0.501 | 0.909 |
| | FOLLICULAR_CELL_ADEN | 5 | 4 | 4 | 7 | 0.034 | 0.289 | 0.289 | 0.046 |
| TONGUE | #M CARCINOMA, SQUAMO | 0 | 0 | 0 | 1 | 0.198 | . | . | 0.318 |
| URINARY BLADDER | #B PAPILLOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| ZYMBAL'S GLANDS | #M CARCINOMA | 2 | 2 | 5 | 5 | 0.024 | 0.366 | 0.029 | 0.034 |

**Table 3B1: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons**
**Female Rats (Water Control)**

| Organ Name | Tumor Name | 0 mg 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 |
|---|---|---|---|---|---|---|---|---|---|
| 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 MEDULLA | #B PHEOCHROMOCYTOMA, | 1 | 0 | 2 | 3 | 0.061 | 1.000 | 0.482 | 0.290 |
| | #M OSTEOSARCOMA | 0 | 0 | 0 | 1 | 0.247 | . | . | 0.494 |
| | #M PHEOCHROMOCYTOMA, | 0 | 0 | 0 | 2 | 0.060 | . | . | 0.241 |
| 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 |
| BRAIN | #B GRANULAR CELL TUM | 0 | 1 | 0 | 0 | 0.746 | 0.506 | . | . |
| | #M ASTROCYTOMA, MALI | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| CERVIX | #B GRANULAR CELL TUM | 2 | 1 | 0 | 1 | 0.684 | 0.884 | 1.000 | 0.875 |
| | #B LEIOMYOMA | 0 | 0 | 0 | 1 | 0.247 | . | . | 0.494 |
| | #M SARCOMA, UNDIFFER | 0 | 0 | 0 | 1 | 0.247 | . | . | 0.494 |
| | #M SCHWANNOMA, MALIG | 2 | 1 | 8 | 1 | 0.630 | 0.879 | 0.038 | 0.866 |
| COLON | #B LEIOMYOMA | 0 | 0 | 0 | 1 | 0.247 | . | . | 0.494 |
| | #M ADENOCARCINOMA, M | 0 | 0 | 0 | 1 | 0.247 | . | . | 0.494 |
| DUODENUM | #M ADENOCARCINOMA, M | 0 | 1 | 0 | 1 | 0.303 | 0.511 | . | 0.488 |
| EARS | #B NEURAL CREST TUMO | 0 | 0 | 1 | 0 | 0.485 | . | 0.488 | . |
| JEJUNUM | #M ADENOCARCINOMA | 1 | 0 | 0 | 1 | 0.427 | 1.000 | 1.000 | 0.741 |
| KIDNEYS | #B ADENOMA | 0 | 1 | 0 | 0 | 0.746 | 0.506 | . | . |
| LIVER | #B ADENOMA, HEPATOCE | 0 | 1 | 1 | 4 | 0.013 | 0.506 | 0.488 | 0.055 |
| | #B CHOLANGIOMA | 0 | 0 | 0 | 1 | 0.247 | . | . | 0.494 |
| | #M CARCINOMA, HEPATO | 0 | 0 | 2 | 0 | 0.485 | . | 0.235 | . |
| | #M CHOLANGIOCARCINOM | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | CHOLANGIOMA+CHOLARGI | 1 | 0 | 0 | 1 | 0.432 | 1.000 | 1.000 | 0.741 |
| | HEPATOCELLULAR_ADENO | 0 | 1 | 3 | 4 | 0.027 | 0.506 | 0.112 | 0.055 |
| LN, ILIAC | #M SCHWANNOMA, MALIG | 0 | 0 | 0 | 1 | 0.247 | . | . | 0.494 |
| MAMMARY GLAND | #B ADENOMA | 4 | 2 | 1 | 5 | 0.179 | 0.899 | 0.967 | 0.485 |
| | #B FIBROADENOMA | 30 | 36 | 32 | 20 | 0.989 | 0.182 | 0.318 | 0.958 |
| | #B LIPOMA | 0 | 0 | 1 | 0 | 0.485 | . | 0.488 | . |
| | #M ADENOCARCINOMA | 9 | 9 | 12 | 12 | 0.205 | 0.624 | 0.268 | 0.309 |
| MAMMARY_GLAND | ADENOMA+CARCINOMA | 12 | 11 | 12 | 16 | 0.127 | 0.685 | 0.518 | 0.249 |

**Table 3B1 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Rats (Water Control)**

| Organ Name | Tumor Name | 0 mg 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 |
|---|---|---|---|---|---|---|---|---|---|
| MESENTERY | #B LIPOMA | 0 | 0 | 1 | 0 | 0.485 | . | 0.488 | . |
| OVARIES | #B ADENOMA | 0 | 0 | 0 | 1 | 0.243 | . | . | 0.488 |
| | #B GRANULOSA CELL TU | 0 | 1 | 0 | 3 | 0.032 | 0.506 | . | 0.116 |
| | #B THECOMA, BENIGN | 0 | 0 | 0 | 2 | 0.058 | . | . | 0.235 |
| | THECOMA_B+M | 0 | 0 | 0 | 2 | 0.058 | . | . | 0.235 |
| PANCREAS | #B ADENOMA, ACINAR C | 0 | 0 | 0 | 6 | 0.000 | . | . | 0.013 |
| | #B ADENOMA, ISLET CE | 0 | 2 | 2 | 0 | 0.730 | 0.253 | 0.235 | . |
| | #M CARCINOMA, ACINAR | 0 | 0 | 2 | 6 | 0.001 | . | 0.235 | 0.012 |
| | #M CARCINOMA, ISLET | 1 | 3 | 0 | 0 | 0.952 | 0.308 | 1.000 | 1.000 |
| | ACINAR_CELL_ADENOMA+ | 0 | 0 | 2 | 12 | 0.000 | . | 0.235 | 0.000 |
| | ISLET_CELL_ADENOMA+C | 1 | 5 | 2 | 0 | 0.944 | 0.101 | 0.473 | 1.000 |
| PAWS | #M FIBROSARCOMA | 0 | 0 | 0 | 1 | 0.247 | . | . | 0.494 |
| PITUITARY | #B ADENOMA, PARS DIS | 62 | 58 | 52 | 31 | 1.000 | 0.690 | 0.966 | 1.000 |
| | #B ADENOMA, PARS INT | 0 | 0 | 1 | 0 | 0.485 | . | 0.488 | . |
| | #M CARCINOMA, PARS D | 1 | 3 | 2 | 0 | 0.884 | 0.325 | 0.482 | 1.000 |
| | ADENOMA+CARCINOMA | 63 | 61 | 54 | 31 | 1.000 | 0.702 | 0.977 | 1.000 |
| SAL. GLAND MAND | #M ADENOCARCINOMA | 0 | 0 | 0 | 1 | 0.243 | . | . | 0.488 |
| SKELETAL MUSCLE | #M SARCOMA, UNDIFFER | 0 | 0 | 1 | 0 | 0.485 | . | 0.488 | . |
| SKIN | #B FIBROMA | 0 | 0 | 1 | 1 | 0.180 | . | 0.488 | 0.494 |
| | #M ADENOCARCINOMA, S | 0 | 0 | 0 | 1 | 0.243 | . | . | 0.488 |
| | #M FIBROSARCOMA | 0 | 0 | 1 | 0 | 0.485 | . | 0.488 | . |
| | #M MYXOSARCOMA | 0 | 0 | 0 | 1 | 0.247 | . | . | 0.494 |
| | #M SCHWANNOMA, MALIG | 0 | 1 | 1 | 2 | 0.114 | 0.506 | 0.488 | 0.241 |
| | FIBROMA+FIBROSARCOMA | 0 | 0 | 2 | 1 | 0.194 | . | 0.235 | 0.494 |
| | SEBACEOUS_CELL_ADENO | 0 | 0 | 0 | 1 | 0.243 | . | . | 0.488 |
| SOFT TISSUE- AB | #B LIPOMA | 0 | 2 | 0 | 0 | 0.803 | 0.253 | . | . |
| SOFT TISSUE- TH | #B HIBERNOMA, BENIGN | 1 | 0 | 1 | 3 | 0.061 | 1.000 | 0.735 | 0.299 |
| | #M HIBERNOMA, MALIGN | 0 | 1 | 1 | 2 | 0.117 | 0.511 | 0.488 | 0.247 |
| | #M SARCOMA, UNDIFFER | 0 | 1 | 0 | 0 | 0.746 | 0.506 | . | . |
| SOFT_TISSUE | HIBERNOMAS | 1 | 1 | 2 | 5 | 0.022 | 0.758 | 0.482 | 0.107 |
| SPINAL CORD | #M SCHWANNOMA, MALIG | 0 | 0 | 0 | 1 | 0.243 | . | . | 0.488 |
| SPLEEN | #M OSTEOSARCOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| STOMACH, GLAN | #B LEIOMYOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |

**Table 3B1 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Rats (Water Control)**

| Organ Name | Tumor Name | 0 mg 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 |
|---|---|---|---|---|---|---|---|---|---|
| SYSTEMIC TUMORS | #M FIBROUS HISTIOCYT | 0 | 0 | 0 | 1 | 0.247 | . | . | 0.494 |
| | #M HEMANGIOSARCOMA | 0 | 1 | 1 | 1 | 0.288 | 0.506 | 0.488 | 0.494 |
| | #M LYMPHANGIOSARCOMA | 0 | 0 | 1 | 0 | 0.485 | . | 0.488 | . |
| | #M LYMPHOMA, MALIGNA | 0 | 1 | 0 | 0 | 0.746 | 0.506 | . | . |
| | | 1 | 1 | 1 | 1 | 0.499 | 0.753 | 0.735 | 0.741 |
| | #M MESOTHELIOMA, MAL | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #M MYELOMA, PLASMA C | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #M SARCOMA, HISTIOCY | 0 | 0 | 0 | 2 | 0.060 | . | . | 0.241 |
| SYSTEMIC_TUMORS | MALIGNANT_LYMPHOMA | 1 | 2 | 1 | 1 | 0.594 | 0.500 | 0.735 | 0.741 |
| THYMUS | #B THYMOMA, BENIGN | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| THYROID GLANDS | #B ADENOMA, C-CELL | 9 | 8 | 3 | 2 | 0.993 | 0.722 | 0.982 | 0.995 |
| | #B ADENOMA, FOLLICUL | 0 | 1 | 2 | 9 | 0.000 | 0.506 | 0.235 | 0.001 |
| | #M CARCINOMA, C-CELL | 3 | 0 | 1 | 0 | 0.952 | 1.000 | 0.933 | 1.000 |
| | #M CARCINOMA, FOLLIC | 0 | 2 | 2 | 5 | 0.012 | 0.253 | 0.235 | 0.024 |
| THYROID_GLANDS | C_CELL_ADENOMA+CARCI | 12 | 8 | 4 | 2 | 0.998 | 0.898 | 0.990 | 0.999 |
| | FOLLICULAR_CELL_ADEN | 0 | 3 | 4 | 14 | 0.000 | 0.129 | 0.053 | 0.000 |
| TONGUE | #B PAPILLOMA, SQUAMO | 0 | 0 | 0 | 1 | 0.247 | . | . | 0.494 |
| URINARY BLADDER | #B GRANULAR CELL TUM | 0 | 0 | 1 | 1 | 0.180 | . | 0.488 | 0.494 |
| | #B PAPILLOMA | 0 | 0 | 1 | 0 | 0.485 | . | 0.488 | . |
| UTERUS | #B ADENOMA, ENDOMETR | 0 | 0 | 0 | 1 | 0.243 | . | . | 0.488 |
| | #B LEIOMYOMA | 0 | 0 | 0 | 1 | 0.247 | . | . | 0.494 |
| | #B POLYP, ENDOMETRIA | 2 | 5 | 4 | 12 | 0.001 | 0.217 | 0.305 | 0.004 |
| | #M ADENOCARCINOMA | 1 | 0 | 1 | 2 | 0.154 | 1.000 | 0.741 | 0.482 |
| | #M SARCOMA, ENDOMETR | 0 | 0 | 0 | 1 | 0.247 | . | . | 0.494 |
| | #M SCHWANNOMA, MALIG | 0 | 0 | 1 | 0 | 0.485 | . | 0.488 | . |
| | POLYP+SARCOMA | 2 | 5 | 4 | 13 | 0.001 | 0.217 | 0.305 | 0.002 |
| VAGINA | #B GRANULAR CELL TUM | 0 | 0 | 1 | 1 | 0.180 | . | 0.488 | 0.494 |
| | #B LEIOMYOMA | 0 | 0 | 0 | 1 | 0.243 | . | . | 0.488 |
| | #B POLYP, VAGINAL | 1 | 1 | 0 | 0 | 0.934 | 0.753 | 1.000 | 1.000 |
| | #M CARCINOMA, SQUAMO | 0 | 1 | 0 | 0 | 0.746 | 0.506 | . | . |
| | #M LEIOMYOSARCOMA | 0 | 0 | 0 | 1 | 0.247 | . | . | 0.494 |
| | #M SCHWANNOMA, MALIG | 0 | 0 | 0 | 2 | 0.060 | . | . | 0.241 |
| ZYMBAL'S GLANDS | #M CARCINOMA | 0 | 1 | 2 | 5 | 0.006 | 0.506 | 0.235 | 0.026 |

**Table 3B2: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Rats (Corn-oil Control)**

| Organ Name | Tumor Name | 0 mg 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 |
|---|---|---|---|---|---|---|---|---|---|
| ADRENAL CORTEX | #B ADENOMA | 1 | 2 | 1 | 7 | 0.004 | 0.509 | 0.735 | 0.027 |
| | #M CARCINOMA | 2 | 1 | 2 | 3 | 0.193 | 0.875 | 0.656 | 0.455 |
| ADRENAL MEDULLA | #B PHEOCHROMOCYTOMA, | 1 | 0 | 2 | 3 | 0.059 | 1.000 | 0.473 | 0.282 |
| | #M OSTEOSARCOMA | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.488 |
| | #M PHEOCHROMOCYTOMA, | 0 | 0 | 0 | 2 | 0.059 | . | . | 0.236 |
| ADRENAL_CORTEX | ADENOMA+CARCINOMA | 3 | 3 | 3 | 10 | 0.004 | 0.662 | 0.616 | 0.028 |
| ADRENAL_MEDULLA | PHEOCHROMOCYTOMA_B+M | 1 | 0 | 2 | 5 | 0.008 | 1.000 | 0.473 | 0.091 |
| BRAIN | #B GRANULAR CELL TUM | 0 | 1 | 0 | 0 | 0.741 | 0.500 | . | . |
| | #M ASTROCYTOMA, MALI | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| CERVIX | #B GRANULAR CELL TUM | 1 | 1 | 0 | 1 | 0.525 | 0.753 | 1.000 | 0.741 |
| | #B LEIOMYOMA | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.488 |
| | #B POLYP | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #M SARCOMA, UNDIFFER | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.488 |
| | #M SCHWANNOMA, MALIG | 0 | 1 | 8 | 1 | 0.414 | 0.500 | 0.002 | 0.482 |
| COLON | #B LEIOMYOMA | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.488 |
| | #M ADENOCARCINOMA, M | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.488 |
| DUODENUM | #M ADENOCARCINOMA, M | 0 | 1 | 0 | 1 | 0.299 | 0.506 | . | 0.482 |
| EARS | #B NEURAL CREST TUMO | 0 | 0 | 1 | 0 | 0.482 | . | 0.482 | . |
| HEART | #M SCHWANNOMA, MALIG | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| JEJUNUM | #M ADENOCARCINOMA | 0 | 0 | 0 | 1 | 0.241 | . | . | 0.482 |
| KIDNEYS | #B ADENOMA | 0 | 1 | 0 | 0 | 0.741 | 0.500 | . | . |
| LIVER | #B ADENOMA, HEPATOCE | 0 | 1 | 1 | 4 | 0.013 | 0.500 | 0.482 | 0.053 |
| | #B CHOLANGIOMA | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.488 |
| | #M CARCINOMA, HEPATO | 0 | 0 | 2 | 0 | 0.482 | . | 0.230 | . |
| | CHOLANGIOMA+CHOLARGI | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.488 |
| | HEPATOCELLULAR_ADENO | 0 | 1 | 3 | 4 | 0.026 | 0.500 | 0.108 | 0.053 |
| LN, ILIAC | #M SCHWANNOMA, MALIG | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.488 |
| MAMMARY GLAND | #B ADENOMA | 4 | 2 | 1 | 5 | 0.170 | 0.888 | 0.963 | 0.457 |
| | #B FIBROADENOMA | 23 | 36 | 32 | 20 | 0.910 | 0.010 | 0.031 | 0.640 |
| | #B LIPOMA | 0 | 0 | 1 | 0 | 0.482 | . | 0.482 | . |
| | #M ADENOCARCINOMA | 9 | 9 | 12 | 12 | 0.185 | 0.583 | 0.232 | 0.271 |

**Table 3B2 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Rats (Corn-oil Control)**

| Organ Name | Tumor Name | 0 mg 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 |
|---|---|---|---|---|---|---|---|---|---|
| MAMMARY_GLAND | ADENOMA+CARCINOMA | 11 | 11 | 12 | 16 | 0.084 | 0.551 | 0.380 | 0.149 |
| MESENTERY | #B LIPOMA | 0 | 0 | 1 | 0 | 0.482 | . | 0.482 | . |
| OVARIES | #B ADENOMA | 1 | 0 | 0 | 1 | 0.425 | 1.000 | 1.000 | 0.735 |
| | #B GRANULOSA CELL TU | 0 | 1 | 0 | 3 | 0.032 | 0.500 | . | 0.112 |
| | #B LEIOMYOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #B THECOMA, BENIGN | 0 | 0 | 0 | 2 | 0.057 | . | . | 0.230 |
| | #M THECOMA, MALIGNAN | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | THECOMA_B+M | 1 | 0 | 0 | 2 | 0.145 | 1.000 | 1.000 | 0.473 |
| PANCREAS | #B ADENOMA, ACINAR C | 0 | 0 | 0 | 6 | 0.000 | . | . | 0.012 |
| | #B ADENOMA, ISLET CE | 2 | 2 | 2 | 0 | 0.910 | 0.683 | 0.656 | 1.000 |
| | #M CARCINOMA, ACINAR | 0 | 0 | 2 | 6 | 0.001 | . | 0.230 | 0.011 |
| | #M CARCINOMA, ISLET | 0 | 3 | 0 | 0 | 0.880 | 0.121 | . | . |
| | ACINAR_CELL_ADENOMA+ | 0 | 0 | 2 | 12 | 0.000 | . | 0.230 | 0.000 |
| | ISLET_CELL_ADENOMA+C | 2 | 5 | 2 | 0 | 0.969 | 0.208 | 0.656 | 1.000 |
| PAWS | #M FIBROSARCOMA | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.488 |
| PITUITARY | #B ADENOMA, PARS DIS | 58 | 58 | 52 | 31 | 1.000 | 0.377 | 0.849 | 1.000 |
| | #B ADENOMA, PARS INT | 0 | 0 | 1 | 0 | 0.482 | . | 0.482 | . |
| | #M CARCINOMA, PARS D | 0 | 3 | 2 | 0 | 0.804 | 0.129 | 0.236 | . |
| | ADENOMA+CARCINOMA | 58 | 61 | 54 | 31 | 1.000 | 0.220 | 0.763 | 1.000 |
| SAL. GLAND MAND | #M ADENOCARCINOMA | 0 | 0 | 0 | 1 | 0.241 | . | . | 0.482 |
| SKELETAL MUSCLE | #M SARCOMA, UNDIFFER | 0 | 0 | 1 | 0 | 0.482 | . | 0.482 | . |
| SKIN | #B ADENOMA, SEBACEOU | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #B FIBROMA | 0 | 0 | 1 | 1 | 0.178 | . | 0.482 | 0.488 |
| | #M ADENOCARCINOMA, S | 0 | 0 | 0 | 1 | 0.241 | . | . | 0.482 |
| | #M CARCINOMA, SQUAMO | 2 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #M FIBROSARCOMA | 0 | 0 | 1 | 0 | 0.482 | . | 0.482 | . |
| | #M MYXOSARCOMA | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.488 |
| | #M SCHWANNOMA, MALIG | 1 | 1 | 1 | 2 | 0.243 | 0.747 | 0.729 | 0.474 |
| | FIBROMA+FIBROSARCOMA | 0 | 0 | 2 | 1 | 0.192 | . | 0.230 | 0.488 |
| | SEBACEOUS_CELL_ADENO | 1 | 0 | 0 | 1 | 0.423 | 1.000 | 1.000 | 0.729 |
| SOFT TISSUE- AB | #B LIPOMA | 0 | 2 | 0 | 0 | 0.799 | 0.247 | . | . |
| SOFT TISSUE- TH | #B HIBERNOMA, BENIGN | 0 | 0 | 1 | 3 | 0.018 | . | 0.482 | 0.116 |
| | #M HIBERNOMA, MALIGN | 0 | 1 | 1 | 2 | 0.115 | 0.506 | 0.482 | 0.241 |
| | #M SARCOMA, UNDIFFER | 0 | 1 | 0 | 0 | 0.741 | 0.500 | . | . |
| SOFT_TISSUE | HIBERNOMAS | 0 | 1 | 2 | 5 | 0.007 | 0.506 | 0.236 | 0.029 |

**Table 3B2 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons**
**Female Rats (Corn-oil Control)**

| Organ Name | Tumor Name | 0 mg 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 |
|---|---|---|---|---|---|---|---|---|---|
| SPINAL CORD | #M SCHWANNOMA, MALIG | 0 | 0 | 0 | 1 | 0.241 | . | . | 0.482 |
| SYSTEMIC TUMORS | #M FIBROUS HISTIOCYT | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.488 |
| | #M HEMANGIOSARCOMA | 1 | 1 | 1 | 1 | 0.499 | 0.753 | 0.735 | 0.741 |
| | #M LYMPHANGIOSARCOMA | 0 | 0 | 1 | 0 | 0.482 | . | 0.482 | . |
| | #M LYMPHOMA, MALIGNA | 0 | 1 | 0 | 0 | 0.741 | 0.500 | . | . |
| | | | | 1 | 1 | 0.284 | 0.500 | 0.482 | 0.488 |
| | #M MESOTHELIOMA, MAL | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #M SARCOMA, HISTIOCY | 0 | 0 | 0 | 2 | 0.059 | . | . | 0.236 |
| SYSTEMIC_TUMORS | MALIGNANT_LYMPHOMA | 0 | 2 | 1 | 1 | 0.402 | 0.247 | 0.482 | 0.488 |
| TAIL | #B NEURAL CREST TUMO | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| THYROID GLANDS | #B ADENOMA, C-CELL | 4 | 8 | 3 | 2 | 0.924 | 0.177 | 0.743 | 0.882 |
| | #B ADENOMA, FOLLICUL | 1 | 1 | 2 | 9 | 0.000 | 0.753 | 0.473 | 0.006 |
| | #M CARCINOMA, C-CELL | 0 | 0 | 1 | 0 | 0.482 | . | 0.482 | . |
| | #M CARCINOMA, FOLLIC | 1 | 2 | 2 | 5 | 0.031 | 0.500 | 0.473 | 0.086 |
| THYROID_GLANDS | C_CELL_ADENOMA+CARCI | 4 | 8 | 4 | 2 | 0.920 | 0.177 | 0.590 | 0.882 |
| | FOLLICULAR_CELL_ADEN | 2 | 3 | 4 | 14 | 0.000 | 0.511 | 0.305 | 0.001 |
| TONGUE | #B PAPILLOMA, SQUAMO | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.488 |
| URINARY BLADDER | #B GRANULAR CELL TUM | 0 | 0 | 1 | 1 | 0.178 | . | 0.482 | 0.488 |
| | #B PAPILLOMA | 0 | 0 | 1 | 0 | 0.482 | . | 0.482 | . |
| UTERUS | #B ADENOMA, ENDOMETR | 0 | 0 | 0 | 1 | 0.241 | . | . | 0.482 |
| | #B LEIOMYOMA | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.488 |
| | #B POLYP, ENDOMETRIA | 1 | 5 | 4 | 12 | 0.001 | 0.096 | 0.152 | 0.001 |
| | #M ADENOCARCINOMA | 1 | 0 | 1 | 2 | 0.152 | 1.000 | 0.735 | 0.473 |
| | #M SARCOMA, ENDOMETR | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.488 |
| | #M SCHWANNOMA, MALIG | 0 | 0 | 1 | 0 | 0.482 | . | 0.482 | . |
| | POLYP+SARCOMA | 1 | 5 | 4 | 13 | 0.000 | 0.096 | 0.152 | 0.000 |
| VAGINA | #B GRANULAR CELL TUM | 0 | 0 | 1 | 1 | 0.178 | . | 0.482 | 0.488 |
| | #B LEIOMYOMA | 1 | 0 | 0 | 1 | 0.423 | 1.000 | 1.000 | 0.729 |
| | #B POLYP, VAGINAL | 0 | 1 | 0 | 0 | 0.741 | 0.500 | . | . |
| | #M CARCINOMA, SQUAMO | 0 | 1 | 0 | 0 | 0.741 | 0.500 | . | . |
| | #M LEIOMYOSARCOMA | 0 | 0 | 0 | 1 | 0.246 | . | . | 0.488 |
| | #M SCHWANNOMA, MALIG | 0 | 0 | 0 | 2 | 0.059 | . | . | 0.236 |
| ZYMBAL'S GLANDS | #M CARCINOMA | 1 | 1 | 2 | 5 | 0.018 | 0.753 | 0.473 | 0.091 |

**Table 3B3: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons**
**Female Rats (Combined Controls)**

| Organ Name | Tumor Name | 0 mg Cont N=130 | 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 |
|---|---|---|---|---|---|---|---|---|---|
| ADRENAL CORTEX | #B ADENOMA | 2 | 2 | 1 | 7 | 0.002 | 0.416 | 0.686 | 0.006 |
| | #M CARCINOMA | 2 | 1 | 2 | 3 | 0.083 | 0.707 | 0.380 | 0.183 |
| ADRENAL MEDULLA | #B PHEOCHROMOCYTOMA, | 2 | 0 | 2 | 3 | 0.053 | 1.000 | 0.380 | 0.183 |
| | #M OSTEOSARCOMA | 0 | 0 | 0 | 1 | 0.195 | . | . | 0.323 |
| | #M PHEOCHROMOCYTOMA, | 0 | 0 | 0 | 2 | 0.037 | . | . | 0.103 |
| ADRENAL_CORTEX | ADENOMA+CARCINOMA | 4 | 3 | 3 | 10 | 0.001 | 0.441 | 0.393 | 0.002 |
| ADRENAL_MEDULLA | PHEOCHROMOCYTOMA_B+M | 2 | 0 | 2 | 5 | 0.006 | 1.000 | 0.380 | 0.036 |
| BRAIN | #B GRANULAR CELL TUM | 0 | 1 | 0 | 0 | 0.589 | 0.333 | . | . |
| | #M ASTROCYTOMA, MALI | 2 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| CERVIX | #B GRANULAR CELL TUM | 3 | 1 | 0 | 1 | 0.658 | 0.807 | 1.000 | 0.795 |
| | #B LEIOMYOMA | 0 | 0 | 0 | 1 | 0.195 | . | . | 0.323 |
| | #B POLYP | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #M SARCOMA, UNDIFFER | 0 | 0 | 0 | 1 | 0.195 | . | . | 0.323 |
| | #M SCHWANNOMA, MALIG | 2 | 1 | 8 | 1 | 0.362 | 0.704 | 0.002 | 0.683 |
| COLON | #B LEIOMYOMA | 0 | 0 | 0 | 1 | 0.195 | . | . | 0.323 |
| | #M ADENOCARCINOMA, M | 0 | 0 | 0 | 1 | 0.195 | . | . | 0.323 |
| DUODENUM | #M ADENOCARCINOMA, M | 0 | 1 | 0 | 1 | 0.189 | 0.338 | . | 0.318 |
| EARS | #B NEURAL CREST TUMO | 0 | 0 | 1 | 0 | 0.383 | . | 0.318 | . |
| HEART | #M SCHWANNOMA, MALIG | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| JEJUNUM | #M ADENOCARCINOMA | 1 | 0 | 0 | 1 | 0.347 | 1.000 | 1.000 | 0.536 |
| KIDNEYS | #B ADENOMA | 0 | 1 | 0 | 0 | 0.589 | 0.333 | . | . |
| LIVER | #B ADENOMA, HEPATOCE | 0 | 1 | 1 | 4 | 0.004 | 0.333 | 0.318 | 0.010 |
| | #B CHOLANGIOMA | 0 | 0 | 0 | 1 | 0.195 | . | . | 0.323 |
| | #M CARCINOMA, HEPATO | 0 | 0 | 2 | 0 | 0.383 | . | 0.099 | . |
| | #M CHOLANGIOCARCINOM | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | CHOLANGIOMA+CHOLARGI | 1 | 0 | 0 | 1 | 0.353 | 1.000 | 1.000 | 0.544 |
| | HEPATOCELLULAR_ADENO | 0 | 1 | 3 | 4 | 0.008 | 0.333 | 0.031 | 0.010 |
| LN, ILIAC | #M SCHWANNOMA, MALIG | 0 | 0 | 0 | 1 | 0.195 | . | . | 0.323 |
| MAMMARY GLAND | #B ADENOMA | 8 | 2 | 1 | 5 | 0.248 | 0.902 | 0.971 | 0.423 |
| | #B FIBROADENOMA | 53 | 36 | 32 | 20 | 0.906 | 0.024 | 0.072 | 0.859 |
| | #B LIPOMA | 0 | 0 | 1 | 0 | 0.383 | . | 0.318 | . |

**Table 3B3 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Rats (Combined Controls)**

| Organ Name | Tumor Name | 0 mg Cont N=130 | 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 |
|---|---|---|---|---|---|---|---|---|---|
| MAMMARY GLAND | #M ADENOCARCINOMA | 18 | 9 | 12 | 12 | 0.150 | 0.572 | 0.184 | 0.223 |
| MAMMARY_GLAND | ADENOMA+CARCINOMA | 23 | 11 | 12 | 16 | 0.090 | 0.606 | 0.409 | 0.141 |
| MESENTERY | #B LIPOMA | 0 | 0 | 1 | 0 | 0.383 | . | 0.318 | . |
| OVARIES | #B ADENOMA | 1 | 0 | 0 | 1 | 0.347 | 1.000 | 1.000 | 0.536 |
| | #B GRANULOSA CELL TU | 0 | 1 | 0 | 3 | 0.013 | 0.333 | . | 0.032 |
| | #B LEIOMYOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #B THECOMA, BENIGN | 0 | 0 | 0 | 2 | 0.036 | . | . | 0.099 |
| | #M THECOMA, MALIGNAN | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | THECOMA_B+M | 1 | 0 | 0 | 2 | 0.095 | 1.000 | 1.000 | 0.237 |
| PANCREAS | #B ADENOMA, ACINAR C | 0 | 0 | 0 | 6 | 0.000 | . | . | 0.001 |
| | #B ADENOMA, ISLET CE | 2 | 2 | 2 | 0 | 0.798 | 0.407 | 0.380 | 1.000 |
| | #M CARCINOMA, ACINAR | 0 | 0 | 2 | 6 | 0.000 | . | 0.099 | 0.001 |
| | #M CARCINOMA, ISLET | 1 | 3 | 0 | 0 | 0.873 | 0.108 | 1.000 | 1.000 |
| | ACINAR_CELL_ADENOMA+ | 0 | 0 | 2 | 12 | 0.000 | . | 0.099 | 0.000 |
| | ISLET_CELL_ADENOMA+C | 3 | 5 | 2 | 0 | 0.927 | 0.079 | 0.505 | 1.000 |
| PAWS | #M FIBROSARCOMA | 0 | 0 | 0 | 1 | 0.195 | . | . | 0.323 |
| PITUITARY | #B ADENOMA, PARS DIS | 120 | 58 | 52 | 31 | 1.000 | 0.584 | 0.963 | 1.000 |
| | #B ADENOMA, PARS INT | 0 | 0 | 1 | 0 | 0.383 | . | 0.318 | . |
| | #M CARCINOMA, PARS D | 1 | 3 | 2 | 0 | 0.771 | 0.117 | 0.244 | 1.000 |
| | ADENOMA+CARCINOMA | 121 | 61 | 54 | 31 | 1.000 | 0.382 | 0.923 | 1.000 |
| SAL. GLAND MAND | #M ADENOCARCINOMA | 0 | 0 | 0 | 1 | 0.192 | . | . | 0.318 |
| SKELETAL MUSCLE | #M SARCOMA, UNDIFFER | 0 | 0 | 1 | 0 | 0.383 | . | 0.318 | . |
| SKIN | #B ADENOMA, SEBACEOU | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #B FIBROMA | 0 | 0 | 1 | 1 | 0.112 | . | 0.318 | 0.323 |
| | #M ADENOCARCINOMA, S | 0 | 0 | 0 | 1 | 0.192 | . | . | 0.318 |
| | #M CARCINOMA, SQUAMO | 2 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #M FIBROSARCOMA | 0 | 0 | 1 | 0 | 0.383 | . | 0.318 | . |
| | #M MYXOSARCOMA | 0 | 0 | 0 | 1 | 0.195 | . | . | 0.323 |
| | #M SCHWANNOMA, MALIG | 1 | 1 | 1 | 2 | 0.127 | 0.557 | 0.536 | 0.244 |
| | FIBROMA+FIBROSARCOMA | 0 | 0 | 2 | 1 | 0.119 | . | 0.099 | 0.323 |
| | SEBACEOUS_CELL_ADENO | 1 | 0 | 0 | 1 | 0.347 | 1.000 | 1.000 | 0.536 |
| SOFT TISSUE- AB | #B LIPOMA | 0 | 2 | 0 | 0 | 0.662 | 0.109 | . | . |
| SOFT TISSUE- TH | #B HIBERNOMA, BENIGN | 1 | 0 | 1 | 3 | 0.027 | 1.000 | 0.536 | 0.103 |
| | #M HIBERNOMA, MALIGN | 0 | 1 | 1 | 2 | 0.052 | 0.338 | 0.318 | 0.106 |

**Table 3B3 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Rats (Combined Controls)**

| Organ Name | Tumor Name | 0 mg Cont N=130 | 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 |
|---|---|---|---|---|---|---|---|---|---|
| SOFT TISSUE- TH | #M SARCOMA, UNDIFFER | 0 | 1 | 0 | 0 | 0.589 | 0.333 | . | . |
| SOFT_TISSUE | HIBERNOMAS | 1 | 1 | 2 | 5 | 0.005 | 0.564 | 0.244 | 0.017 |
| SPINAL CORD | #M SCHWANNOMA, MALIG | 0 | 0 | 0 | 1 | 0.192 | . | . | 0.318 |
| SPLEEN | #M OSTEOSARCOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| STOMACH, GLAN | #B LEIOMYOMA | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| SYSTEMIC TUMORS | #M FIBROUS HISTIOCYT | 0 | 0 | 0 | 1 | 0.195 | . | . | 0.323 |
| | #M HEMANGIOSARCOMA | 1 | 1 | 1 | 1 | 0.326 | 0.557 | 0.536 | 0.544 |
| | #M LYMPHANGIOSARCOMA | 0 | 0 | 1 | 0 | 0.383 | . | 0.318 | . |
| | #M LYMPHOMA, MALIGNA | 0 | 1 | 0 | 0 | 0.589 | 0.333 | . | . |
| | | 1 | 1 | 1 | 1 | 0.326 | 0.557 | 0.536 | 0.544 |
| | #M MESOTHELIOMA, MAL | 2 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #M MYELOMA, PLASMA C | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| | #M SARCOMA, HISTIOCY | 0 | 0 | 0 | 2 | 0.037 | . | . | 0.103 |
| SYSTEMIC_TUMORS | MALIGNANT_LYMPHOMA | 1 | 2 | 1 | 1 | 0.397 | 0.258 | 0.536 | 0.544 |
| TAIL | #B NEURAL CREST TUMO | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| THYMUS | #B THYMOMA, BENIGN | 1 | 0 | 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 |
| THYROID GLANDS | #B ADENOMA, C-CELL | 13 | 8 | 3 | 2 | 0.980 | 0.415 | 0.937 | 0.982 |
| | #B ADENOMA, FOLLICUL | 1 | 1 | 2 | 9 | 0.000 | 0.557 | 0.237 | 0.000 |
| | #M CARCINOMA, C-CELL | 3 | 0 | 1 | 0 | 0.873 | 1.000 | 0.788 | 1.000 |
| | #M CARCINOMA, FOLLIC | 1 | 2 | 2 | 5 | 0.007 | 0.258 | 0.237 | 0.012 |
| THYROID_GLANDS | C_CELL_ADENOMA+CARCI | 16 | 8 | 4 | 2 | 0.991 | 0.599 | 0.934 | 0.994 |
| | FOLLICULAR_CELL_ADEN | 2 | 3 | 4 | 14 | 0.000 | 0.214 | 0.081 | 0.000 |
| TONGUE | #B PAPILLOMA, SQUAMO | 0 | 0 | 0 | 1 | 0.195 | . | . | 0.323 |
| URINARY BLADDER | #B GRANULAR CELL TUM | 0 | 0 | 1 | 1 | 0.112 | . | 0.318 | 0.323 |
| | #B PAPILLOMA | 0 | 0 | 1 | 0 | 0.383 | . | 0.318 | . |
| UTERUS | #B ADENOMA, ENDOMETR | 0 | 0 | 0 | 1 | 0.192 | . | . | 0.318 |
| | #B LEIOMYOMA | 0 | 0 | 0 | 1 | 0.195 | . | . | 0.323 |
| | #B POLYP, ENDOMETRIA | 3 | 5 | 4 | 12 | 0.000 | 0.079 | 0.141 | 0.000 |
| | #M ADENOCARCINOMA | 2 | 0 | 1 | 2 | 0.163 | 1.000 | 0.686 | 0.380 |
| | #M SARCOMA, ENDOMETR | 0 | 0 | 0 | 1 | 0.195 | . | . | 0.323 |
| | #M SCHWANNOMA, MALIG | 0 | 0 | 1 | 0 | 0.383 | . | 0.318 | . |
| | POLYP+SARCOMA | 3 | 5 | 4 | 13 | 0.000 | 0.079 | 0.141 | 0.000 |
| VAGINA | #B GRANULAR CELL TUM | 0 | 0 | 1 | 1 | 0.112 | . | 0.318 | 0.323 |

**Table 3B3 (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Rats (Combined Controls)**

| Organ Name | Tumor Name | 0 mg Cont N=130 | 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 |
|---|---|---|---|---|---|---|---|---|---|
| VAGINA | #B LEIOMYOMA | 1 | 0 | 0 | 1 | 0.347 | 1.000 | 1.000 | 0.536 |
| | #B POLYP, VAGINAL | 1 | 1 | 0 | 0 | 0.832 | 0.557 | 1.000 | 1.000 |
| | #M CARCINOMA, SQUAMO | 0 | 1 | 0 | 0 | 0.589 | 0.333 | . | . |
| | #M LEIOMYOSARCOMA | 0 | 0 | 0 | 1 | 0.195 | . | . | 0.323 |
| | #M SCHWANNOMA, MALIG | 0 | 0 | 0 | 2 | 0.037 | . | . | 0.103 |
| ZYMBAL'S GLANDS | #M CARCINOMA | 1 | 1 | 2 | 5 | 0.004 | 0.557 | 0.237 | 0.013 |

**Table 4A: Intercurrent Mortality Rate**
**Male Mice (Five Groups)**

| Week | WATER CONTROL1 NO.OF DEATH | PERCENT | WATER CONTROL2 NO.OF DEATH | PERCENT | 600mg NO.OF DEATH | PERCENT | 1000mg NO.OF DEATH | PERCENT | POSITIVE CONTROL NO.OF DEATH | PERCENT |
|---|---|---|---|---|---|---|---|---|---|---|
| 0-10 | . | . | . | . | 1 | 4.0% | . | . | 1 | 6.3% |
| 11-15 | . | . | . | . | . | . | . | . | 4 | 31.3% |
| 16-20 | . | . | . | . | . | . | . | . | 11 | 100.0% |
| Term. Sac. | 25 | 100.0% | 25 | 100.0% | 25 | 100.0% | 25 | 100.0% | . | . |

**Table 4B: Intercurrent Mortality Rate**
**Female Mice (Five groups)**

| Week | WATER CONTROL1 NO.OF DEATH | PERCENT | WATER CONTROL2 NO.OF DEATH | PERCENT | 600mg NO.OF DEATH | PERCENT | 1000mg NO.OF DEATH | PERCENT | POSITIVE CONTROL NO.OF DEATH | PERCENT |
|---|---|---|---|---|---|---|---|---|---|---|
| 0-10 | . | . | . | . | . | . | 1 | 4.0% | 1 | 6.7% |
| 11-15 | . | . | . | . | . | . | . | . | 3 | 26.7% |
| 16-20 | 1 | 4.0% | . | . | . | . | 1 | 8.0% | 11 | 100.0% |
| Term. Sac. | 24 | 100.0% | 25 | 100.0% | 25 | 100.0% | 23 | 100.0% | . | . |

**Table 5A1: Intercurrent Mortality Comparison**
**Male Mice (Groups 1, 3, 4)**

| Test | P-Value (across three groups) | P-Value (Water control 1 vs HPN-100 600mg) | P-Value (Water control 1 vs HPN-100 1000 mg) |
|---|---|---|---|
| Dose Response | 0.9851 | 0.8875 | 1.000 |
| Homogeneity | 0.3679 | 0.3173 | . |

**Table 5A2: Intercurrent Mortality Comparison**
**Male Mice (Groups 2, 3, 4)**

| Test | P-Value (across three groups) | P-Value (Water control 2 vs HPN-100 600mg) | P-Value (Water control 2 vs HPN-100 1000 mg) |
|---|---|---|---|
| Dose Response | 0.9851 | 0.8875 | 1.000 |
| Homogeneity | 0.3679 | 0.3173 | . |

**Table 5A3: Intercurrent Mortality Comparison**
**Male Mice (Groups combined 1 and 2, 3, 4)**

| Test | P-Value (across three groups) | P-Value (Combined Water controls vs HPN-100 600mg) | P-Value (Combined Water controls vs HPN-100 1000 mg) |
|---|---|---|---|
| Dose | 0.9626 | 0.8697 | 1.000 |
| Homogeneity | 0.2231 | 0.1573 | . |

**Table 5B1: Intercurrent Mortality Comparison**
**Female Mice (Groups 1, 3, 4)**

| Test | P-Value (across three groups) | P-Value (Water control 1 vs HPN-100 600mg) | P-Value (Water control 1 vs HPN-100 1000 mg) |
|---|---|---|---|
| Dose Response | 0.9054 | 0.8875 | 0.8806 |
| Homogeneity | 0.3501 | 0.3173 | 0.5396 |

**Table 5B2: Intercurrent Mortality Comparison**
**Female Mice (Groups 2, 3, 4)**

| Test | P-Value (across three groups) | P-Value (Water control 2 vs HPN-100 600mg) | P-Value (Water control 2 vs HPN-100 1000 mg) |
|---|---|---|---|
| Dose Response | 0.7907 | 1.000 | 0.7750 |
| Homogeneity | 0.1299 | . | 0.1531 |

**Table 5B3: Intercurrent Mortality Comparison**
**Female Mice (Groups combined 1 and 2, 3, 4)**

| Test | P-Value (across three groups) | P-Value (Combined Water controls vs HPN-100 600mg) | P-Value (Combined Water controls vs HPN-100 1000 mg) |
|---|---|---|---|
| Dose | 0.8457 | 0.9351 | 0.7999 |
| Homogeneity | 0.2058 | 0.4795 | 0.2051 |

**Table 6A1: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Groups 1, 3, 4)**

| Organ Name | Tumor Name | 0 mg Cont N=25 | 600 mg Low N=25 | 1000 mg Med N=25 | P_Value Dos Resp | P_Value C vs. L | P_Value C vs. M |
|---|---|---|---|---|---|---|---|
| ALL_SITES | HAEMANGIOSARCOMAS | 1 | 1 | 1 | 0.631 | 0.745 | 0.755 |
| LUNG | ADENOMA+CARCINOMA | 3 | 0 | 2 | 0.796 | 1.000 | 0.826 |
| liver | hepatocellular adeno | 0 | 0 | 1 | 0.338 | . | 0.500 |
| lungs with bron | alveolar-bronchiolar | 3 | 0 | 2 | 0.796 | 1.000 | 0.826 |
| | hemangiosarcoma | 0 | 1 | 0 | 0.662 | 0.490 | . |
| skin, dorsal | hemangiosarcoma | 0 | 0 | 1 | 0.338 | . | 0.500 |
| spleen | hemangiosarcoma | 1 | 0 | 0 | 1.000 | 1.000 | 1.000 |

**Table 6A2: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons**
**Male Mice (Groups 2, 3, 4)**

| Organ Name | Tumor Name | 0 mg Cont N=25 | 600 mg Low N=25 | 1000 mg Med N=25 | P_Value Dos Resp | P_Value C vs. L | P_Value C vs. M |
|---|---|---|---|---|---|---|---|
| ALL_SITES | HAEMANGIOSARCOMAS | 0 | 1 | 1 | 0.333 | 0.490 | 0.500 |
| LUNG | ADENOMA+CARCINOMA | 5 | 0 | 2 | 0.955 | 1.000 | 0.951 |
| liver | hepatocellular adeno | 0 | 0 | 1 | 0.338 | . | 0.500 |
| lungs with bron | alveolar-bronchiolar | 5 | 0 | 2 | 0.955 | 1.000 | 0.951 |
| | hemangiosarcoma | 0 | 1 | 0 | 0.662 | 0.490 | . |
| skin, dorsal | hemangiosarcoma | 0 | 0 | 1 | 0.338 | . | 0.500 |

**Table 6A3: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Groups combined water controls, 3, 4)**

| Organ Name | Tumor Name | 0 mg Cont N=50 | 600 mg Low N=25 | 1000 mg Med N=25 | P_Value Dos Resp | P_Value C vs. L | P_Value C vs. M |
|---|---|---|---|---|---|---|---|
| ALL_SITES | HAEMANGIOSARCOMAS | 1 | 1 | 1 | 0.404 | 0.547 | 0.559 |
| LUNG | ADENOMA+CARCINOMA | 8 | 0 | 2 | 0.948 | 1.000 | 0.912 |
| liver | hepatocellular adeno | 0 | 0 | 1 | 0.253 | . | 0.333 |
| lungs with bron | alveolar-bronchiolar | 8 | 0 | 2 | 0.948 | 1.000 | 0.912 |
| | hemangiosarcoma | 0 | 1 | 0 | 0.495 | 0.324 | . |
| skin, dorsal | hemangiosarcoma | 0 | 0 | 1 | 0.253 | . | 0.333 |
| spleen | hemangiosarcoma | 1 | 0 | 0 | 1.000 | 1.000 | 1.000 |

**Table 6B1: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Mice (Groups 1, 3, 4)**

| Organ Name | Tumor Name | 0 mg Cont N=25 | 600 mg Low N=25 | 1000 mg Med N=25 | P_Value Dos Resp | P_Value C vs. L | P_Value C vs. M |
|---|---|---|---|---|---|---|---|
| ALL_SITES | HAEMANGIOSARCOMAS | 1 | 1 | 3 | 0.191 | 0.755 | 0.289 |
| LUNG | ADENOMA+CARCINOMA | 1 | 0 | 2 | 0.355 | 1.000 | 0.484 |
| ear | papilloma | 0 | 1 | 0 | 0.662 | 0.500 | . |
| | squamous cell carcin | 0 | 0 | 1 | 0.324 | . | 0.490 |
| harderian gland | adenoma | 0 | 0 | 2 | 0.102 | . | 0.235 |
| liver | hemangiosarcoma | 0 | 0 | 1 | 0.324 | . | 0.490 |
| lungs with bron | alveolar-bronchiolar | 1 | 0 | 2 | 0.355 | 1.000 | 0.484 |
| ovaries | hemangioma | 0 | 1 | 0 | 0.662 | 0.500 | . |
| spleen | hemangiosarcoma | 1 | 1 | 2 | 0.367 | 0.755 | 0.484 |
| thymus | thymoma | 1 | 2 | 0 | 0.738 | 0.500 | 1.000 |

**Table 6B2: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons**
**Female Mice (Groups 2, 3, 4)**

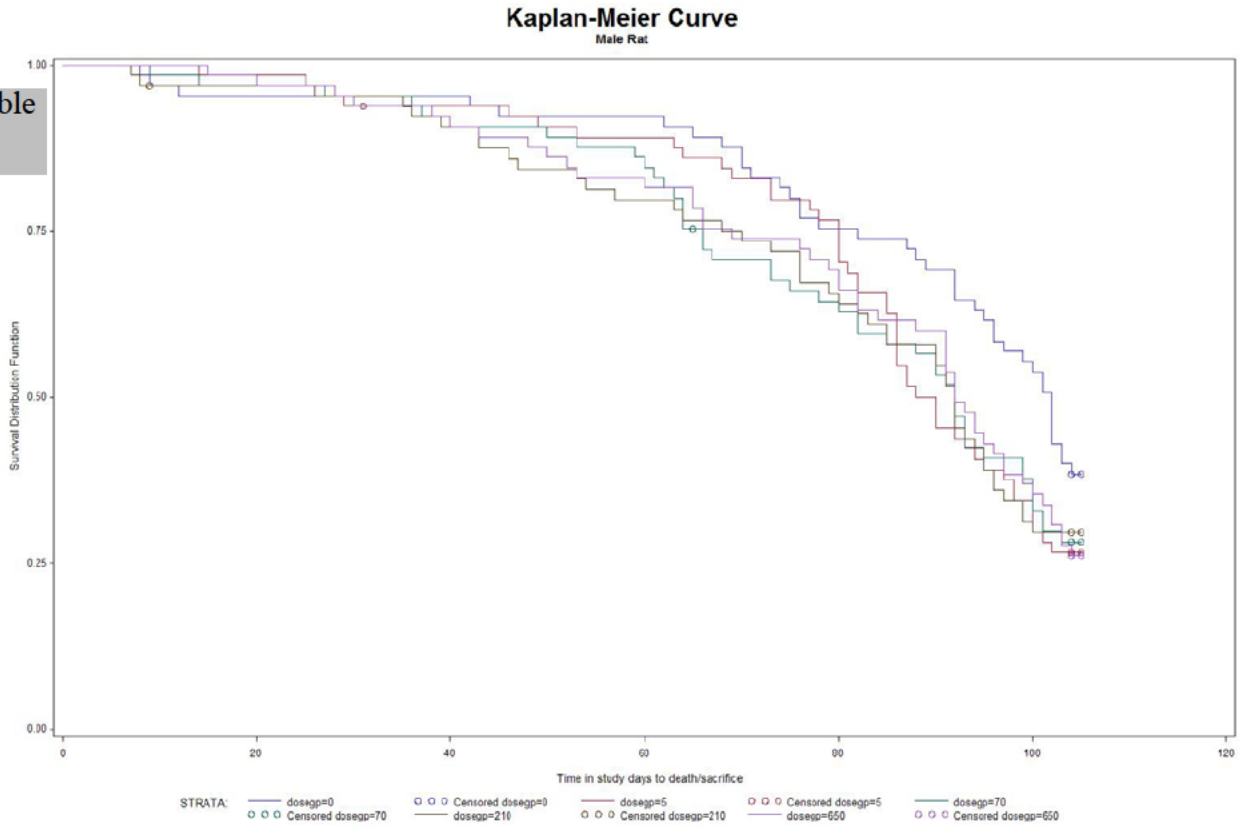
| Organ Name | Tumor Name | 0 mg Cont N=25 | 600 mg Low N=25 | 1000 mg Med N=25 | P_Value Dos Resp | P_Value C vs. L | P_Value C vs. M |
|---|---|---|---|---|---|---|---|
| ALL_SITES | HAEMANGIOSARCOMAS | 2 | 1 | 3 | 0.384 | 0.883 | 0.480 |
| LUNG | ADENOMA+CARCINOMA | 1 | 0 | 2 | 0.355 | 1.000 | 0.484 |
| ear | papilloma | 0 | 1 | 0 | 0.662 | 0.500 | . |
| | squamous cell carcin | 0 | 0 | 1 | 0.324 | . | 0.490 |
| harderian gland | adenoma | 1 | 0 | 2 | 0.355 | 1.000 | 0.484 |
| liver | hemangiosarcoma | 0 | 0 | 1 | 0.324 | . | 0.490 |
| lungs with bron | alveolar-bronchiolar | 1 | 0 | 2 | 0.355 | 1.000 | 0.484 |
| ovaries | hemangioma | 0 | 1 | 0 | 0.662 | 0.500 | . |
| spleen | hemangiosarcoma | 1 | 1 | 2 | 0.367 | 0.755 | 0.484 |
| thymus | thymoma | 0 | 2 | 0 | 0.435 | 0.245 | . |
| uterus | hemangiosarcoma | 1 | 0 | 0 | 1.000 | 1.000 | 1.000 |

**Table 6B3: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Mice (Groups combined water controls, 3, 4)**

| Organ Name | Tumor Name | 0 mg Cont N=50 | 600 mg Low N=25 | 1000 mg Med N=25 | P_Value Dos Resp | P_Value C vs. L | P_Value C vs. M |
|---|---|---|---|---|---|---|---|
| ALL_SITES | HAEMANGIOSARCOMAS | 3 | 1 | 3 | 0.261 | 0.811 | 0.297 |
| LUNG | ADENOMA+CARCINOMA | 2 | 0 | 2 | 0.360 | 1.000 | 0.391 |
| ear | papilloma | 0 | 1 | 0 | 0.495 | 0.333 | . |
| | squamous cell carcin | 0 | 0 | 1 | 0.242 | . | 0.324 |
| harderian gland | adenoma | 1 | 0 | 2 | 0.191 | 1.000 | 0.244 |
| liver | hemangiosarcoma | 0 | 0 | 1 | 0.242 | . | 0.324 |
| lungs with bron | alveolar-bronchiolar | 2 | 0 | 2 | 0.360 | 1.000 | 0.391 |
| ovaries | hemangioma | 0 | 1 | 0 | 0.495 | 0.333 | . |
| spleen | hemangiosarcoma | 2 | 1 | 2 | 0.319 | 0.710 | 0.391 |
| thymus | thymoma | 1 | 2 | 0 | 0.492 | 0.256 | 1.000 |
| uterus | hemangiosarcoma | 1 | 0 | 0 | 1.000 | 1.000 | 1.000 |

**Figure 1A: Kaplan-Meier Survival Functions for Male Rats**

Male Rats




X-Axis: Weeks, Y-Axis: Survival rates

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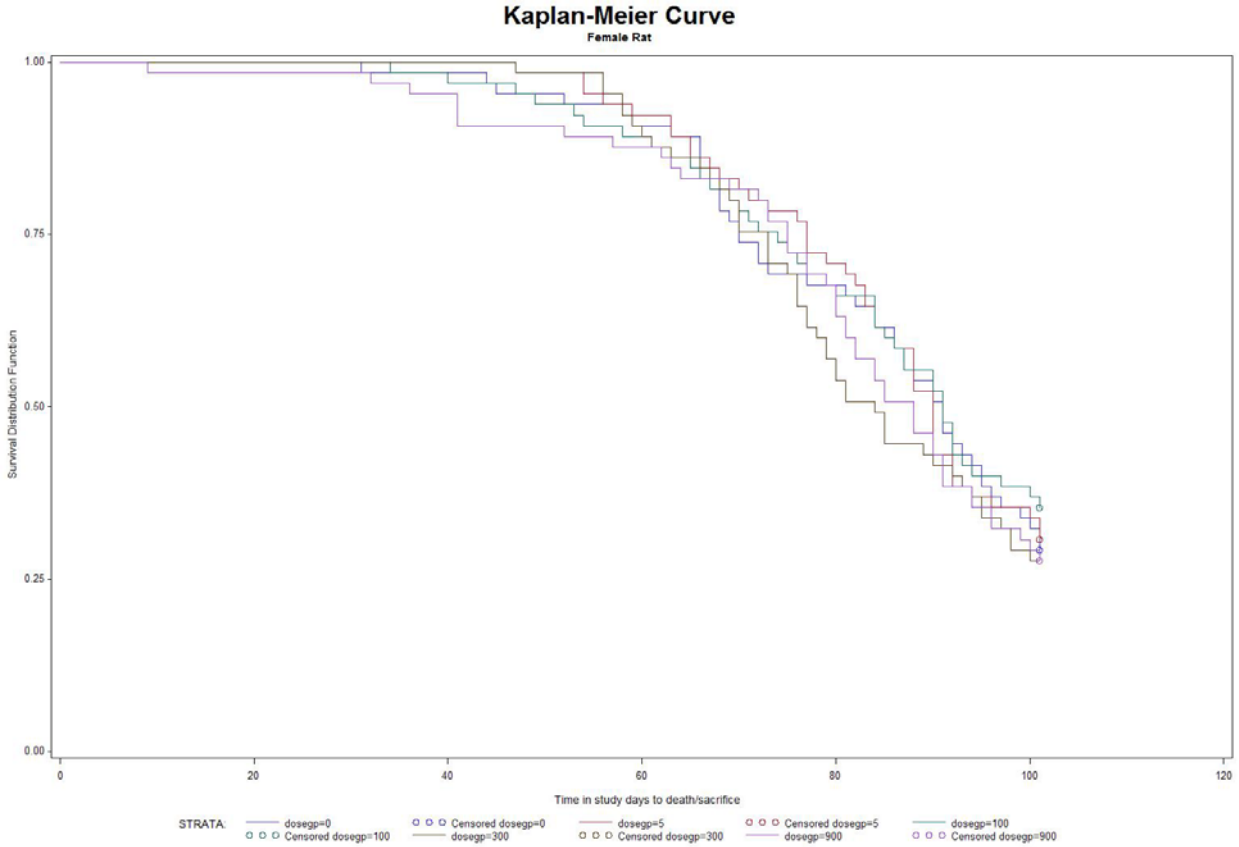
**Figure 1B: Kaplan-Meier Survival Functions for Female Rats**

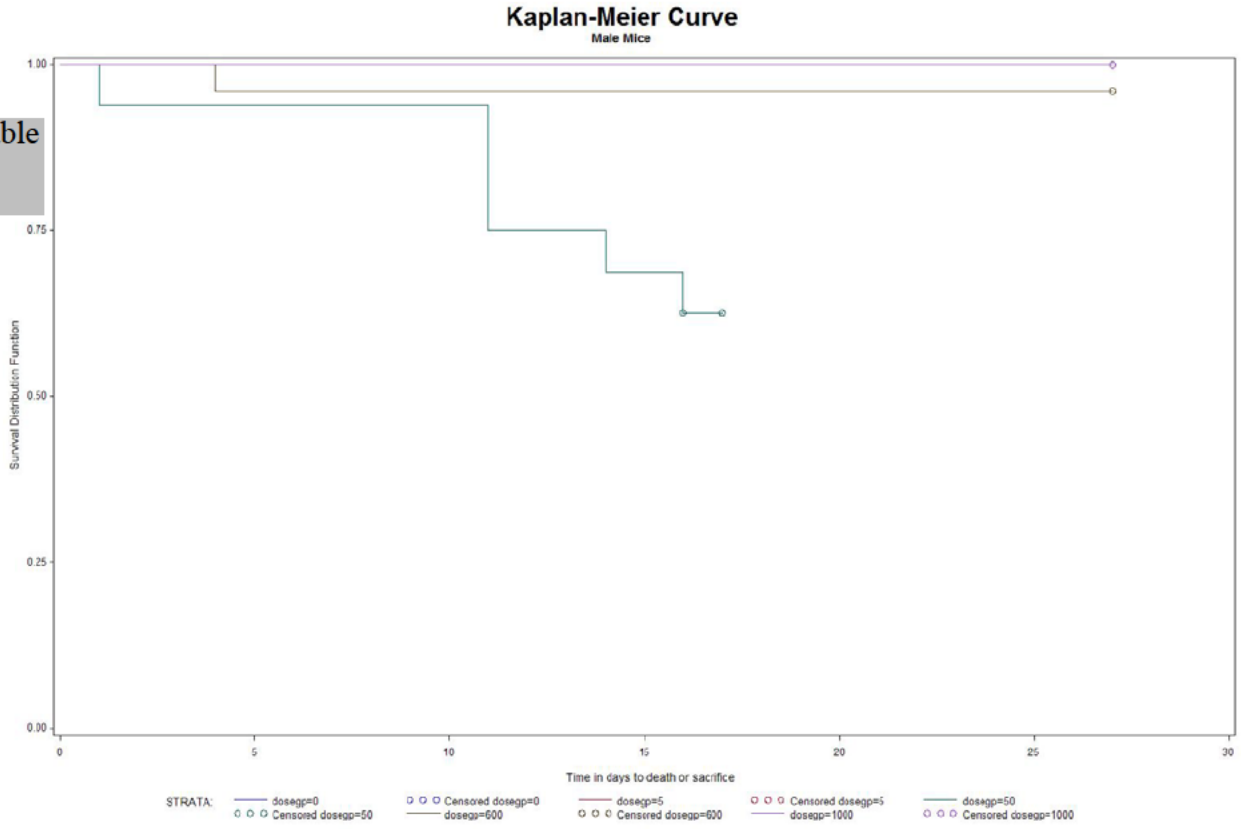
Female Rats




X-Axis: Weeks, Y-Axis: Survival rates

**Figure 2A: Kaplan-Meier Survival Functions for Male Mice**

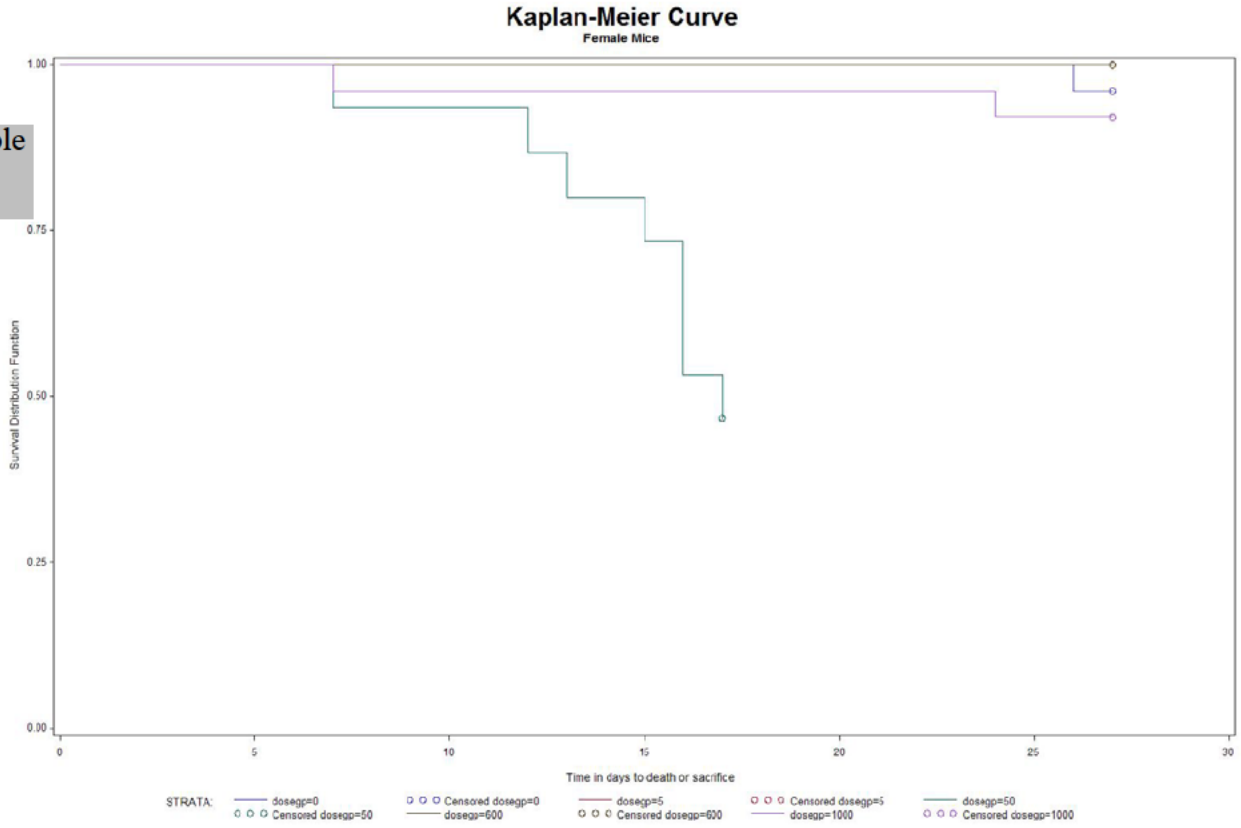
Male Mice (Five groups)




X-Axis: Weeks, Y-Axis: Survival rates

**Figure 2B: Kaplan-Meier Survival Functions for Female Mice**

Female Mice (Five groups)




X-Axis: Weeks, Y-Axis: Survival rates

## 7. References:

1. Bailer AJ, Portier CJ (1988). "Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples." *Biometrics*, 44, 417-431.

2. Bieler, G. S. and Williams, R. L. (1993). "Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity". *Biometrics* 49, 793-801.

3. Cox D. R. (1972) "Regression models and life tables", *Journal of the Royal Statistical Society*, B, 34, 187-220.

4. Gehan (1965) "A generalized Wilcoxon test for comparing arbitrarily singly censored samples", *Biometrika*, 52, 203-223.

5. Haseman, J (1983), "A re-examination of false-positive rates for carcinogenesis studies", *Fundamental and Applied Toxicology*, 3: 334-339.

6. Lin, K.K. and Rahman, M.A. (1998), "Overall false positive rates in tests for linear trend in tumor incidence in animal carcinogenicity studies of new drugs", *Journal of Biopharmaceutical Statistics,* 8(1), 1-15.

7. Rahman, M.A. and Lin, K.K. (2008), "A comparison of False Positive Rates of Peto and Poly-3 Methods for Long-Term Carcinogenicity Data Analysis Using Multiple Comparison Adjustment Method Suggested by Lin and Rahman", *Journal of Biopharmaceutical Statistics,* 18:5, 849-858.

8. Peto, R., M.C. Pike, N.E. Day, R.G. Gray, P.N. Lee, S. Parish, J. Peto, Richards, and J.Wahrendorf (1980), "Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments", Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, *Annex to supplement, World Health Organization, Geneva,* 311-426.

9. Tarone RE (1975), "Test for trend in life table analysis", *Biometrika*, 62: 679-82.

10. U.S. Department of Health and Human Services, "Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals", Center for Drug E valuation and Research, Food and Drug Administration, Sliver Spring, Maryland, 2001.

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MIN MIN
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KARL K LIN
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Concur with review

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

| NDA/BLA Number: 203-284 | Applicant: Hyperion Therapeutics, Inc. | Stamp Date: 23DEC2011 |
|---|---|---|
| Drug Name: RAVICTI™ (glycerol phenylbutyrate; HPN-100) | NDA/BLA Type: Type 1 NDA; 505(b)(1) | Indication: Adjunctive therapy for chronic management of adults and children (6-17 years of age) with urea cycle disorders |

On **initial** overview of the NDA/BLA application for filing:

| | Content Parameter for RTF | Yes | No | NA | Comments |
|---|---|---|---|---|---|
| 1A | Paper Submission: Index is sufficient to locate necessary reports, tables, data, etc. | | | X | This was an electronic submission by the sponsor. |
| 1B | Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc. | X | | | This electronic submission was eCTD compliant and of satisfactory quality. |
| 2 | ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.) | X | | | There were adequate and complete clinical study reports (CSRs), which were ICH E3 compliant, along with ISE and ISS reports submitted. |
| 3 | Safety and efficacy were investigated for gender, racial, and geriatric subgroups (if applicable). | | X | | No subgroup analyses for gender, race and age (e.g. geriatric) were presented for the sole adequate and well-controlled study (HPN-100-006) in this submission. |
| 4 | Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets). | X | | | All data sets provided were of satisfactory quality and were mostly compliant with CDISC data standards. Appropriate data definition files in Define.XML and Define.PDF format were included. |

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____YES____**
If the NDA/BLA is not fileable from the statistical perspective, please state below the reasons and provide comments to be sent to the Applicant.
**N/A**

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

| Content Parameter (possible review concerns for 74-day letter) | Yes | No | NA | Comment |
|---|---|---|---|---|
| Designs utilized are appropriate for the indications requested. | X | | | The designs utilized were adequate. |
| Endpoints and methods of analysis are specified in the protocols/statistical analysis plans. | X | | | The endpoints and methods of analysis were specified in the CSRs including the protocols and Statistical Analysis Plans (SAPs). |
| Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available. | | | X | There were no traditional interim analyses conducted. |
| Appropriate references for novel statistical methodology (if present) are included. | | | X | The statistical methodology was not novel per se hence no references were presented. |
| Safety data organized to permit analyses across clinical trials in the NDA/BLA. | X | | | Safety datasets were submitted for each study individually; however this data can be integrated. |
| Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate. | X | | | Multiple missing data handling strategies were administered which included various imputation approaches for primary analysis purposes. |

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Please communicate below any additional requests to the Applicant for the 74-day letter.

There were no additional requests by the statistical review team to the Applicant for the 74-day letter. There were no issues.

**Background**

As the regulatory agent on behalf of Ucyclyd Pharma, Inc., a wholly-owned subsidiary of Medicis Pharmaceutical Corporation, Hyperion has submitted this New Drug Application (NDA) for RAVICTI™ (HPN-100) pursuant to Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21, Part 314 of the Code of Federal Regulations. The proposed indication for RIVICTI is as an adjuvant therapy for chronic management of adult and pediatric patients ≥ 6 years of age with urea cycle disorders (UCD) involving deficiencies of the following enzymes; carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate (ASL) or arginase (ARG) as well as the mitochondrial transporter ornithine translocase (HHH deficiency).

The active ingredient in RAVICTI (to be administered as a tablet TID with meals) is glycerol phenylbutyrate. RAVICTI has undergone clinical development under IND 73,480 in patients with UCDs, and has been developed specifically to establish safety and efficacy in this patient population. Currently, there are FDA-approved treatment options for patients with UCDs i.e. BUPHENYL® (NaPBA).

Hyperion obtained Fast Track designation from the Agency on October 4, 2010. The review cycle established by the Division of Gastroenterology and Inborn Error Products (DGIEP) was a standard 10 month cycle. The application also qualifies for Orphan Exception under section 736(a)(1)(E) of the Federal Food, Drug and Cosmetic Act. Hyperion did obtain *Orphan Designation* from the Office or Orphan Products Development (OOPD) on July 27, 2009.

This NDA was submitted electronically in eCTD format. The submission was sent via the FDA Electronic Submissions Gateway (ESG) and its content along with the electronic data sets and labeling information have been stored in the electronic document room (EDR) at this path location: \\Cdsesub1\evsprod\NDA203284. The submission can consequently be accessed directly at the previous path specified.

**Brief Overview and Summary of Relevant Trials**

RIVICTI has been studied by Hyperion for the treatment of UCDs, and its clinical efficacy and safety has been principally evaluated through two studies: a Phase 3, multicenter, randomized, double-blind, double-dummy, placebo controlled, cross-over non-inferiority study (HPN-100-006) which serves as the lone adequate and well controlled study of this clinical development program as per 21 CFR 314.126; and a Phase 3, multicenter, open-label study (HPN-100-007) which is a long term extension study of new UCD patients or patients rolling over from trial HPN-100-006.

The following table presents information on the two relevant trials contained in the submission.

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

| Type of Study; Phase | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Regimen; Route | Number of Dosed Subjects | Patient Diagnosis | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Efficacy and Safety; Phase 3 | HPN-100-006 | To assess the non-inferiority of HPN-100 to NaPBA by evaluating blood ammonia levels in adult subjects with UCDs from OTC, CPS, and ASS who were being treated with NaPBA for control of their UCD | Multicenter, randomized, double-blind, double-dummy, placebo controlled, cross-over, non-inferiority | Treatment Arm A: NaPBA followed by HPN-100 placebo;<br><br>Treatment Arm B: HPN-100 followed by NaPBA placebo;<br><br>TID with meals; Tablets | Total: 46 | UCD Patients | 4 weeks (2 weeks each treatment) | Complete; Full |
| Efficacy and Safety; Phase 3 | HPN-100-007 | Long term ammonia control and safety in adult and pediatric patients | Multicenter, open-label, extension | HPN-100; TID with meals; tablets | Total: 60 of whom 40 participated in HPN-100-006 | UCD Patients | 12 months | Complete; Full |

## Review Issues

There are no review issues to report at this time.

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BEHRANG VALI
03/29/2012

MICHAEL E WELCH
03/29/2012