CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 205060 (505b1)
Supporting document/s:	0
Applicant's letter date:	7/3/2013
CDER stamp date:	7/5/2013
Product:	Epanova® (omefas) capsules
Indication:	Hypertriglyceridemia
Applicant:	Omthera Pharmaceuticals, Inc.
Review Division:	DMEP
Reviewer:	Parvaneh Espandiari
Supervisor/Team Leader:	Karen Davis Bruno
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Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of [NDA205060] are owned by [Omthera] or are data for [Omthera] has obtained a written right of reference. Any information or data necessary for approval of [NDA205060] that Omthera does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of [NDA205060].

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1 Executive Summary

1.1 Introduction

Omthera proposes Epanova soft gelatin capsules (omefas) under NDA 205060 for the treatment of severe hypertriglyceridemia (≥500 mg/dL). Epanova is a novel omega-3 carboxylic acid, a complex mixture of polyunsaturated free fatty acids, with active components of eicosapentaenoic acid (EPA, 55%), docosahexaenoic acid (DHA, 20%), and docosapentaenoic acid (DPA, (b) (4)%) in their free fatty acid forms from fish oil. The proposed clinical dose is for 2 g/day (2 capsules) and (b) (4) 4 g/day (4 capsules) (b) (4) . Epanova appears to have a higher absorption of EPA and DHA compared to approved fish oil Lovaza (omega-3 ethyl ester form), which requires pancreatic lipases to change to the omega-3 fatty acid. The Sponsor has filed a 505(b)(1) application.

1.2 Brief Discussion of Nonclinical Findings

General toxicity

Nonclinical studies were conducted with omefas (extracted from Epanova soft gel capsules) oral (gavage) in mice and rats and with Epanova soft gel capsules oral in dogs. These studies showed the intended pharmacological effect of Epanova by decreased plasma levels of total cholesterol and triglycerides. The liver was the potential target organ toxicity across species based on increased liver enzyme activities. Increased liver enzyme activities in some studies associated with increased liver weight and liver focal necrosis. In the 36-week dog study, 2/4 dogs at 1000mg/kg/day were noted with microscopic findings in the heart (1/4, granuloma /macrophage aggregates, epicardial, focal), and in the aorta (1/4, mineralization, adventitial focal). Safety margins to the MHRD (4g/day based on a body surface area comparison) were established for 5 fold in the 4-week mouse study at 4000mg/kg/day omefas, 2 fold in the 26-week rat study at 6oomg/kg/day omefas, and 3 fold in the 39-week dog study at 300mg/kg/day Epanova soft gel capsules.

A full panel of genotoxicity was completed; Epanova did not exhibit genetic toxicity in the Ames assay, the chromosomal aberration study, and in the *in vivo* rat micronucleus study.

Two carcinogenicity studies were conducted in rats (2-year) and in Tg.rasH2 mice (26-week) oral (gavage) with omefas. In the Tg.rasH2 mice study, no drug-related tumors up to 2000 mg/kg/day omefas were observed (5 fold safety margin to the MHRD of 4 g/day based on a body surface area comparison).

In the rat study, benign sex cord stromal tumors of the ovaries were reported in 2000mg/kg/day omefas treated females (5 fold to the MHRD of 4g/day based on a body surface area comparison). This finding was statistically significant for both trend (P=0.0005) and pairwise comparison (P=0.0054). The benign ovarian sex cord tumor at 2000mg/kg/day exceeded

concurrent control and historical controls despite deviations from the protocol regarding the early discontinuation of dosing and termination for all treated animals (females were dosed for at least 65 weeks). Mortality for this study was statistically significant and cause of death was non-neoplastic based on microscopic dose-response gavage/reflux-related findings in the respiratory tract.

Findings from the reproductive and developmental toxicity studies suggested no treatment effects on reproductive performance, early embryonic development, maternal or fetal toxicity in rats up to 2000mg/kg/day (5 fold to MHRD based on a body surface area).

In pregnant rabbits, there was no effect on maternal up to 500mg/kg/day (about 2.4 fold to MHRD of 4g/day based on a body surface area). NOAEL for the embryo-fetal development was established at 100mg/kg/day (about 0.5 fold to MHRD of 4g/day) because of skeletal malformation and ossification effects (variations) as well as visceral variations at 500 mg/kg/day. At higher exposure, 750mg/kg/day omefas, mortality (with evidence of abortion) and fetal skeletal variation were noted.

In the pre/post natal rat oral study, at 2000mg/kg/day, F0 animals showed mortality (9/24) due to difficulties during or shortly after parturition. Therefore, at this dose level, there were fewer live litters and fewer pups for evaluation. At F1, there were no effects on growth or development or on their ability to initiate and maintain a pregnancy. However, there was an increased incidence of pup (F2) mortality at 600 and 2000mg/kg/day. The safety margin to the MHRD dose (4g/day based on surface area) were established for the F0 generation 1.5 fold (at 600 mg/kg/day omefas) and for the F1 generation 0.25 fold (at 100 mg/kg/day omefas). The TK data was not submitted; therefore, it is not known if pregnancy alters after exposure.

Late in the review cycle, CMC identified (b) (4) as a drug substance impurity in Epanova capsules and requested that Pharm/Tox assess safety. (b) (4) is an established rodent carcinogen, genotoxicant and is listed by the International Agency for Research on Cancer (IARC) as a likely human carcinogen. Based on this a risk analysis was performed and considered along with the sponsor's submitted justification for the proposed specification. The Agency informed the Sponsor that their specification for (b) (4) (b) (4) ppm) should be as low as possible because of the concern. The sponsor has indicated that (b) (4), this specification was lower than those based on ICHM7 guidelines for genotoxic impurities and that they (b) (4) .

1.3 Recommendations

1.3.1 Approvability

Pharm/Tox recommends approval of Epanova for the proposed indication of severe hypertriglyceridemia (≥500 mg/dL) up to 4g/day.

1.3.2 Additional Non Clinical Recommendations

No further nonclinical studies are required.

1.3.3 Labeling

8.1 Pregnancy
Sponsor's proposed labeling

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. It is unknown whether EPANOVA can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. EPANOVA should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

In female rats given oral gavage doses of 100, 600, and 2,000 mg/kg/day beginning 2 weeks prior to mating and continuing through day 6 of gestation, no adverse effects were observed in the high dose group (5 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison).

In pregnant rats given oral gavage doses of 100, 600, and 2,000 mg/kg/day from gestation day 6 through (b) (4) were observed (5 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison).

In a multigenerational developmental study in pregnant rats given oral gavage doses of 100, 600, and 2,000 mg/kg/day from gestation day 6 through lactation day 21, (b) (4) dams given the highest dose (b) (4) (5 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison). There were no abnormalities observed in offspring (F1) from treated dams. However, survival was decreased from day 10 of lactation onward in second generation offspring (F2) from dams given 600 mg/kg/day (1.5 times the human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison).

In pregnant rabbits given oral gavage doses of 100, 500, and 750 mg/kg/day from gestation day 6 through (b) (4) were observed in the fetuses in groups given up to 500 mg/kg/day (2 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison). At 750 mg/kg/day, several rabbits aborted and evidence of maternal toxicity was observed, and there was an increase in the incidence of fetuses with (b) (4) (4 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison).

Reviewer's Recommended Changes:
Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. It is unknown whether EPANOVA can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. EPANOVA should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.
In female rats given oral gavage doses of 100, 600, and 2,000 mg/kg/day beginning 2 weeks prior to mating and continuing through day 6 of gestation, no adverse effects were observed in

the high dose group (5 times human systemic exposure following an oral dose of 4 grams/day based on body surface area comparison).
In pregnant rats given oral gavage doses of 100, 600, and 2,000 mg/kg/day from gestation day 6 through organogenesis , late embryonic deaths and embryos with skeletal variations were observed (5 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison).

In pregnant rabbits given oral gavage doses of 100, 500, and 750 mg/kg/day from gestation day 6 through organogenesis, skeletal malformations, variations in ossification, and visceral variations were observed in the fetuses in groups given up to 500 mg/kg/day (2 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison). At 750 mg/kg/day, several rabbits aborted and evidence of maternal toxicity was observed, and there was an increase in the incidence of fetuses with malformations and variations (4 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison).

In a multigenerational developmental study in pregnant rats given oral gavage doses of 100, 600, and 2,000 mg/kg/day from gestation day 6 through lactation day 21, difficulties during and shortly after parturition led to morbidity/mortality in 9/24 dams given the highest dose(5 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison). There were no abnormalities observed in offspring (F1) from treated dams. However, survival was decreased from day 10 of lactation onward in second generation offspring (F2) from dams given 600 mg/kg/day (1.5 times the human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison).

8.2 Labor and Delivery (There is no 8.2 section in the proposed labeling).
There are no human studies that have investigated the effects of Epanova on preterm labor or labor at term. However, animal studies showed that omega-3 fatty acids caused delayed parturition and associated fetal death in rats (5 times the human systemic exposure following an oral dose of 4 g/day based on body surface area comparison), and premature birth and abortion in rabbits (4 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison).

8.3 Nursing Mothers

Studies with omega-3 fatty acids derived from fish oil have demonstrated excretion in human milk. The effect of this excretion is unknown; caution should be exercised when EPANOVA is administered to a nursing mother.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

"In a 6-month carcinogenicity study (b) (4) Tg.rasH2 transgenic mice with oral gavage doses of 500, 1000, 2000, and 4000 mg/kg/day, (b) (4) increase in the incidence of tumors (b) (4) . (b) (4)

In a rat carcinogenicity study with oral gavage doses of 100, 600, and 2,000 mg/kg/day, males were treated for 84 to 95 weeks (b) (4)

(b) (4) (up to 5 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison). (b) (4)

EPANOVA was not mutagenic or clastogenic with or without metabolic activation in the bacterial mutagenesis (Ames) test with *Salmonella typhimurium* and *Escherichia coli* or in the chromosomal aberration assay in Chinese hamster ovary cells. EPANOVA was negative in the *in vivo* rat bone marrow micronucleus assay.

In a rat fertility study with oral gavage doses of 100, 600, and 2,000 mg/kg/day, males were treated (b) (4) 4 weeks prior to mating, and females were treated for 2 weeks prior to and throughout mating until day 6 of gestation. No adverse effect on male or female fertility was observed at 2,000 mg/kg/day (5 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison)."

Reviewer's Recommended Changes:

In a Sprague-Dawley rat carcinogenicity study with oral gavage doses of 100, 600, and 2,000 mg/kg/day omega-3 carboxylic acid, males were treated for 84 to 95 weeks without an increased incidence of tumors. In female rats treated for 66 to 95 weeks at 2000 mg/kg/day, an increased incidence of benign ovarian sex cord stromal tumors were observed (up to 5 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison).

In a 6-month carcinogenicity study in Tg.rasH2 transgenic mice with oral gavage doses of 500, 1000, 2000, and 4000 mg/kg/day omega-3 carboxylic acid, without any increase in the incidence of tumors.

EPANOVA was not mutagenic or clastogenic with or without metabolic activation in the bacterial mutagenesis (Ames) test with *Salmonella typhimurium* and *Escherichia coli* or in the chromosomal aberration assay in Chinese hamster ovary cells. EPANOVA was negative in the *in vivo* rat bone marrow micronucleus assay.

In a rat fertility study with oral gavage doses of 100, 600, and 2,000 mg/kg/day, males were treated from 4 weeks prior to mating, and females were treated for 2 weeks prior to and throughout mating until day 6 of gestation. No adverse effect on male or female fertility was observed at 2,000 mg/kg/day (5 times human systemic exposure following an oral dose of 4 grams/day based on a body surface area comparison).

Justification for Changes:

Carcinogenesis finding for the rat was taken from Executive CAC committee finding, where a statistically significant increased incidence of benign sex cord stromal of the ovarian in female rats was observed at 2000mg/kg/day omefas.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional):

EPA: (5Z, 8Z, 11Z, 14Z, 17Z)-eicosa-5,8,11,14,17-pentaenoic acid; CAS 10417-94-4

DHA: (4Z, 7Z, 10Z, 13Z, 16Z, 19Z)-docosa-4,7,10,13,16,19-hexaenoic acid; CAS 6217-54-5

DPA: (7Z, 10Z, 13Z, 16Z, 19Z)-docosa-7,10,13,16,19-pentaenoic acid; CAS 24880-45-3

Generic Name:

N/A

Code Name:

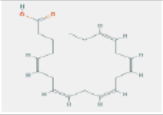
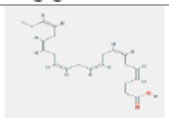
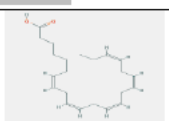
Epanova / omega-3-free fatty acids, capsules

Chemical Name:

N/A

Molecular Formula/Molecular Weight/Structure or Biochemical Description

Table 2.3.S-1. Structure Summaries for the Three Most Abundant Omega-3 Fatty Acids Contained in Omefas

	Attribute	
EPA	Molecular Formula	$C_{20}H_{30}O_2$
	Molecular Weight	302.451 g/mol
	Amount contained in omefas	500 to 600 mg/g
	Structure	
DHA	Molecular Formula	$C_{22}H_{32}O_2$
	Molecular Weight	328.488 g/mol
	Amount contained in omefas	150 to 250 mg/g
	Structure	
DPA	Molecular Formula	$C_{22}H_{34}O_2$
	Molecular Weight	330.504 g/mol
	Amount contained in omefas	(b) (4)
	Structure	

Pharmacologic Class:

Omega – 3 Fatty acids

Planned Clinical Route of Administration:

Oral use

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND (b) (4) (submitted to the Division of Gastroenterology Products on July 30, 2002); IND 107616 (Epanova, omefas Capsules); IND (b) (4); PINDs: (b) (4) and (b) (4) NDA 21-654 (Lovaza: IND (b) (4)); and DMFs: (b) (4)

2.3 Drug Formulation

Epanova is a soft gelatin capsule with 1000 mg substance (omefas), which contains (b) (4) mg of polyunsaturated fatty acids (omega-3 fatty acids of EPA, 500-600 mg; DHA, 150-250 mg; and DPA (b) (4) mg). These compounds obtained from crude fish oil.

Epanova capsules also have the following inactive ingredients of: 3 mg α-tocopherol (in a carrier of vegetable oil), gelatin, glycerol, sorbitol, and purified water (components of the capsule shell). Coating and ink components to the EPANOVA capsules also contain ethyl acrylate and methyl methacrylate copolymer dispersion, talc, titanium dioxide, iron oxide red, polysorbate 80, and carboxymethylcellulose sodium (coating components), pharmaceutical glaze, titanium dioxide, n-butyl alcohol, propylene glycol and isopropanol (ink components).

Nonclinical studies were conducted with omefas (extracted from Epanova capsules) oral (gavage) in rodents and with Epanova capsules oral in dogs (Sponsor's Tables):

Table 2.3.P-1. Composition of Epanova Soft Gelatin Capsules

Ingredient	Function	Specification	Weight per capsule (mg)
Omefas	Active ingredient	see *Section 3.2.S.4.1*	1,000
Capsule Shell			
Gelatin (porcine gelatin)	Capsule shell	USP/NF	
Sorbitol		USP/NF	
Glycerol		Ph. Eur	
Purified Water		USP/NF	
Total shell weight			
Capsule Coating			
Poly(ethyl acrylate, methyl methacrylate) (as dispersion)		USP/NF	
Talc		USP/NF	
Titanium dioxide		USP/NF	
Iron oxide red		USP/NF	
Polysorbate 80		USP/NF	
Carboxymethylcellulose sodium		USP/NF	
Total coating weight			
Total capsule weight			1,470
*			
**			

b(4)

Ingredient	Regulatory Status	Weight per capsule (mg) and variations in %
Drug substance	Active substance	1000 mg ±
Excipients		
Vitamin E (alpha-tocopherol)	USP complying NF/FCC complying	
Capsule Shell		
Gelatin (porcine gelatin)	Ph.Eur./USP/NF complying	
Sorbitol	Ph.Eur. complying	
Glycerin	Ph.Eur. complying	
Purified Water	USP complying	
Total shell weight:		
Capsule coating		
Poly(ethyl acrylate, methyl methacrylate)	Ph.Eur. complying	
Talc	Ph.Eur.complying	
Titanium dioxide	Ph.Eur.complying	
Iron oxide red	USP complying	
Polysorbate 80	Ph.Eur. complying	
Carboxymethylcellulose sodium	Ph.Eur./USP complying	
Total coating weight:		

b(4)

2.4 Comments on Novel Excipients

There are no novel excipients in Epanova capsules.

2.5 Comments on Impurities/Degradants of Concern

The majority of impurities/degradants are related to [redacted]

In the late review cycle, CMC identified a process impurity in the drug substance which was identified as [redacted]. Pharm/Tox was requested to assess the safety the Sponsor's specification limit of [redacted] ([redacted]ppm) as an impurity in Epanova capsules.

[redacted] is a rodent carcinogen and likely human carcinogen based on IARC classifications. Drug-related sex chord stromal ovarian tumors are seen in the Sponsor's 2-year rat study with omefas (extracted from capsules). Interestingly ovarian stromal tumors are part of the tumor profile of [redacted] in the Sponsor's justification provided by [redacted] (Table 3.3.1-2, Page 7 of the [redacted]: ovarian granulosa-a subtype of ovarian stromal tumors). The NTP 2004 carci study with [redacted], sex chord stromal tumors are also observed. Moreover, in the [redacted]'s report, results of the mouse study for 70 weeks (not a carci study) suggests [redacted]mg/kg [redacted] is not associated with tumors. Most carci studies are 104 weeks duration.

Omthera's rat carci study shows omefas-related ovarian stromal tumors at 2000 mg/kg/day and the rat no effect level (NOAEL) for tumors was at 600 mg/kg/day. The human equivalent dose is 5.8 g/day which is slightly higher (1.45X) than the human therapeutic dose of Epanova (4 g/day). [redacted] is present at [redacted] ppm (or [redacted]mg/kg) in drug lot #36355 that was used in the rat carci studies; human equivalent dose to the rat NOAEL was with approximately [redacted] ng of [redacted] with no tumors.

In the Sponsor rat carci study, at 2000 mg/kg/day, there is ovarian tumors. At this dose level, the human equivalent dose is 323 mg/kg or 19.38 g/day for a 60 kg person (5X higher than therapeutic dose of 4 g/day Epanova).). [redacted] is present at [redacted] ppm (or [redacted]mg/kg) in drug lot #36355 that was used in the rat carci studies; human equivalent dose to the rat NOAEL was with approximately [redacted] ng of ethyl carbamate.

If the spec is set at [redacted] ppm ([redacted]mg/kg) and the therapeutic dose of Epanova is 4 g/day (0.004 kg/d); therefore, [redacted] mg ([redacted]ug) of [redacted] is ingested. This is [redacted] as high as the total daily dose associated with tumors in rat (not an acceptable level). If the spec is set at [redacted] ppm ([redacted] mg/kg) and the therapeutic dose of Epanova is 4 g/day (0.004 kg/d) then [redacted] mg ([redacted] ug) of [redacted] could be ingested this is [redacted] lower than the rat exposure without the ovarian tumors.

Consequently, the Agency informed the Sponsor that their specification for [redacted] ([redacted]ppm) was not supported by the preclinical data which would support a specification of [redacted] ppm. The Agency requested that the Sponsor to revise their specification as low as technically possible because of the safety signal for carcinogenicity. While the sponsor agreed they indicated that the levels present at the spec of [redacted] ppm were within ICHM7 guidelines, they [redacted]

Sponsor's Tables regarding the impurities:

Table 3.2.S.3.2-6. Environmental Pollutants of Concern for Omefas

(b) (4)

[redacted]

Table 3.2.S.3.2-14. List of Chemical Impurities of Concern for Omefas

(b) (4)

[redacted]

Drug substance batches used in non-clinical toxicology studies (Sponsor's Tables):

Table 2.3.S-6. Impurity Data for Omefas

(b) (4)

[redacted]

Table 2.3.S-6. Impurity Data for Omefas

(b) (4)

[redacted]

Table 2.3.S-6. Impurity Data for Omefas

(b) (4)

Table 2.3.S-6. Impurity Data for Omefas

(b) (4)

ND = Not Detected
NLT = Not Less Than
NMT = Not More Than
NT = Not Tested

2.6 Proposed Clinical Population and Dosing Regimen

The (b) (4) daily dose is 2 g/day (2 capsules) and (b) (4) 4 g/day (4 capsules) (b) (4) .

Regulatory Background

- Originally, IND (b) (4) was submitted for the treatment of Crohn's disease to the Division of Gastroenterology Products (transferred to Omthera in Dec. 2009).

- On 25/3/2010, Omthera submitted IND 107616 for Epanova for treatment of hyper-triglyceridemia to the Division of Metabolism and Endocrinology Products.

- On 2/6/2010, the end-of-phase 2 meeting was held for the development program and also two pre-NDA meetings were held on 17/11/2012 (CMC specific pre-NDA meeting) and 14/11/2012 012 (nonclinical development strategy). The Agency agreed that the nonclinical development strategy was reasonable, and the proposed clinical package was adequate for submission of the NDA.

- On 8/7/2013, the NDA 205060 (Epanova) was submitted as 505(b)(1) application.

3 Studies Submitted

Table 2.4-1. Nonclinical Safety Studies Conducted with Omefas

Type of Study & Title	Species/Test System	Omefas Doses (mg/kg/day)	GLP	Study Number	Test Facility	Status
Repeat-Dose Toxicity						
EPANOVA: Non-GLP 14-Day Repeated Dose Oral Toxicity Study in CByB6F1 Mice	Mouse/ CByB6F1	2000, 4000	No	*AD29PL.2G3R.NG.BTL*	(b) (4)	Complete
4-Week Dose Range-finding Oral Gavage Toxicity and Toxicokinetic Study with Omefas in 001178-W (wild type) Mice	Mouse/ Tg.rasH2 (wild type)	0, 1000, 2000, 4000	Yes	*8232576*		Complete
2-Week Dose-Range-Finding Study for a 4-Week Subacute Toxicity Study of Omefas® (Active Principle of EPANOVA®) by Repeat Oral Administration to CD® Rats	Rat/CD®	0, 300, 3000, 5000	Yes	*20129/06*		Complete
EPANOVA: 13 Week Oral (Gavage) Bridging Toxicology Study in Rats	Rat/Sprague Dawley	0, 100, 600, 2000; 2160 (Omacor® comparator)	Yes	*518986*		Complete
A 26 Week Toxicity Study of EPANOVA by Oral Gavage in Rats	Rat/Sprague Dawley	0, 100, 600, 2000	Yes	*519251*		Complete
EPANOVA: Preliminary Dose Finding Study in Rabbits	Rabbit/New Zealand White	1500, 750	No	*495629*		Complete
Dose-Range-Finding Study for a 4-Week Subacute Toxicity Study of EPANOVA® Coated Capsules by Repeated Oral Administration to Beagle Dogs	Dog/Beagle	Phase 1 (escalating dose): 1500, 2000, 2500, 3000 Phase 2 (fixed dose level): 2000, 3000	Yes	*20130/06*		Complete
4-Week Subacute Toxicity Study of EPANOVA® Coated Capsules by Oral Administration to Beagle Dogs	Dog/Beagle	0, 300, 1000, 3000	Yes	*22005*		Complete
EPANOVA: 39 Week Oral (Gavage) Toxicity Study in Dogs	Dog/Beagle	0, 50, 300, 1000	Yes	*519026*		Complete

Table 2.4-1. Nonclinical Safety Studies Conducted with Omefas

Type of Study & Title	Species/Test System	Omefas Doses (mg/kg/day)	GLP	Study Number	Test Facility	Status
Genotoxicity						
EPANOVA: Testing for Mutagenic Activity with *Salmonella typhimurium* TA 1535, TA 100, TA 1537 and TA 98 and *Escherichia coli* WP2*uvr*A	*S typhimurium* & *E coli*	17 to 5000 µg/plate	Yes	*789390*	(b) (4)	Complete
EPANOVA: Chromosomal Aberrations Assay with Chinese Hamster Ovary Cell Cultures *In Vitro*	CHO cells	5 to 30 µg/mL (with S9); 5 to 100 µg/mL (without S9)	Yes	*789406*		Complete
EPANOVA: Micronucleus Test in Bone Marrow Cells of CD Rats: 0 h + 24 h Oral Dosing and 48 h Sampling	Rat/Sprague Dawley	0, 2000	Yes	*789411*		Complete
Carcinogenicity						
4-Week Oral Gavage Oncogenicity Study with EPANOVA in 001178-T (Hemizygous) Mice	Mouse/001178-T (hemizygous)	0, 460, 1390, 4600	No	*8240763*		Complete[a]
EPANOVA: 26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 Mice	Mouse/ Tg.rasH2 (hemizygous)	0, 500, 1000, 2000, 4000	Yes	*AD29PL.7G8R. BTL*		Complete
A 104 Week Carcinogenicity Study of EPANOVA by Oral Gavage in Rats	Rat/Sprague Dawley	0, 100, 600, 2000	Yes	*518911*		Complete[b]
Reproductive and Developmental Toxicity						
The Effects on Fertility and Early Embryonic Development to Implantation of EPANOVA in Rats Dosed by Oral Gavage	Rat/Sprague Dawley	0, 100, 600, 2000	Yes	*495655*		Complete
A Developmental Toxicity Study of EPANOVA by Oral Gavage in Rats	Rat/Sprague Dawley	0, 100, 600, 2000	Yes	*495634*		Complete

Table 2.4-1. Nonclinical Safety Studies Conducted with Omefas

Type of Study & Title	Species/Test System	Omefas Doses (mg/kg/day)	GLP	Study Number	Test Facility	Status
Reproductive and Developmental Toxicity						
EPANOVA: Developmental Toxicity Study in Rabbits dosed by Oral Gavage	Rabbit/New Zealand White	0, 100, 500, 750	Yes	*495660*	(b) (4)	Complete
EPANOVA: Pre and Postnatal Oral (Gavage) Study in Rats	Rat/Sprague Dawley	0, 100, 600, 2000	Yes	*495440*		Complete

[a] The intended study duration was 26 weeks. The study was terminated after 4 weeks of dosing due to unexpectedly high mortality.
[b] Life-span dosing was not achieved due to high mortality. Male rats were dosed for at least 83 weeks, and females for at least 65 weeks.

3.1 Studies Reviewed

All

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

IND (b) (4) (submitted to the Division of Gastroenterology Products on July 30, 2002).

IND 107616 (submitted to DMEP).

4 Pharmacology

The Sponsor did not conduct pharmacology studies. Based on scientist literatures, dietary supplement with fish oil containing EPA and DHA would be therapeutically beneficial for inflammatory diseases (e.g. Crohn's disease) by inhibiting inflammatory mediators such as prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) as well as cytokines such as IL-1β and TNF-α.

General primary/secondary/safety pharmacology studies were not conducted with Epanova because pharmacology of EPA and DHA in animals and humans is well established in the published literature.

Based on published literature with polyunsaturated omega-3 fatty acids, these lipids inhibit hepatic triglycerides and have been implicated in inhibition of apoprotein synthesis. This effect on apolipoprotein B100 synthesis and reduction in VLDL occurs in conjunction with transcription factors. EPA and DHA target the genes governing cellular triglyceride (TG) production and those activating oxidation of excess hepatic fatty acids. In conjunction with transcription factors EPA and DHA can replace arachidonic acid in membrane phospholipids resulting in reduced inflammatory eicosanoids (e.g. thromboxane, leukotriene B4) from cyclooxygenase, lipoxygenase and cytochrome P450 pathways once released from the membrane instead of arachidonate which is the precursor of these inflammatory precursors. Polyunsaturated omega-3 fatty acids decrease lipids by inhibiting hepatic TGs and possibly apoprotein synthesis.

The lipid lowering effects EPA have been observed in rodent, rabbits and primates including humans. EPA reduces hepatic fat in cells and lipoproteins in plasma, total cholesterol, phospholipids and triglycerides. The mechanism of omega-3 fatty acids in lowering TGs are by reducing hepatic TG secretion and enhancing the rate of clearance from the circulation. Apoprotein plays an important role in the development of hypertriglyceridemia, particularly in inhibiting the actions of lipoprotein lipase and hepatic lipase, which slows TG hydrolysis. Apoprotein also interferes with the interactions of TG-rich liporteins with hepatic Apo B and E receptors slowing the removal of these particles from plasma. The effect of omega-3s on apoprotein is independent of PPARα. EPA and DHA down regulate SREBP-1c the transcription factor that controls lipogenesis. By regulating different transcription factors than EPA, DHA reduces apoprotein production resulting in enhanced conversion of VLDL to LDL and formation of larger circulating lipid particles reflected in a larger LDL/ApoB. DHA, regulates hepatic nuclear factor-4α, FOXO1, and carbohydrate response element binding protein.

5.1 PK/ADME

The Sponsor did not submit the general ADME studies. Submitted relevant information is summarized below:

"After oral ingestion, EPA and DHA is rapidly absorbed from the small intestine and transferred to the general circulation via the lymphatic system and distributed within tissues throughout the body (including the brain, retina, heart and fat). The majority of EPA in plasma is bound to plasma protein." The speed and extent of absorption is promoted by bile.

Table 2.4-2. Summary of Pharmacokinetic Parameters of 14C-Ethyl-EPA, EPA, and DHA from Omthera TK Studies and Published Literature

Species, Sex	Test Article/ Analyte	Dose	T½ (hr) (α phase, ß phase)	AUC (µg·hr/mL)	C_{max} (µg/mL)	T_{max} (hr)	Study Report/ Reference
Rat, Male	EPA	30 mg/kg (single dose)	11.7, 33.6	499.4	12.9	9	*Ishiguro et al., 1987b*
Rat, Male	EPA	100 mg/kg (single dose)	4.4, 35.5	1478.3	43.8	6	*Ishiguro et al., 1987b*
Rat, Male	EPA	1000 mg/kg (single dose)	4.3, 30.5	7628.6	204.0	6	*Ishiguro et al., 1987b*
Rat, Male	EPA	33.8 mg/kg (repeat dose)	NE	1354	72.7	1	*519026*
Rat, Male	EPA	62.04 mg/kg (repeat dose)	12.04	2288	203	1	*518986*
Rat, Male	EPA	186 mg/kg (repeat dose)	NE	1123	65.0	5.5	*519026*
Rat, Male	EPA	366.6 mg/kg (repeat dose)	7.01	8089	751	4	*518986*
Rat, Male	EPA	620 mg/kg (repeat dose)	NE	10260	491	6.25	*519026*
Mouse, Male	EPA	1000 mg/kg (repeat dose)	NE	5966	422	4	*8232576*
Rat, Male	EPA	1240.8 mg/kg (repeat dose)	4.42	17990	2670	4	*518986*
Mouse, Male	EPA	2000 mg/kg (repeat dose)	NE	10014	613	8	*8232576*
Mouse, Male	EPA	4000 mg/kg (repeat dose)	NE	12117	718	8	*8232576*

Table 2.4-2. Summary of Pharmacokinetic Parameters of 14C-Ethyl-EPA, EPA, and DHA from Omthera TK Studies and Published Literature

Species, Sex	Test Article/ Analyte	Dose	T½ (hr) (α phase, ß phase)	AUC (µg·hr/mL)	C_{max} (µg/mL)	T_{max} (hr)	Study Report/ Reference
Rat, Female	EPA	30 mg/kg (single dose)	6.9, 24.7	504.9	14.8	9	*Ishiguro et al., 1987b*
Rat, Female	EPA	33.8 mg/kg (repeat dose)	NE	1109	67.8	2	*519026*
Rat, Female	EPA	62.04 mg/kg (repeat dose)	17.67	2337	187	1	*518986*
Rat, Female	EPA	186 mg/kg (repeat dose)	NE	1017	55.2	2.88	*519026*
Rat, Female	EPA	366.6 mg/kg (repeat dose)	16.56	7693	424	2	*518986*
Rat, Female	EPA	620 mg/kg (repeat dose)	NE	9.348	582	5	*519026*
Mouse, Female	EPA	1000 mg/kg (repeat dose)	NE	4448	326	2	*8232576*
Rat, Female	EPA	1240.8 mg/kg (repeat dose)	7.59	13790	1710	4	*518986*
Mouse, Female	EPA	2000 mg/kg (repeat dose)	NE	7328	431	4	*8232576*
Mouse, Female	EPA	4000 mg/kg (repeat dose)	NE	12763	722	8	*8232576*
Rat, Male	DHA	11.9 mg/kg (repeat dose)	NE	1471	73.3	0.75	*519026*
Rat, Male	DHA	21.89 mg/kg (repeat dose)	97.72	17380	158	1	*518986*

Table 2.4-2. Summary of Pharmacokinetic Parameters of 14C-Ethyl-EPA, EPA, and DHA from Omthera TK Studies and Published Literature

Species, Sex	Test Article/ Analyte	Dose	T½ (hr) (α phase, ß phase)	AUC (µg·hr/mL)	C_{max} (µg/mL)	T_{max} (hr)	Study Report/ Reference
Rat, Male	DHA	65.7 mg/kg (repeat dose)	NE	1295	63.1	2.25	*519026*
Rat, Male	DHA	129.65 mg/kg (repeat dose)	9.75	5308	392	2	*518986*
Rat, Male	DHA	219 mg/kg (repeat dose)	NE	4604	222	1.25	*519026*
Rat, Male	DHA	437.8 mg/kg (repeat dose)	5.39	7229	796	4	*518986*
Mouse, Male	DHA	1000 mg/kg (repeat dose	NE	10102	502	1	*8232576*
Rat, Male	DHA	1300 mg/kg (repeat dose)	NE	883	141	NE	*Hadley et al., 2010*
Mouse, Male	DHA	2000 mg/kg (repeat dose)	NE	10305	518	2	*8232576*
Rat, Male	DHA	2500 mg/kg (repeat dose)	NE	1193	188	NE	*Hadley et al., 2010*
Mouse, Male	DHA	4000 mg/kg (repeat dose)	NE	8717	623	2	*8232576*
Rat, Male	DHA	5000 mg/kg (repeat dose)	NE	4564	335	NE	*Hadley et al., 2010*
Rat, Female	DHA	11.9 mg/kg (repeat dose)	NE	1666	85.2	0.50	*519026*
Rat, Female	DHA	21.89 mg/kg (repeat dose)	113.34	19060	154	1	*518986*

Table 2.4-2. Summary of Pharmacokinetic Parameters of 14C-Ethyl-EPA, EPA, and DHA from Omthera TK Studies and Published Literature

Species, Sex	Test Article/ Analyte	Dose	T½ (hr) (α phase, ß phase)	AUC (µg·hr/mL)	C_{max} (µg/mL)	T_{max} (hr)	Study Report/ Reference
Rat, Female	DHA	65.7 mg/kg (repeat dose)	NE	1852	87.8	0.13	*519026*
Rat, Female	DHA	129.65 mg/kg (repeat dose)	71.20	13590	233	2	*518986*
Rat, Female	DHA	219 mg/kg (repeat dose)	NE	4395	258	4	*519026*
Rat, Female	DHA	437.8 mg/kg (repeat dose)	8.19*	6873*	897	4	*518986*
Mouse, Female	DHA	1000 mg/kg (repeat dose)	Not provided	7673	419	24	*8232576*
Rat, Female	DHA	1300 mg/kg (repeat dose)	NE	1330	188	NE	*Hadley et al., 2010*
Mouse, Female	DHA	2000 mg/kg (repeat dose)	NE	8354	522	2	*8232576*
Rat, Female	DHA	2500 mg/kg (repeat dose)	NE	2705	201	NE	*Hadley et al., 2010*
Mouse, Female	DHA	4000 mg/kg (repeat dose)	NE	8186	445	2	*8232576*
Rat, Female	DHA	5000 mg/kg (repeat dose)	NE	3496	391	NE	*Hadley et al., 2010*
Dog, Male	EPA	30 mg/kg (single dose)	16.1, 81.6	1210.3	15.1	24	*Ishiguro et al., 1987b*

* Estimate considered unreliable.
NE – Not estimated

The Sponsor submitted the report of GLP study "Investigation of the influence of omefas on the *in vitro* permeation of Methotrexate across Caco-2 cell monolayer- STP 033/00". This study was designed to determine the effect of omefas interacts with active transporter systems in an *in vitro* model of the intestinal barrier. Findings of this study suggested that omefas at 0.5% and 1% have no influence on the transport of Methotrexate.

Below publications were submitted by the Sponsor regarding the distribution of omega-3:

2.4.3.2 Distribution

DHA and EPA have a synergy with other cell membrane nutrients, specifically phospholipids and antioxidants. Depending on the requirements of the tissue, the phospholipids phosphatidylcholine (PC), phosphatidylserine (PS) and phosphatidylethanolamine (PE) can carry substantial amounts of DHA in their "tail" positions. These phospholipid "parent molecules" also anchor EPA within the membrane lipid bilayer (*Kidd, 2007*)

The n-3 polyunsaturated fatty acids (PUFAs) (EPA and DHA) when consumed undergoes digestion in the small intestine which allows for absorption, transport into blood, and subsequent assimilation within tissues themselves through the body (including brain, retina, heart and other tissues) (*DHA EPA Omega 3 Institute, 2011*).

The radioactivity protein binding rates of EPA in plasma of male rats at 1, 9 and 24 hours post dose, were 95.1%, 96.5% and 98.5%, respectively, in rats dosed with 30 mg/kg and 86.7%, 93.8% and 98.8%, respectively, in rats dosed with 1000 mg/kg (*Ishiguro et al., 1987b*; *Section 2.6.5-6*). In dogs, the corresponding protein binding after 9 and 24 hours were 96.7% and 98.7% after an oral administration of 30 mg/kg.

Metabolism

EPA and DHA are metabolic intermediates and components of human and animal diets. Very small amounts are found in a free, unesterified form. EPA and DHA are metabolized by esterases in the GI tract to release unesterified forms which can be absorbed and incorporated into triglycerides, cholesterol esters and phospholipids in tissues. Elimination of EPA, DHA, their ethyl esters and metabolites would follow the same metabolic fate as any other lipid i.e. β=-oxidation followed by tricarboxylic acid cycle and excretion as CO2 and water.

Based on submitted publications by the Sponsor, EPA and DHA are inhibitors of CYP2C9 (diclofenac 4-hydroxylation)- and CYP2C19 (mephenytoin 4-hydroxylation)-catalyzed metabolic reactions and to a lesser extent inhibited CYP1A2 (phenacetin O-deethylation), CYP2E1 (chlorzoxazone 6-hydroxylation) and CYP3A4 (midazolam 1-hydroxylation). Metabolic activity of these two compounds decreased by CYP4A11, CYP4F2 and CYP4F12 and increased by CYP3Aand CYP4F3B after incubation in human microsomes.

The Sponsor conducted studies to detect the potential inhibitory effect of omefas on different CYP450 isoenzymes (Study No. 03101701 and 300101). Findings of these studies suggested that the effect of omefas on CYP450 isoenzymes activities was concentration dependent and up to 10 μM showed no inhibition potential (a safety margin of up to 100-fold of the physiologically relevant concentration). Therefore, up to 10 μM omefas, the significant drug-drug interaction is not expected (Sponsor Table):

Inhibition of CYP450 Marker Reactions by Omefas® at Different Concentrations

CYP Enzyme	Marker Reaction	% Inhibition at 0.1 µM omefas[1]	% Inhibition at 1 µM omefas[1]	% Inhibition at 10 µM omefas[1]	Positive Control[2]
2B6	S-mephenytoin N-demethylation	4.1 ± 14.2	2.5 ± 11.9	2.5 ± 13.9	81.5 ± 2.8
2C8	paclitaxel 6α-hydroxylation	9.3 ± 11.9	-1.8± 10.3	12.7 ± 10.2	87.1 ± 1.3
2C9	diclofenac 4'-hydroxylation	-5.6 ± 16.9	-8.3 ± 14.7	-11.9 ± 17.7	52.5 ± 8.3

[1] mean of triplicates ± standard error

[2] positive controls: 50 µM Triethylphenylphosphoramide (CYP2B6); 10 µM Quercetin (CYP2C8); 1 µM Sulfaphenazole (CYP2C9)

A large proportion (~50% of an oral dose) of radiolabeled EPA and DHA was eliminated in expired air. The remainder was excreted in feces and urine.

5.2 Toxicokinetics

The Sponsor conducted TK studies in mice, rats and dogs. Findings of these studies generally suggested that the levels of EPA and DHA increased over time and with dose levels (Sponsor's Table):

Table 2.6.7-3. Toxicokinetics: Overview of Toxicokinetics Data					Test Article: Omefas	
	Steady State AUC (µg·hr/mL)					
Daily Dose (mg/kg/day)	Mouse[a]		Rat[b]		Dog[c]	
	M	F	M	F	M	F
50					1354 (EPA) 1471 (DHA)	1109 (EPA) 1666 (DHA)
100			1725 (EPA) 2679 (DHA)	1466 (EPA) 2665 (DHA)		
300					1123 (EPA) 1295 (DHA)	1017 (EPA) 1852 (DHA)
600			7216 (EPA) 4235 (DHA)	4808 (EPA) 2889 (DHA)		
1000	5966 (EPA) 10102 (DHA)	4448 (EPA) 7673 (DHA)			10260 (EPA) 4604 (DHA)	9348 (EPA) 4395 (DHA)
2000	10014 (EPA) 10305 (DHA)	7328 (EPA) 8354 (DHA)	17400 (EPA) 6813 (DHA)	11780 (EPA) 5690 (DHA)		
4000	12117 (EPA) 8717 (DHA)	12763 (EPA) 8186 (DHA)				

[a] = 4-week oral repeat dose study in mice (AUC data from Day 28)
[b] = 13-week oral repeat dose study in rats (AUC data from Week 13)
[c] = 39-week oral repeat dose study in dogs (AUC data from Week 39)

6 General Toxicology

6.1 Single-Dose Toxicity

No single-dose toxicity study was submitted.

6.2 Repeat-Dose Toxicity

Mice Studies

A non-GLP 14-Day oral toxicity study was conducted orally in CByB6F1 mice up to 4000 mg/kg/day to determine the dose-selection for the 4-week dose-range finding study. NOAEL was at 4000mg/kg/day.

Study Tittle: 4-Week Dose Range-finding Oral Gavage Toxicity and Toxicokinetic Study with Omefas in 001178-W (wild type) Mice (Study # 1008185)

Reviewed study in DARRTS (P/T review #1).

Key Study Findings:

Epanova up to 4000mg/kg/day was well tolerated (no mortality, abnormal clinical signs, microscopic findings). Clinical chemistry changes were reported for the intended action of Epanova in decrease in cholesterol concentration for ≥LD-treated animals and decrease in triglyceride concentration in males at HD and females at ≥MD. NOAEL was at 4000 mg/kg/day (5 fold safety margin to MRHD of 4g/day based on the body surface area comparison).

Rat Studies:

A 14-Day dose-range-finding study was conducted with omefas up to 5000mg/kg/day for a 4-week-dose-range finding study. NOAEL was at 5000mg/kg/day.

Reviewed study in DARRTS (P/T review #2).

Study Tittle: 4-WEEK SUBACUTE TOXICITY STUDY OF OMEFAS® (ACTIVE PRINCIPLE OF EPANOVA®) BY ORAL ADMINISTRATION TO RATS (Study #: 22004)

Reviewed study in DARRTS (P/T review #2).

Key Study Findings:

The repeat-dose toxicity study with omefas at 0, 300, 3000, and 5000 mg/kg/day in rats by oral (gavage) for 28 days showed no treatment-related effects in any groups except for the liver enzyme activities. In this study, the plasma levels of total cholesterol and triglycerides were decreased (25 to 48% and 14 to 29%, respectively) in all treatment groups. In addition, the plasma levels of ALT and AP were increased (39 to 85% and 40 to 66%, respectively) in all the 3,000 and 5,000mg/kg/day treated animals with no other related changes in liver. NOAEL was at 10000 mg/kg/day (3 fold safety margin to MRHD of 4g/day based on the body surface area comparison).

Study Title: Epanova: 13 Week oral (gavage) Bridging toxicity and Toxicokinetics Study in Rats	
Study no.:	518986
Study report location:	(b) (4)
Conducting laboratory and location:	

Date of study initiation:	14 October 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Epanova, lot #:626100 and with density of 0.924 g/cm3, a purity of 100%; Omthera, lot #:2548561 and 1184921and purity of 100%

Reviewer: Because of the available carcinogenicity data with Lovaza, the *Sponsor conducted this bridging toxicity study to determine the dose selection for the rat carcinogenicity study with Epanova*.

Key Study Findings

- Both formulations (Epanova or Omacor) showed expected pharmacologic effects by decreased in the serum levels of cholesterol and triglyceride levels (Epanova at ≥600 mg/kg/day or Omacor at 2160 mg/kg/day). However, the higher bioavailability for omefas was noted compared to Omacor-treated animals (AUC for EPA and DHA was 1.7- and 2.5-fold higher, respectively).

- Body weight gains and food consumption were lower in omefas HD-treated animals compared to comparator; but not to control animals. These differences were not considered for the dose selection for the Epanova carcinogenicity studies.

- At HD for both formulations, increased live enzyme activities were reported for levels of ALP, AP, and AST; these changes were correlated to microscopic findings in liver at the same dose level.

- Histopathology findings were reported mostly for HD-treated animals for both formulations in kidney, lung and liver as follows: Kidney: dose-related trend in mild microscopic basophilic cortical tubules in all Epanova-treated males and with the comparator and in one female at HD (more incidence at HD-treated animals compared to comparator treated animals). This finding was not correlated with any other renal-related function changes. Lung: alveolar macrophage accumulation in lungs was noted in all treated animals; however, with higher incidence and greater severity at HD-treated males. Liver: cholangiohepatitis with widespread biliary proliferation with hepatocellular necrosis in one Epanove HD-treated male.

- The NOAEL was established at 600mg/kg/day; 1.5 fold to MHRD of 4g/day based on the body surface area comparison. The Sponsor NOAEL was at 2000mg/kg/day.

Methods	
Doses:	Epanova:100, 600, 2000mg/kg/day Comparator: 2160mg/kg/day
Frequency of dosing:	Once daily (7 days/week) for 13 weeks
Route of administration:	Oral gavage
Dose volume:	2.2, 0.11, 0.65, 2.2 for Epanova and and 2.4 mL/kg for comparator
Formulation/Vehicle:	Corn Oil (2.2 mL/kg)

Species/Strain:	Sprague-Dawley rats
Number/Sex/Group:	10/sex/group
Age:	6 Week old
Weight:	205-273g, while females were 147-202 g
Satellite groups:	3/sex/group
Unique study design:	10/sex/group except for control 3/sex/group
Deviation from study protocol:	Not remarkable

Observations and Results

Mortality

Unremarkable

Mortality was not in a dose-response relationship. Signs of gavage injury were reported in 2 animals (1/LD female; 1/MD male) and no histopathological findings were reported in other two animals (1/LD female; 1/HD male) (Sponsor's Table):

Animal/ Sex	Dose Level (mg/kg/day)	Day	Fate	Clinical Observations	Major Macroscopic/Microscopic Findings
65F	100	35	KP	Swollen/not using front left fore limb, leaning to one side, piloerection, hunched posture and subdued behaviour.	Oesophageal rupture, the front left limb was abnormal in shape at the axillary position. Inflammatory changes affecting the tissues adjacent to the oesophagus
68F		37	KP	Convulsions lasting approximately 5 min, tongue swollen, prostrate, piloerection, bulging eyes and abnormal respiration.	Tongue swollen, thoracic cavity and both horns of the uterus contained fluid, ovaries dark; left lung lobe pale; right lung lobe pale focus, middle accessory dark. Mild accumulations of alveolar macrophages
28M	600	89	KP	Abnormal respiration, swollen ventral thorax, subdued behaviour, rolling gait, piloerection, hunched posture, thin appearance and weight loss.	Oesophageal rupture, abnormal stomach contents, intestines distended by gas, thoracic cavity contained fluid, all lung lobes discoloured and spongy, all liver lobes dark, skin around neck, muzzle and forelimbs red. Inflammatory changes affecting the tissues adjacent to the oesophagus, which, extended to include the surfaces of the lung and heart
33M	2000	22	KP	Open lesion on dorsal neck, eyes pale, skin pale on the extremities.	Dry skin scab at dorsal neck, all lung lobes dark, axillary lymph nodes enlarged Focal skin ulceration and axillary lymph node histiocytosis

KP = Killed Prematurely

Clinical Signs

Unremarkable

Fur staining around the muzzle was reported with a dose-response relationship (1 male at LD; 3 males at MD; 7 males and 1 female at HD; and 1 male in Comparator).

Body Weights

Unremarkable

No dose-response relationship was reported for body weight gain (increased body weight gain at LD- treated animals and MD- treated females); body weight gain was lower (ss) in HD-treated animals compared to the Comparator group (not to the control).

Feed Consumption

Increased food consumption (ss) was reported in all Epanova- treated animals from Week 4 (males) and Week 5 (females) compared to controls. In addition, HD- Epanova- treated animals had lower food consumption compared to the Comparator (ss from week 4 in males and at week 4 for females). The comparator- treated- males had higher (ss) food consumption compared to controls.

Ophthalmoscopy

Unremarkable

Hematology

Unremarkable

Clinical Chemistry

Clinical chemistry findings were summarized as follows:

- The expected pharmacological actions of both compounds were reported as decreased levels of cholesterol and triglyceride (ss for cholesterol at Week 7 and ss for both cholesterol and triglyceride at Week 14) for all MD and HD-treated animals and for the Comparator-treated animals. Epanove HD-treated-males compared to the Comparator-treated-animals had ss lower cholesterol levels at Week 14.

- Other clinical chemistry changes were reported mostly at HD for both formulations at Week 14 for increases levels of alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST). The levels of calcium were lower (ss) at both time points in MD and HD- females (not in a dose response at week 14) and the Comparator. The levels of globulin were lower (ss) for MD (week 7) and HD (Week 14) in Epanove-treated-males and the Comparator at week 7 and in Epanova HD- treated-males at Week 14.

Sponsor's Tables below were modified by reviewer to only show these data:

Week 7

Group	1	2	3	4	5
Test Item	Control	----------	Epanova	----------	Comparator
Dosage (mg/kg/day)	0	100	600	2000	2160

Group / sex		Ca mmol/L	ALP iu/L	ALT iu/L	AST iu/L	Glob g/L	Chol mmol/L	Trig mmol/L
1M	Mean	2.65	120	51	76	21	1.9	1.10
	SD	0.05	30	6	5	3	0.4	0.69
	n	9	9	9	9	9	9	9
2M	Mean	2.61	100	58	82	19	1.7	1.10
	SD	0.05	18	5	12	3	0.2	0.58
	n	10	8	8	8	10	8	8
3M	Mean	2.60	88[b]	57	83	18[a]	1.4[c]	0.98
	SD	0.07	23	7	10	3	0.3	0.11
	n	8	10	10	10	9	10	10
4M	Mean	2.50[c]	121	60	94[b]	14[c]	1.3[c]	0.68
	SD	0.07	32	18	14	2	0.1	0.23
	n	8	9	9	9	8	9	9
5M	Mean	2.56[b]	106	62[b]	85	17[b]	1.2[c]	0.84
	SD	0.07	23	8	11	2	0.2	0.30
	n	9	10	10	10	9	10	10

Significantly different from Group 1:a=p<0.05,b=p<0.0
Significantly different from Group 5:d=p<0.05,e=p<0.01,f=p<

Group	1	2	3	4	5
Test Item	Control	----------	Epanova	----------	Comparator
Dosage (mg/kg/day)	0	100	600	2000	2160

Group / sex		Ca mmol/L	ALP iu/L	ALT iu/L	AST iu/L	Glob g/L	Chol mmol/L	Trig mmol/L
1F	Mean	2.64	142	62	79	15	2.0	1.22
	SD	0.06	40	12	11	2	0.4	0.20
	n	9	7	7	7	9	7	7
2F	Mean	2.59	123	67	77	15	1.9	1.60
	SD	0.08	34	9	9	2	0.3	0.64
	n	8	9	9	9	8	9	9
3F	Mean	2.58[a]	145	68	93	16	1.6[a]	1.36
	SD	0.07	23	13	20	2	0.3	0.37
	n	9	9	9	9	9	9	9
4F	Mean	2.56[b]	160	67[c]	112[c]	18	1.1[cd]	0.83
	SD	0.04	28	12	27	4	0.2	0.31
	n	9	8	8	8	9	8	8
5F	Mean	2.53[c]	154	82[b]	101[a]	17	1.5[b]	1.05
	SD	0.06	24	11	11	6	0.4	0.34
	n	10	10	10	10	10	10	10

Significantly different from Group 1:a=p<0.05,b=p<0.01,c=p<0.001
Significantly different from Group 5:d=p<0.05,e=p<0.01,f=p<0.001

Week 14

Group	1	2	3	4	5
Test Item	Control	----------	Epanova	----------	Comparator
Dosage (mg/kg/day)	0	100	600	2000	2160

Group / sex		Ca mmol/L	ALP iu/L	ALT iu/L	AST iu/L	Glob g/L	Chol mmol/L	Trig mmol/L
1M	Mean	2.63	142	62	79	23	2.0	1.22
	SD	0.03	40	12	11	1	0.4	0.20
	n	7	7	7	7	7	7	7
2M	Mean	2.65	123	67	77	23	1.9	1.60
	SD	0.04	34	9	9	4	0.3	0.64
	n	9	9	9	9	9	9	9
3M	Mean	2.63	145	68	93	20	1.6[a]	1.36
	SD	0.05	23	13	20	3	0.3	0.37
	n	9	9	9	9	9	9	9
4M	Mean	2.61	160	67[c]	112[c]	18[cd]	1.1[cd]	0.83
	SD	0.06	28	12	27	3	0.2	0.31
	n	8	8	8	8	8	8	8
5M	Mean	2.66	154	82[b]	101[a]	21	1.5[b]	1.05
	SD	0.04	24	11	11	3	0.4	0.34
	n	10	10	10	10	10	10	10

Significantly different from Group 1:a=p<0.05,b=p<0.01,c=p<0.001
Significantly different from Group 5:d=p<0.05,e=p<0.01,f=p<0.001

Group	1	2	3	4	5
Test Item	Control	----------	Epanova	----------	Comparator
Dosage (mg/kg/day)	0	100	600	2000	2160

Group / sex		Ca mmol/L	ALP iu/L	ALT iu/L	AST iu/L	Glob g/L	Chol mmol/L	Trig mmol/L
1F	Mean	2.80	79	61	93	15	2.2	1.79
	SD	0.09	15	26	62	2	0.4	0.50
	n	10	10	10	10	10	10	10
2F	Mean	2.68[a]	73	74	94	16	2.1	1.49
	SD	0.10	20	16	20	2	0.2	0.76
	n	7	7	7	7	7	7	7
3F	Mean	2.68[a]	62	57	83	17	1.6[c]	1.22[b]
	SD	0.09	15	10	13	3	0.5	0.46
	n	10	10	10	10	10	10	10
4F	Mean	2.84[b]	102[ad]	63	166	19[b]	1.3[c]	0.85[c]
	SD	0.62	36	21	235	3	0.3	0.23
	n	10	10	10	10	10	10	10
5F	Mean	2.66[b]	81	61	84	18[a]	1.4[c]	1.11[b]
	SD	0.07	18	9	13	3	0.3	0.34
	n	10	10	10	10	10	10	10

Significantly different from Group 1:a=p<0.05,b=p<0.01,c=p<0.001
Significantly different from Group 5:d=p<0.05,e=p<0.01,f=p<0.001

Week 7

Comparison with:	Alkaline phosphatase	Alanine aminotransferase	Aspartate aminotransferase
Males receiving 2000mg Epanova/kg/day			
Controls	120.4 p<0.05	109.4	138.1 p<0.01
Comparator	114.4	90.9	111.5
Males receiving Comparator			
Controls	105.2	120.3	123.8 p<0.05
Females receiving 2000mg Epanova/kg/day			
Controls	100.8	117.7	123.7 p<0.01
Comparator	114.2	96.8	110.6
Females receiving Comparator			
Controls	88.3	121.6 p<0.01	111.8

Values calculated as a Percentage (%) of the control or Comparator

Week 14

Comparison with:	Alkaline phosphatase	Alanine aminotransferase	Aspartate aminotransferase
Males receiving (2000mg Epanova/kg/day)			
Controls	112.7	108.1	141.8 p<0.001
Comparator	103.9	81.7 p<0.01	110.9
Males receiving Comparator			
Controls	108.5	132.3 p<0.01	127.9 p<0.05
Females receiving (2000mg Epanova/kg/day)			
Controls	129.1 p<0.05	103.3	178.5
Comparator	125.9 p<0.05	103.3	197.6
Females receiving Comparator			
Controls	102.5	100.0	90.3

Values calculated as a Percentage (%) of the control or Comparator

Urinalysis

Unremarkable

Gross Pathology

No significant changes were reported except for pale pancreas in two HD- treated- females.

Organ Weights

Observed changes were not remarkable and not associate to any other changes.

Histopathology

Adequate Battery? Yes

Peer Review Performed? Yes

Histopathology findings were reported mostly for HD- treated animals for both formulations in kidney, lung, liver and hearts.

Kidney: dose-related trend in mild microscopic basophilic cortical tubules in all Epanova treated males and with the comparator and in one female at HD. This finding was reported with more incidences at HD-omefas treated animals compared to comparator treated animals (not correlated with any other renal-related function changes).

Lung: treatment-related alveolar macrophage accumulation in lungs in all treated animals; this finding was not in a dose response trend; however, higher incidence with greater severity was reported at HD- treated males.

Liver: cholangiohepatitis with widespread biliary proliferation with hepatocellular necrosis in one Epanove HD-treated male.

Heart: moderate inflammation of the epicardial surface of the heart and mild inflammation of the pleura (probably due to gavage injury) in one Epanova HD- treated-female (Sponsor's Tables):

Summary of Kidney and lung Microscopic Findings (Day 92/93)

	Males					Females				
Group	1	2	3	4	5	1	2	3	4	5
Dose (mg/kg/day)	0	100	600	2000	2160	0	100	600	2000	2160
No. animals examined	10	10	9	9	10	10	8	10	10	10
Kidney (No. Examined)	10	10	9	9	10	10	8	10	10	10
Cortex; Basophilia, tubular	(0)	(1)	(2)	(5)	(3)	(0)	(0)	(0)	(1)	(0)
Mild	0	1	2	5	3	0	0	0	1	0
Lung (No. Examined)	10	10	9	9	10	10	8	10	10	10
Accumulation; alveolar macrophage	(2)	(1)	(2)	(4)	(1)	(0)	(2)	(1)	(3)	(0)
Mild	2	1	1	1	1	0	2	1	3	0
Moderate	0	0	1	3	0	0	0	0	0	0

Numbers in parentheses represent the number of animals with the finding.

Sponsor's Tables were modified by reviewer to show below significant histopathological findings:

Removal Reason: TERMINAL EUTHANASIA	MALES					FEMALES				
	0 mg/kg/d	100 mg/kg/d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d	0 mg/kg/d	100 mg/kg/d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d
Number of Animals on Study :	10	10	9	9	10	10	8	10	10	10
Number of Animals Completed:	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
HEART;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	9	8	9	6	9	10	8	10	9	10
Infiltration; mononuclear; focal	(1)	(2)	(0)	(3)	(1)	(0)	(0)	(0)	(0)	(0)
mild	1	2	0	3	1	0	0	0	0	0
Inflammation; chronic-active; Epicardium	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
moderate	0	0	0	0	0	0	0	0	1	0
KIDNEY;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	9	8	5	4	4	8	7	10	8	9
Hydronephrosis	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
mild	0	0	0	0	0	0	0	0	1	0
Basophilia; tubular; Cortex; bilateral; multifocal	(0)	(1)	(0)	(3)	(1)	(0)	(0)	(0)	(1)	(0)
mild	0	1	0	3	1	0	0	0	1	0
LIVER;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	5	6	4	5	5	7	3	8	6	5
Congestion	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(1)	(0)
mild	0	0	0	0	1	0	0	0	1	0
LUNG;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	6	5	4	4	4	7	5	9	5	7
Congestion; focal	(0)	(0)	(2)	(0)	(1)	(0)	(1)	(0)	(0)	(2)
mild	0	0	2	0	1	0	1	0	0	2
Congestion; multifocal	(2)	(4)	(1)	(2)	(4)	(3)	(0)	(0)	(1)	(0)
mild	2	4	1	2	4	3	0	0	1	0
Edema; alveolar	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	1	0	0	0	0	0	0
Fibrosis; pleural; multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
mild	0	0	0	0	0	0	0	0	0	1
Infiltration; neutrophilic; Alveolus; focal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	0	1	0	0	0	0	0
Inflammation; chronic-active; Pleura	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
mild	0	0	0	0	0	0	0	0	1	0
Accumulation; alveolar; macrophage; focal	(1)	(1)	(0)	(1)	(1)	(0)	(2)	(0)	(0)	(0)
mild	1	1	0	1	1	0	2	0	0	0
Accumulation; alveolar; macrophage; multifocal	(1)	(0)	(2)	(3)	(0)	(0)	(0)	(1)	(3)	(0)
mild	1	0	1	0	0	0	0	1	3	0
moderate	0	0	1	3	0	0	0	0	0	0
THYMUS;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	8	9	8	7	9	9	7	9	9	10
Inflammation; acute	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
mild	0	0	0	0	0	0	0	0	1	0
Necrosis; focal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
mild	0	0	0	0	0	0	0	0	1	0

Sponsor's Table:

Observations: Neo-Plastic and Non Neo-Plastic	MALES					FEMALES				
Removal Reason: TERMINAL EUTHANASIA	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d
Number of Animals on Study :	10	10	9	9	10	10	8	10	10	10
Number of Animals Completed:	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
ADRENAL GLAND;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	8	8	10	8	10	10	9
Vacuolation; cortical; Zona Fasciculata	(0)	(0)	(0)	(1)	(2)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	1	2	0	0	0	0	0
Infiltration; fatty; focal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
mild	0	0	0	0	0	0	0	0	0	1
AORTA;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
BONE, STERNUM;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
BRAIN;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
CERVIX;										
Examined	(-)	(-)	(-)	(-)	(-)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	-	-	-	-	-	10	8	10	10	10
EPIDIDYMIS;										
Examined	(10)	(10)	(9)	(9)	(10)	(-)	(-)	(-)	(-)	(-)
Within Normal Limits	10	10	8	9	10	-	-	-	-	-
Aspermia	0	0	1	0	0	-	-	-	-	-
EYE;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	9	10	9	9	10	10	8	10	10	10
Infiltration, Mixed Cell; corneal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
mild	1	0	0	0	0	0	0	0	0	0
HARDERIAN GLAND;										
Examined	(10)	(10)	(8)	(9)	(10)	(10)	(8)	(10)	(9)	(10)
Within Normal Limits	10	8	7	9	10	10	8	10	8	10

Observations: Neo-Plastic and Non Neo-Plastic	MALES					FEMALES				
Removal Reason: TERMINAL EUTHANASIA	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d
Number of Animals on Study :	10	10	9	9	10	10	8	10	10	10
Number of Animals Completed:	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
HARDERIAN GLAND; (continued)										
Not Examined: NOT PRESENT ON SLIDE	0	0	1	0	0	0	0	0	1	0
Infiltration, Mononuclear Cell; focal	(0)	(1)	(1)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
mild	0	1	1	0	0	0	0	0	1	0
Infiltration, Mononuclear Cell; multifocal	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	1	0	0	0	0	0	0	0	0
HEART;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	9	8	9	6	9	10	8	10	9	10
Infiltration; mononuclear; focal	(1)	(2)	(0)	(3)	(1)	(0)	(0)	(0)	(0)	(0)
mild	1	2	0	3	1	0	0	0	0	0
Inflammation; chronic-active; Epicardium	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
moderate	0	0	0	0	0	0	0	0	1	0
INTESTINE, CECUM;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
INTESTINE, COLON;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
INTESTINE, DUODENUM;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
INTESTINE, ILEUM;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
INTESTINE, JEJUNUM;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
INTESTINE, RECTUM;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10

Observations: Neo-Plastic and Non Neo-Plastic	MALES					FEMALES				
Removal Reason: TERMINAL EUTHANASIA	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d
Number of Animals on Study :	10	10	9	9	10	10	8	10	10	10
Number of Animals Completed:	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
KIDNEY;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	9	8	5	4	4	8	7	10	8	9
Fibrosis; Cortex; unilateral; focal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	0	1	0	0	0	0	0
Hydronephrosis	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
mild	0	0	0	0	0	0	0	0	1	0
Mineralization; Corticomedullary Junction	(0)	(0)	(0)	(0)	(0)	(1)	(1)	(0)	(0)	(1)
mild	0	0	0	0	0	1	1	0	0	1
Infiltration, Mononuclear Cell; bilateral; multifocal	(1)	(1)	(1)	(0)	(1)	(1)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	1	0	0	0	0	0
mild	0	1	1	0	0	1	0	0	0	0
Infiltration, Mononuclear Cell; unilateral; focal	(0)	(0)	(1)	(1)	(1)	(0)	(0)	(0)	(0)	(0)
mild	0	0	1	1	1	0	0	0	0	0
Basophilia; tubular; Cortex; bilateral; multifocal	(0)	(1)	(0)	(3)	(1)	(0)	(0)	(0)	(1)	(0)
mild	0	1	0	3	1	0	0	0	1	0
Basophilia; tubular; Cortex; unilateral; focal	(0)	(0)	(2)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	2	1	0	0	0	0	0	0
Basophilia; tubular; Cortex; unilateral; multifocal	(0)	(0)	(0)	(1)	(2)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	1	2	0	0	0	0	0
LIVER;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	5	6	4	5	5	7	3	8	6	5
Congestion	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(1)	(0)
mild	0	0	0	0	1	0	0	0	1	0
Hypertrophy; hepatocellular; Centrilobular	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
mild	1	0	0	0	0	0	0	0	0	0
Infiltration; mononuclear; focal	(1)	(2)	(1)	(1)	(2)	(2)	(1)	(0)	(1)	(2)
mild	1	2	1	1	2	2	1	0	1	2
Infiltration; mononuclear; multifocal	(3)	(2)	(4)	(2)	(2)	(1)	(3)	(2)	(2)	(3)
mild	3	2	4	2	2	1	3	2	2	3
Vacuolation; glycogen; Periportal; hepatocellular; diffuse	(0)	(0)	(1)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
mild	0	0	1	0	0	0	1	0	0	0
Cholangiohepatitis	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
moderate	0	0	0	1	0	0	0	0	0	0

Observations: Neo-Plastic and Non Neo-Plastic	MALES					FEMALES				
Removal Reason: TERMINAL EUTHANASIA	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d
Number of Animals on Study :	10	10	9	9	10	10	8	10	10	10
Number of Animals Completed:	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
LUNG;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	6	5	4	4	4	7	5	9	5	7
Congestion; focal	(0)	(0)	(2)	(0)	(1)	(0)	(1)	(0)	(0)	(2)
mild	0	0	2	0	1	0	1	0	0	2
Congestion; multifocal	(2)	(4)	(1)	(2)	(4)	(3)	(0)	(0)	(1)	(0)
mild	2	4	1	2	4	3	0	0	1	0
Edema; alveolar	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	1	0	0	0	0	0	0
Fibrosis; pleural; multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
mild	0	0	0	0	0	0	0	0	0	1
Infiltration; neutrophilic; Alveolus; focal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	0	1	0	0	0	0	0
Inflammation; chronic-active; Pleura	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
mild	0	0	0	0	0	0	0	0	1	0
Accumulation; alveolar; macrophage; focal	(1)	(1)	(0)	(1)	(1)	(0)	(2)	(0)	(0)	(0)
mild	1	1	0	1	1	0	2	0	0	0
Accumulation; alveolar; macrophage; multifocal	(1)	(0)	(2)	(3)	(0)	(0)	(0)	(1)	(3)	(0)
mild	1	0	1	0	0	0	0	1	3	0
moderate	0	0	1	3	0	0	0	0	0	0
LYMPH NODE, MESENTERIC;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	9	10	9	8	10	10	8	10	10	10
Hyperplasia; lymphocytic	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	1	0	0	0	0	0	0
Plasmacytosis	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
mild	1	0	0	0	0	0	0	0	0	0
LYMPH NODE, MANDIBULAR;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(7)	(10)	(10)	(10)
Within Normal Limits	7	6	9	8	9	10	6	8	9	9
Not Examined: NOT PRESENT ON SLIDE	0	0	0	0	0	0	1	0	0	0
Plasmacytosis	(3)	(4)	(0)	(1)	(1)	(0)	(1)	(2)	(1)	(1)
mild	2	4	0	1	1	0	1	2	1	1
moderate	1	0	0	0	0	0	0	0	0	0

Observations: Neo-Plastic and Non Neo-Plastic	MALES					FEMALES				
Removal Reason: TERMINAL EUTHANASIA	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d
Number of Animals on Study :	10	10	9	9	10	10	8	10	10	10
Number of Animals Completed:	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
MAMMARY GLAND;										
Examined	(10)	(10)	(8)	(8)	(10)	(9)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	8	8	10	9	8	10	10	10
Not Examined: NOT PRESENT ON SLIDE	0	0	1	1	0	1	0	0	0	0
SKELETAL MUSCLE;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	8	9	8	10	8	10	10	10
Infiltration; mononuclear; Interstitium; multifocal	(0)	(0)	(1)	(0)	(2)	(0)	(0)	(0)	(0)	(0)
mild	0	0	1	0	2	0	0	0	0	0
NERVE, OPTIC;										
Examined	(10)	(9)	(9)	(9)	(9)	(7)	(7)	(10)	(9)	(10)
Within Normal Limits	10	9	9	9	9	7	7	10	9	10
Not Examined: NOT PRESENT ON SLIDE	0	1	0	0	1	3	1	0	1	0
NERVE, SCIATIC;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
OVARY;										
Examined	(-)	(-)	(-)	(-)	(-)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	-	-	-	-	-	10	8	10	10	10
PANCREAS;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
PARATHYROID GLAND;										
Examined	(8)	(10)	(9)	(9)	(10)	(8)	(8)	(10)	(10)	(9)
Within Normal Limits	8	10	9	9	10	8	8	10	10	9
Not Examined: NOT PRESENT ON SLIDE	2	0	0	0	0	2	0	0	0	1
PITUITARY GLAND;										
Examined	(10)	(10)	(9)	(8)	(10)	(10)	(8)	(9)	(10)	(10)
Within Normal Limits	9	10	9	8	10	10	8	9	10	10
Not Examined: NOT FOUND AT TRIMMING	0	0	0	0	0	0	0	1	0	0
Not Examined: NOT PRESENT ON SLIDE	0	0	0	1	0	0	0	0	0	0

Observations: Neo-Plastic and Non Neo-Plastic	MALES					FEMALES				
Removal Reason: TERMINAL EUTHANASIA	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d
Number of Animals on Study :	10	10	9	9	10	10	8	10	10	10
Number of Animals Completed:	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
PITUITARY GLAND; (continued)										
Cyst	1	0	0	0	0	0	0	0	0	0
PROSTATE GLAND;										
Examined	(10)	(10)	(9)	(9)	(10)	(-)	(-)	(-)	(-)	(-)
Within Normal Limits	10	10	7	8	7	-	-	-	-	-
Infiltration; mononuclear; Interstitium; multifocal	(0)	(0)	(2)	(1)	(3)	(-)	(-)	(-)	(-)	(-)
mild	0	0	2	1	3	-	-	-	-	-
SEMINAL VESICLE;										
Examined	(10)	(10)	(9)	(9)	(10)	(-)	(-)	(-)	(-)	(-)
Within Normal Limits	10	10	9	9	10	-	-	-	-	-
SKIN;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
SPINAL CORD;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
SPLEEN;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
STOMACH;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	9	10	9	9	10	10	8	10	10	10
Hyperkeratosis	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
mild	1	0	0	0	0	0	0	0	0	0
TESTIS;										
Examined	(10)	(10)	(9)	(9)	(10)	(-)	(-)	(-)	(-)	(-)
Within Normal Limits	10	10	8	9	10	-	-	-	-	-
Degeneration; Germinal Epithelium; unilateral; diffuse	(0)	(0)	(1)	(0)	(0)	(-)	(-)	(-)	(-)	(-)
marked	0	0	1	0	0	-	-	-	-	-

Observations: Neo-Plastic and Non Neo-Plastic	MALES					FEMALES				
Removal Reason: TERMINAL EUTHANASIA	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d
Number of Animals on Study :	10	10	9	9	10	10	8	10	10	10
Number of Animals Completed:	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
THYMUS;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	8	9	8	7	9	9	7	9	9	10
Congestion	(2)	(1)	(1)	(2)	(1)	(1)	(1)	(1)	(0)	(0)
minimal	2	1	0	1	0	1	1	0	0	0
mild	0	0	1	1	1	0	0	1	0	0
Inflammation; acute	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
mild	0	0	0	0	0	0	0	0	1	0
Necrosis; focal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
mild	0	0	0	0	0	0	0	0	1	0
THYROID GLAND;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
TONGUE;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
TRACHEA;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
URETER;										
Examined	(9)	(10)	(9)	(9)	(10)	(9)	(8)	(9)	(10)	(9)
Within Normal Limits	9	10	9	9	10	9	8	9	10	9
Not Examined: NOT PRESENT ON SLIDE	1	0	0	0	0	1	0	1	0	1
URINARY BLADDER;										
Examined	(9)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	9	10	9	9	10	10	8	10	10	10
Not Examined: NOT PRESENT ON SLIDE	1	0	0	0	0	0	0	0	0	0
UTERUS;										
Examined	(-)	(-)	(-)	(-)	(-)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	-	-	-	-	-	9	5	8	6	8
Dilation	(-)	(-)	(-)	(-)	(-)	(1)	(3)	(2)	(4)	(2)
mild	-	-	-	-	-	1	3	2	4	2

Observations: Neo-Plastic and Non Neo-Plastic	MALES					FEMALES				
Removal Reason: TERMINAL EUTHANASIA	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d
Number of Animals on Study :	10	10	9	9	10	10	8	10	10	10
Number of Animals Completed:	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
VAGINA;										
Examined	(-)	(-)	(-)	(-)	(-)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	-	-	-	-	-	9	8	8	10	10
Mucification	(-)	(-)	(-)	(-)	(-)	(1)	(0)	(2)	(0)	(0)
mild	-	-	-	-	-	0	0	2	0	0
moderate	-	-	-	-	-	1	0	0	0	0
SUBMAXILLARY SALIVARY GLAND;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
SUBLINGUAL SALIVARY GLAND;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
OESOPHAGUS;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
FEMORAL BONE (STIFLE);										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
MARROW SMEAR;										
Examined	(10)	(10)	(9)	(9)	(10)	(10)	(8)	(10)	(10)	(10)
Within Normal Limits	10	10	9	9	10	10	8	10	10	10
SKIN, OTHER;										
Examined	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
Within Normal Limits	0	1	0	0	0	0	0	0	0	0
Ulceration; focal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
mild	0	0	0	0	0	0	0	0	0	1
TAIL;										
Examined	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Within Normal Limits	0	0	1	0	0	0	0	0	0	0

Observations: Neo-Plastic and Non Neo-Plastic	MALES					FEMALES				
Removal Reason: MORIBUND EUTHANASIA	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d
Number of Animals on Study :	0	0	1	1	0	0	2	0	0	0
Number of Animals Completed:	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
ADRENAL GLAND;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
AORTA;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
BONE, STERNUM;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
BRAIN;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
CERVIX;										
Examined	(-)	(-)	(-)	(-)	(-)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	-	-	-	-	-	0	2	0	0	0
EPIDIDYMIS;										
Examined	(0)	(0)	(1)	(1)	(0)	(-)	(-)	(-)	(-)	(-)
Within Normal Limits	0	0	1	1	0	-	-	-	-	-
EYE;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
HARDERIAN GLAND;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
HEART;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	0	1	0	0	2	0	0	0
Inflammation; chronic-active; Epicardium	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	1	0	0	0	0	0	0	0

Observations: Neo-Plastic and Non Neo-Plastic	MALES					FEMALES				
Removal Reason: MORIBUND EUTHANASIA	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d
Number of Animals on Study :	0	0	1	1	0	0	2	0	0	0
Number of Animals Completed:	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
INTESTINE, CECUM;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	0	1	0	0	2	0	0	0
Dilation	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	1	0	0	0	0	0	0	0
INTESTINE, COLON;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
INTESTINE, DUODENUM;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	0	1	0	0	2	0	0	0
Dilation	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	1	0	0	0	0	0	0	0
INTESTINE, ILEUM;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
INTESTINE, JEJUNUM;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	0	1	0	0	2	0	0	0
Dilation	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	1	0	0	0	0	0	0	0
INTESTINE, RECTUM;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
KIDNEY;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	0	1	0	0	1	0	0	0
Mineralization; Corticomedullary Junction	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
mild	0	0	0	0	0	0	1	0	0	0
Infiltration, Mononuclear Cell; unilateral; focal	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	1	0	0	0	0	0	0	0

Observations: Neo-Plastic and Non Neo-Plastic	MALES					FEMALES				
Removal Reason: MORIBUND EUTHANASIA	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d
Number of Animals on Study :	0	0	1	1	0	0	2	0	0	0
Number of Animals Completed:	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
LIVER;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	0	1	0	0	1	0	0	0
Congestion	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	1	0	0	0	0	0	0	0
Infiltration; mononuclear; multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
mild	0	0	0	0	0	0	1	0	0	0
LUNG;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	0	1	0	0	1	0	0	0
Edema; alveolar	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
marked	0	0	1	0	0	0	0	0	0	0
Inflammation; chronic-active; Pleura	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
marked	0	0	1	0	0	0	0	0	0	0
Accumulation; alveolar; macrophage; multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
mild	0	0	0	0	0	0	1	0	0	0
LYMPH NODE, AXILLARY;										
Examined	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
Within Normal Limits	0	0	0	0	0	0	0	0	0	0
Histiocytosis; sinusoidal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	1	0	0	0	0	0	0
LYMPH NODE, MESENTERIC;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
LYMPH NODE, MANDIBULAR;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
MAMMARY GLAND;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
SKELETAL MUSCLE;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)

Observations: Neo-Plastic and Non Neo-Plastic	MALES					FEMALES				
Removal Reason: MORIBUND EUTHANASIA	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d
Number of Animals on Study :	0	0	1	1	0	0	2	0	0	0
Number of Animals Completed:	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
SKELETAL MUSCLE; (continued)										
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
NERVE, OPTIC;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
NERVE, SCIATIC;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
OVARY;										
Examined	(-)	(-)	(-)	(-)	(-)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	-	-	-	-	-	0	2	0	0	0
PANCREAS;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
PARATHYROID GLAND;										
Examined	(0)	(0)	(0)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	0	1	0	0	2	0	0	0
Not Examined: NOT PRESENT ON SLIDE	0	0	1	0	0	0	0	0	0	0
PITUITARY GLAND;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
PROSTATE GLAND;										
Examined	(0)	(0)	(1)	(1)	(0)	(-)	(-)	(-)	(-)	(-)
Within Normal Limits	0	0	1	1	0	-	-	-	-	-
SEMINAL VESICLE;										
Examined	(0)	(0)	(1)	(1)	(0)	(-)	(-)	(-)	(-)	(-)
Within Normal Limits	0	0	1	1	0	-	-	-	-	-
SKIN;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)

Observations: Neo-Plastic and Non Neo-Plastic	MALES					FEMALES				
Removal Reason: MORIBUND EUTHANASIA	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d
Number of Animals on Study :	0	0	1	1	0	0	2	0	0	0
Number of Animals Completed:	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
SKIN; (continued)										
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
SPINAL CORD;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
SPLEEN;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
STOMACH;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
TESTIS;										
Examined	(0)	(0)	(1)	(1)	(0)	(-)	(-)	(-)	(-)	(-)
Within Normal Limits	0	0	1	1	0	-	-	-	-	-
THYMUS;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	0	1	0	0	2	0	0	0
Inflammation; chronic-active	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
marked	0	0	1	0	0	0	0	0	0	0
THYROID GLAND;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
TONGUE;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
TRACHEA;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0

Observations: Neo-Plastic and Non Neo-Plastic	MALES					FEMALES				
Removal Reason: MORIBUND EUTHANASIA	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d
Number of Animals on Study :	0	0	1	1	0	0	2	0	0	0
Number of Animals Completed:	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
URETER;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(1)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	1	0	0	0
Not Examined: NOT PRESENT ON SLIDE	0	0	0	0	0	0	1	0	0	0
URINARY BLADDER;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
UTERUS;										
Examined	(-)	(-)	(-)	(-)	(-)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	-	-	-	-	-	0	1	0	0	0
Dilation	(-)	(-)	(-)	(-)	(-)	(0)	(1)	(0)	(0)	(0)
mild	-	-	-	-	-	0	1	0	0	0
VAGINA;										
Examined	(-)	(-)	(-)	(-)	(-)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	-	-	-	-	-	0	1	0	0	0
Mucification	(-)	(-)	(-)	(-)	(-)	(0)	(1)	(0)	(0)	(0)
mild	-	-	-	-	-	0	1	0	0	0
SUBMAXILLARY SALIVARY GLAND;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
SUBLINGUAL SALIVARY GLAND;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
OESOPHAGUS;										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	0	1	0	0	1	0	0	0
Inflammation, Acute	(0)	(0)	(1)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
moderate	0	0	1	0	0	0	1	0	0	0
FEMORAL BONE (STIFLE);										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0

Observations: Neo-Plastic and Non Neo-Plastic	MALES					FEMALES				
Removal Reason: MORIBUND EUTHANASIA	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d	0 mg/kg/d	100 mg.kg.d	600 mg/kg/d	2000 mg/kg/d	2160 mg/kg/d
Number of Animals on Study :	0	0	1	1	0	0	2	0	0	0
Number of Animals Completed:	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
MARROW SMEAR:										
Examined	(0)	(0)	(1)	(1)	(0)	(0)	(2)	(0)	(0)	(0)
Within Normal Limits	0	0	1	1	0	0	2	0	0	0
SKIN, OTHER:										
Examined	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
Within Normal Limits	0	0	0	0	0	0	0	0	0	0
Ulceration; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
moderate	0	0	0	1	0	0	0	0	0	0

Toxicokinetics

In general, the levels of DHA and EPA after a single dose or repeat dose increased with increasing dose in all animals. The Tmax for these compounds was reported for 1 to 4 h (Sponsor's Tables):

DHA

Toxicokinetic Parameters Indicative of Systemic Exposure to DHA Following Oral Administration in Males and Females

Sex	Group	Dose (mg/kg/day)	Day/Week	AUC(0-inf) (µg.h/mL)	AUC(0-t) (µg.h/mL)	Cmax (µg/mL)
Male	2	100	Day 1	8113	1927	90.2
			Week 13	17380	2679	158
	3	600	Day 1	6022	3147	245
			Week 13	5308	4235	392
	4	2000	Day 1	8177	4104	274
			Week 13	7229	6813	796
	5 (Omacor)	2160	Day 1	12780*	3472	223
			Week 13	7711	5740	413
Female	2	100	Day 1	7224	1845	92.8
			Week 13	19060	2665	154
	3	600	Day 1	9291	2275	135
			Week 13	13590	2889	233
	4	2000	Day 1	4728	2904	235
			Week 13	6873*	5690	897
	5 (Omacor)	2160	Day 1	47800*	3018	161
			Week 13	8034	4349	347

* estimate considered unreliable

EPA

Toxicokinetic Parameters Indicative of Systemic Exposure to EPA Following Oral Administration in Males and Females

Sex	Group	Dose (mg/kg/day)	Day/Week	AUC(0-inf) (µg.h/mL)	AUC(0-t) (µg.h/mL)	Cmax (µg/mL)
Male	2	100	Day 1 Week 13	1288 2288	1022 1725	78.7 203
	3	600	Day 1 Week 13	3857 8089	3514 7216	361 751
	4	2000	Day 1 Week 13	7279 17990	5578 17400	393 2670
	5 (Omacor)	2160	Day 1 Week 13	7011* 10510	3904 8452	366 814
Female	2	100	Day 1 Week 13	911.7 2337	741.1 1466	66.6 187
	3	600	Day 1 Week 13	2393 7693	2058 4808	168 424
	4	2000	Day 1 Week 13	6723 13790	5460 11780	626 1710
	5 (Omacor)	2160	Day 1 Week 13	29280* 11260	2997 6741	195 615

* estimate considered unreliable

Dosing Formulation Analysis

According to the Sponsor "Stability analysis, as measured by peroxide and anisidine content, was previously performed for the test item extracted from the capsules in [redacted] (b) (4) Study No 426864, which demonstrated that the test item was stable for at least 24 h from extraction under the conditions used in this study. Therefore, no further analysis was conducted. "

A 26-Week Toxicity Study of Epanova by Oral Gavage in Rats	
Study #	[redacted] (b) (4) 519251
Study report location	[redacted] (b) (4)
CRO/Laboratory name	
CRO/Laboratory address	
Date of study initiation	May 03, 2012
GLP compliance statement	Yes
GLP issues identified	None
QA statement	Yes
Drug, lot #, and % purity	Epanova in gelatin capsules; lot #: 626100 ([redacted] (b) (4) 36355 (Omthera); Purity: 99.8%

Key Study Findings

- Mortality was not in a dose-response manner; however, it was higher in the HD-treated animals especially in males. At HD, animals were reported with abnormal sneezing, wheezing respiration, subdued behavior, piloerection, excess salivation, and coughing.

- Increased in liver weight at HD was noted with increased levels of serum ALP (no histopathological findings). Increased in the thyroid weight and liver weight were correlated with low cholesterol and lipid synthesis (pharmacological action of Epanova). At HD, increased lung weight correlated with microscopic findings in the lung.

- NOAEL was at 600mg/kg/day (1.5 fold to MHRD of 4g/day based on a body surface area comparison) based on mortality, increased liver weights and ALP activity at 2000mg/kg/day. The sponsor NOAEL was at 2000mg/kg/day.

Methods	
Doses	0 (corn oil control), 100, 600 and 2000 mg/kg/day Epanova
Frequency of dosing	26 consecutive weeks
Route of administration	Oral
Dose volume	2.2, 0.11, 0.65 and 2.2 mL/kg
Formulation/Vehicle	Corn oil (CAS No. 8001-30-07)
Species/Strain	Sprague-Dawley strain (Crl:CD(SD))
Number/Sex/Group	15/sex/group
Age	8 weeks old
Weight	Males:274-345g; Females: 185-237g
Satellite groups	5/sex/group
Unique study design	None
Deviation from study protocol	On Day 95, all LD animals were overdosed (5X of their actual dose) due the incorrect size of syringe being used for dose administration (1 dose of 182).

Group Number	Animal Identification No.				Test Item	Dose Level (mg/kg/day)	Dose Volume (mL/kg)
	Main Study		Toxicokinetic Study				
	Males	Females	Males	Females			
1	1-15	61-75	121-125	141-145	Corn Oil	0	2.2
2	16-30	76-90	126-130	146-150	Epanova	100	0.11
3	31-45	91-105	131-135	151-155	Epanova	600	0.65
4	46-60	106-120	136-140	156-160	Epanova	2000	2.2

Dose volumes took into account the concentration of EPA and DHA.

Observations and Results

Mortality

Mortality was reported for 9 animals (8 main study and 1 TK study).

Mortality			
Dose Group	Males/Day of Death	Females/Day of Death	Total Death/Dose Group
0	1 (day 8)	None	1
100	1 (day 58)	1 (day 176)	2
600	1 (day 138)	None	1
2000	3 (days: 65, 161,174)	1 (day 5)	4

Reviewer: Mortality was not in a dose-response manner; however, it was higher in the HD-treated animals, especially in males. In Control- treated animals that were dosed with the same volume of oil, there was only one incidence of mortality. In addition, all HD-treated animals were

reported with abnormal sneezing, wheezing respiration, subdued behavior, piloerection, excess salivation, and coughing. Therefore, the cause of death probably was due to oral (gavage) administration of oily, low pH of omefas. It appears that males were more sensitive to higher dose of Epanova compared to female and als levels of EPA and DHA were higher in males compared to females.

See Table below from the Sponsor for premature decedent details:

Text Table 13
Premature decedents

Animal/ Sex	Dose Level (mg/kg/day)	Day of Death	Fate	Notable clinical observations seen immediately before death	Major Macroscopic/Microscopic Findings
14M	0	8	KP	Intermittent and crackling respiration, subdued behaviour, swollen right ventral thorax, piloerection leaning to the one side, limping on right fore foot and fur stained around muzzle.	Enlarged, ventral thorax, may account for swollen ventral thorax (muscle appears gelatinous). Inflammatory cell infiltration in the lung, moderate serosal inflammation in the oesophagus,
24M	100	58	KP	Abnormal respiration, swollen ventral abdomen, rolling gait, piloerection, eyes and skin on extremities, pale, and fur stained around muzzle.	Pale fluid accumulation in abdominal cavity, liver enlarged, all lobes (may account for swollen ventral abdomen), dark fluid accumulation. Marked centrilobular hepatocyte vacuolation, with necrosis and inflammation (relates to necropsy findings)
80 F	100	176	KP	Abnormal respiration, subdued behaviour, body held low, prostrate, body limp, eyes pale and scabs on ears, head, muzzle and tail.	Dark fluid accumulation in abdominal cavity. Many tissues infiltrated by lymphoma cells.
31M	600	138	KP	Animal bit and swallowed plastic gavage. Excess salivation.	Plastic gavage tube in oesophagus.
48M	2000	65	KP	Abnormal respiration, subdued behaviour, rolling gait, ploughing, excess salivation and eyes dark and partially closed.	All lobes of lung failure to collapse. Lung findings 2-5, trachea finding 2.
55M	2000	161	KP	Abnormal and wheezing respiration, prostrate and fur around muzzle wet (red in colour).	Lung dark all lobes, skin dark red at muzzle, blood filled thoracic cavity, dark fluid accumulation in trachea. Lung findings 1, 4 and 9, nasal cavity finding 1 and trachea finding 1.
60M	2000	174	FD	Crackling respiration and excess salivation.	Lung dark, spongy and mottled all lobes. Lung findings 3, 5, 6 and 7, nasal cavity finding 1.
106F	2000	5	FD	Irregular respiration, subdued behaviour, hunched posture, body held low and excess salivation.	Generally autolysed, lung spongy and severely reddened, clear fluid in thoracic cavity.
137F (TK animal)	2000	162	KP	Abnormal respiration, excess salivation and eyes dark and partially closed and fur stained around eyes, muzzle and nose.	Yellow gelatineous contents in duodenum, jejunum and ileum. No histological evaluation performed

KP = Killed Prematurely
FD = Found Dead
Lung findings -1: Desquamation, bronchial/bronchiolar. 2: Collapse, lobar. 3: Degeneration, with inflammation, bronchiolar. 4: Necrosis, broncho-alveolar. 5: Oedema, alveolar. 6: Inflammation, purulent. 7: Alveolar foamy macrophage accumulation. 8: Inflammation, interstitial. 9: Foreign material, alveolar.
Nasal cavity findings - 1: Desquamation, with or without necrosis, epithelial. 2: Degeneration, with inflammation. 3: Degeneration. 4: Olfactory epithelial atrophy, level III. 5: Rhinitis. 6: Exudate. 7: Squamous metaplasia, level I
Trachea findings - 1: Desquamation, epithelial. 2: Atrophy, epithelial

Clinical Signs

Clinical signs of excessive salivation and coughing in males at both HD and MD and females at HD were noted.

Body Weights

Lower body weight and body weight gain were observed in the LD (ss from Week 7) and HD (ss from Week 14) treated animals.

Feed Consumption

No treatment-related effect

Ophthalmoscopy

No treatment-related effect

Hematology

No-treatment-related findings

Clinical Chemistry

Most significant changes were noted for the levels of cholesterol at Weeks 13 and 27 in all treated males and for MD- and HD- treated females. Increased (ss) levels of alkaline phosphatase activities were reported in MD- and HD-treated males at Weeks 13 and 27 (no histological correlates).

Urinalysis

No treatment-related effect

Gross Pathology

In the lung, at HD, pale/dark foci, discoloration, reddened, spongy and failure to collapse were noted (Sponsor's Table):

Summary of Necropsy Findings: Premature Decedents

Group	:	1	2	3	4
Test Item	:	Control	----------	Epanova	----------
Dosage (mg/kg/day)	:	0	100	600	2000

NECROPSY FINDINGS	GROUP	GROUP TOTALS							
		Males				Females			
		Grp 1	Grp 2	Grp 3	Grp 4	Grp 1	Grp 2	Grp 3	Grp 4
HEART									
Foci, dark				1					
Enlargement			1						
LIVER									
Prominent lobular architecture		1		1	2				
Discolouration			1				1		
Enlargement			1	1			1		
LUNG									
Foci, dark					1				
Failure to collapse					1				
Spongy					1				1
Reddened									1
Discolouration				1	2				
LYMPH NODE (AXILLARY)									
Discolouration, both			1						

The absence of a numeral indicates that the lesion specified was not identified

Pathology File Ref.: PLAPOR_519251_MACPD_LL_KEHP1.SPL

Organ Weights

Changes were reported for HD-treated animals as follows:

- Liver: increased (ss) at HD for all treated animals; this change was correlated with increased ALP activity.
- Lung: increased (ss) at HD for all treated animals.
- Thyroid: increased at ≥600 mg/kg/day in females (ss at 600 mg/kg/day). This change was not in a dose–response manner and was ss at MD with a large variability. Increased thyroid, liver and higher ALP activity were due to the effect of Epanova on lipid synthesis and lipid metabolism.
- Other changes: Increased (ss) at HD for males for brain, kidney, spleen and testes weights (body weight-relative). Sponsor's Tables:

Relative Organ Weights (% Body Weight): Group Mean Values

Group	:	1	2	3	4
Test Item	:	Control	-------	Epanova	-------
Dosage (mg/kg/day)	:	0	100	600	2000

Group / sex		Pituitary	Spleen	Thymus	Thyroid	Uterus
1F	Mean	0.0057	0.162	0.0446	0.00509	0.279
	SD	0.0016	0.021	0.0099	0.00141	0.100
	n	15	15	15	15	15
2F	Mean	0.0061	0.148	0.0382	0.00436	0.239
	SD	0.0020	0.018	0.0058	0.00134	0.038
	n	14	14	14	14	14
3F	Mean	0.0054	0.156	0.0417	0.00636[a]	0.255
	SD	0.0015	0.022	0.0139	0.00223	0.077
	n	15	15	15	15	15
4F	Mean	0.0066	0.168	0.0431	0.00621	0.259
	SD	0.0033	0.020	0.0139	0.00148	0.038
	n	13	14	14	14	14

Significantly different from Group 1:a=p<0.05,b=p<0.01,c=p<0.001

Relative Organ Weights (% Body Weight): Group Mean Values

Group	:	1	2	3	4
Test Item	:	Control	----------	Epanova	----------
Dosage (mg/kg/day)	:	0	100	600	2000

Group / sex		Adrenals	Brain	Epididy-mides	Heart	Kidneys	Liver	Lung
1M	Mean	0.00815	0.329	0.21274	0.276	0.594	3.271	0.312
	SD	0.00136	0.029	0.03282	0.024	0.050	0.193	0.036
	n	14	14	14	14	14	14	14
2M	Mean	0.00923	0.361[b]	0.23946[a]	0.273	0.618	3.188	0.305
	SD	0.00148	0.032	0.02178	0.017	0.076	0.275	0.025
	n	13	14	14	14	14	14	14
3M	Mean	0.00812	0.327	0.20233	0.270	0.588	3.471	0.298
	SD	0.00161	0.020	0.05115	0.029	0.077	0.331	0.036
	n	12	14	14	14	14	14	14
4M	Mean	0.01008[b]	0.367[c]	0.23874	0.288	0.668[b]	3.641[b]	0.390[b]
	SD	0.00153	0.017	0.03312	0.020	0.065	0.359	0.118
	n	11	12	12	12	12	12	12

Significantly different from Group 1:a=p<0.05,b=p<0.01,c=p<0.001

Histopathology

Battery Considered Adequate? Yes

Only tissues for control and high dose animals were examined; however, kidney tissues were evaluated from all treated animals.

Peer Review Performed? Yes

Histopathology findings were summarized as follows:

Kidney: Chronic progressive nephropathy (CPN) was reported in all treated-males and HD-treated females. This finding was not correlated with any other-related findings.

Reviewer: This finding has little or no relevance to humans because CPN is a common, age-related renal disease in laboratory rats (Hard and Khan, 2004).

Respiratory tract (lung, nasal cavity, trachea): at HD, microscopic findings were reported for degeneration, necrosis, inflammation, alveolar edema, accumulation of alveolar macrophages, epithelial desquamation, and atrophy. These findings in HD-treated animals were correlated with higher lung weights and abnormal sneezing and/or wheezing respiration, which were due to reflux associated with the administration procedure (Sponsor's Tables):

Text Table 15
Summary Microscopic Findings – Unscheduled Euthanasia

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (mg/kg/day)	**0**	**100**	**600**	**2000**	**0**	**100**	**600**	**2000**
No. animals examined	**1**	**1**	**1**	**3**	**0**	**1**	**0**	**1**
Lung (No. Examined)	(1)	(1)	(1)	(3)	(0)	(1)	(0)	(1)
Desquamation, bronchial/bronchiolar	0	0	0	1	0	0	0	0
Degeneration, with inflammation, bronchiolar, moderate/marked	0	0	0	2	0	0	0	1
Necrosis, broncho-alveolar, mild/severe	0	0	0	2	0	0	0	0
Oedema, alveolar, moderate/marked	0	0	0	2	0	0	0	0
Inflammation, purulent, mild/severe	0	0	0	1	0	0	0	1
Alveolar foamy macrophage accumulation, minimal/mild	0	0	1	1	0	0	0	0
Foreign material, alveolar, minimal	0	0	0	1	0	0	0	1
Nasal Cavity (No. Examined)	(1)	(0)	(1)	(2)	(0)	(1)	(0)	(1)
Desquamation, with or without necrosis, epithelial	0	0	0	2	0	0	0	0
Degeneration, with inflammation, mild	0	0	0	0	0	0	0	1
Exudate, moderate	0	0	0	0	0	0	0	1
Trachea (No. Examined)	(1)	(1)	(1)	(3)	(0)	(1)	(0)	(1)
Desquamation, epithelial	0	0	0	1	0	0	0	0
Atrophy, epithelial, moderate/marked	0	0	0	1	0	0	0	1

Summary of Histological Findings

Group	:	1	2	3	4
Test Item	:	Control	-------	Epanova	------
Dosage (mg/kg/day)	:	0	100	600	2000

HISTOLOGICAL FINDINGS	GROUP	GROUP TOTALS							
		Males				Females			
		Grp 1	Grp 2	Grp 3	Grp 4	Grp 1	Grp 2	Grp 3	Grp 4
KIDNEY		(14)	(14)	(14)	(12)	(15)	(14)	(15)	(14)
No abnormality detected		5	2	3	2	6	4	6	8
Chronic progressive nephropathy									
minimal		3	6	6	5	1	0	2	4
mild		0	0	1	3	0	0	0	0
Total Incidence		3	6	7	8	1	0	2	4
Basophilic tubules, focal									
minimal		3	4	3	0	2	1	2	0
Total Incidence		3	4	3	0	2	1	2	0
Hyaline casts		1	1	1	1	0	1	3	1
Focal transitional cell hyperplasia		2	0	1	0	1	0	0	1
Pyelitis		1	1	1	0	0	1	0	0
Inflammatory cell infiltration, interstitial, focal		0	0	0	1	1	0	0	0
Inflammatory cell infiltration, pelvic		1	0	1	0	0	0	0	0
Mineral deposits, pelvic		0	0	0	0	0	1	0	0
Mineral deposits, medullary		0	0	0	0	5	9	4	1
Pelvic dilation		0	0	0	0	0	0	0	1
LACRIMAL GLAND		(14)			(12)	(15)			(14)
No abnormality detected		10			12	12			14

Figures in brackets represent the number of animals from which this tissue was examined microscopically

Pathology File Ref.: PLAFOR_519251_MECTK_PR_KEEPI.SPL

Toxicokinetics

Findings suggested that levels of EPA and DHA increased over time and with dose level (except for males at Weeks 13 and 26 for MD and HD). In addition, levels of EPA and DHA were higher in males compared to females (Sponsor's Table):

Text Table 14
Mean concentrations of EPA and DHA in µg/mL

	Group/sex/ dose level (mg/kg/day)							
	1M (0)	2M (100)	3M (600)	4M (2000)	1F (0)	2F (100)	3F (600)	4F (2000)
EPA								
Day 1	25	120	767	960	15	90	272	291
Week 13	17	124	1015	1014	13	204	591	653
Week 26	18	177	1397	981	24	265	832	698
DHA								
Day 1	122	138	425	508	78	111	184	203
Week 13	68	124	593	622	84	203	388	421
Week 26	90	203	684	488	183	258	488	423

Dog Studies:

The 2-week dose-range-finding study up to 3000mg/kg/day was conducted to select the doses for the 4-week subacute toxicity study in dogs. NOAEL was at 3000mg/kg/day.

Reviewed Study in DARRTS (P/T review#2).

Study title: a 4-week Subacute Toxicity Study of Epanova® Coated Capsules by Oral Administration to Beagle Dogs (Study #: 22005)

Reviewed Study in DARRTS (P/T review#2).

Key Findings:

In this study, dogs were treated up to 3000mg/kg/day with Epanova coated capsules by oral for 4 weeks. In this study, expected pharmacological action of Epanova was noted for decreased in serum levels of triglyceride and levels of cholesterol. Target organ toxicity was liver. At 3000 mg/kg/day, increased in ALP activity and liver weights were noted, which correlated with microscopically findings of increased in the severity of plant cell structures/increased glycogen in the liver. NOAEL was at 1000 mg/kg/day (about 8 fold to MHRD of 4g/day based on a body surface area comparison).

Study title: Epanova: 39 Week Oral (Gavage) Toxicity Study in Dogs	
Study no.:	Epanove: 39 Week Oral (Gavage) Toxicity Study in Dogs
Study report location:	519026
Conducting laboratory and location:	(b) (4)
Date of study initiation:	19 Oct 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Epanova, lot#: 143948, Density, 0.924 g/mL, Purity, 100%

Key Study Findings

- Expected the pharmacological action of Epanova was noted for decreased in cholesterol levels in all treated animals (ss in females).

- At 1000mg/kg/day, microscopic findings were reported for 2/4 male dogs as follows: in the heart: 1/4 dog with granuloma /macrophage aggregates, epicardial, focal; and in the aorta: 1/4 dog with mineralization, adventitial, focal. In one of these two dog, liver necrosis (focal) was noted.

- NOAEL was at 300mg/kg/day (2.4 fold safety margin to MHRD of 4 g/day based on a body surface area comparison). The Sponsor's NOAEL was at 1000mg/kg.

Methods	
Doses:	0, 50, 300, 1000 mg/kg/day
Frequency of dosing:	7 days/week for 39 weeks
Route of administration:	Oral gavage
Dose volume:	1.1, 0.06, 0.33, 1.1 mL/kg
Formulation/Vehicle:	Corn Oil
Species/Strain:	Beagle dog
Number/Sex/Group:	4/Sex/Group
Age:	6-7 months old
Weight:	4.9-7.2 kg for males and 4.4-7.1 kg for females
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None that affected study outcome

Observations and Results

Mortality

None

Clinical Signs

Treatment-related incidences of liquid/loose faeces were noted at MD and HD-treated animals (control, 4/8; LD, 3/8; MD, 5/8; and HD, 8/8 animals).

Body Weights

Unremarkable (Sponsor's Figures):

Feed Consumption

Unremarkable

Ophthalmoscopy

Unremarkable

ECG

Unremarkable

Hematology

Unremarkable - Statistical significant changes were reported in some values such as haemoglobin, red blood cell count, haematocrit, reticulocytes, white blood cell count and neutrophils. These changes were not in a dose- or time-response manner and did not correlate to any histopathological-related changes.

Clinical Chemistry

Decreased cholesterol levels (pharmacological effect of Epanova) were reported in all Epanova treated animals (11 to 50%); this effect was reported ss only for treated females (at LD and MD for Weeks 13, 26 and 39 and at HD for all intervals). Sponsor's Table:

Cholesterol Changes

Interval	Dose (mg/kg/day)							
	Control (mmol/L)		50		300		1000	
	M	F	M	F	M	F	M	F
Week 13	4.2±0.4	4.6±0.6	-17	-26**	-14	-20*	-24	-48***
Week 26	4.4±0.4	5.0±1.3	-14	-24	-11	-14	-23	-40**
Week 39	4.4±0.6	5.4±1.1	-14	-26*	-14	-20	-18	-50***

Statistically different from control: * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$
Absolute mean values shown for controls. Percentage change from control is shown for treated groups.
Statistical significance is based on absolute mean value comparison, not percentage change.

Other changes were noted as follows:

Alkaline phosphatase (ALP) values increased (nss) in a dose-response in males at Week 13, 26, 39 (large variability) and decreased in females (ss) at LD and HD at Week 39 (not in a dose-response). Aspartate aminotransferase (AST) increased in males and was ss only in HD animals at week 26 (not at the end of the study).

Table below was formed from the Sponsor's Tables:

Clinical Chemistry: Group Mean Values

Group		1	2	3	4
Test Item		Control	------	Epanova	------
Dosage (mg/kg/day)		0	50	300	1000
Pretrial			**Week 13**		**Week 26**			**Week 39**		
Group / sex		ALP iu/L	ALT iu/L	AST iu/L	ALP u/L	ALT iu/L	AST iu/L	ALP u/L	ALT iu/L	AST iu/L	ALP U/L	ALT U/L	AST U/L
1M	Mean	140	22	31	86	30	34	58	31	33	46	30	34
	SD	37	2	6	13	6	6	14	9	3	9	9	3
	n	4	4	4	4	4	4	4	4	4	4	4	4
2M	Mean	189	26	32	94	32	41	79	32	39	62	29	40
	SD	50	5	3	30	5	4	27	8	3	25	3	2
	n	4	4	4	4	4	4	4	4	4	4	4	4
3M	Mean	128	23	34	130	34	38	102	34	35	80	33	35
	SD	32	7	5	46	4	7	32	2	6	41	5	7
	n	4	4	4	4	4	4	4	4	4	4	4	4
4M	Mean	117	24	31	121	33	42	106	35	43[b]	83	35	38
	SD	6	5	4	18	3	4	62	4	4	42	8	4
	n	4	4	4	4	4	4	4	4	4	4	4	4

[a]Significantly different from Group 1:a=p<0.05,b=p<0.01,c=p<0.001

Clinical Chemistry: Group Mean Values

Group	1	2	3	4
Test Item	Control	------	Epanova	------
Dosage (mg/kg/day)	0	50	300	1000

		Pretrial			Week 13			Week 26			Week 39		
Group / sex		ALP iu/L	ALT iu/L	AST iu/L	ALP iu/L	ALT iu/L	AST iu/L	ALP iu/L	ALT iu/L	AST iu/L	ALP I/L	ALT U/L	AST U/L
1F	Mean	106	26	37	83	31	39	67	35	38	69	30	35
	SD	16	3	10	12	3	9	8	6	9	11	1	7
	n	4	4	4	4	4	4	4	4	4	4	4	4
2F	Mean	134	23	33	81	30	37	55	27	34	45[a]	30	35
	SD	57	7	4	31	7	3	15	6	2	16	10	5
	n	4	4	4	4	4	4	4	4	4	4	4	4
3F	Mean	152	23	30	96	29	33	69	28	30	54	28	32
	SD	37	2	5	14	3	5	7	3	7	8	6	7
	n	4	4	4	4	4	4	4	4	4	4	4	4
4F	Mean	123	28	39	82	32	45	67	28	37	48[a]	34	39
	SD	13	12	7	11	7	5	16	6	5	8	3	6
	n	4	4	4	4	4	4	4	4	4	4	4	4

[a]Significantly different from Group 1:a=p<0.05,b=p<0.01,c=p<0.001

Urinalysis

Unremarkable

Gross Pathology

At HD in males, one dog was reported for dilation of heart and two dogs for discolouration of lymph nodes.

Organ Weights

Unremarkable

Histopathology

Adequate Battery: Yes

Peer Review: Yes

Histological Findings

Microscopic findings were reported for 2/4 male dogs at 1000mg/kg/day as follow: heart: 1/4 dog with granuloma /macrophage aggregates, epicardial, focal; and aorta: 1/4 dog with mineralization, adventitial, focal. One of these 2 dogs also was noted with liver necrosis, focal.

Sponsor's Tables:

Summary of Histological Findings

Group	1	2	3	4
Test Item	Control	-------	Epanova	-------
Dosage (mg/kg/day)	0	50	300	1000

		GROUP TOTALS							
		Males				Females			
HISTOLOGICAL FINDINGS	GROUP	Grp 1	Grp 2	Grp 3	Grp 4	Grp 1	Grp 2	Grp 3	Grp 4
ADRENAL GLAND		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	3	3
Extramedullary haemopoiesis, cortical, focal		0	0	0	0	0	0	0	1
Macrovesicular vacuolation		0	0	0	0	0	0	1	1
AORTA		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		3	4	4	2	4	4	4	4
Mineralisation, adventitial, focal		1	0	0	2	0	0	0	0
HEART		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	2	4	4	4	4
Granuloma/macrophage aggregates, epicardial, focal		0	0	0	1	0	0	0	0
Dilatation, lymphatic, localised		0	0	0	1	0	0	0	0
LIVER		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		3	3	4	3	3	0	3	2
Inflammatory cell foci		1	1	0	1	1	4	1	2
Oil red O stain positive for fat		1	0	1	0	0	2	3	2
Oil red O stain negative for fat		3	4	3	4	4	2	1	2
Necrosis, focal		0	0	0	1	0	0	0	0
LYMPH NODE (MESENTERIC)		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
Pigmented macrophages		0	0	0	0	0	0	0	1
SALIVARY GLAND (SUBMAXILLARY)		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	3	4	4	3	4
Inflammatory cell foci		0	0	0	1	0	0	1	0
UTERUS						(4)	(4)	(4)	(4)
No abnormality detected						3	4	3	4
Cystic endometrial hyperplasia						1	0	0	0
Adenomyosis, localised						0	0	1	0

Figures in brackets represent the number of animals from which this tissue was examined microscopically

Pathology File Ref.: PLAFOR_519026_MIC_LBE_KEEP1.SPL

Summary of Histological Findings

Group	:	1	2	3	4
Test Item	:	Control	-------	Epanova	-------
Dosage (mg/kg/day)	:	0	50	300	1000

		GROUP TOTALS							
		Males				Females			
HISTOLOGICAL FINDINGS	GROUP	Grp 1	Grp 2	Grp 3	Grp 4	Grp 1	Grp 2	Grp 3	Grp 4
ADRENAL GLAND		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	3	3
Extramedullary haemopoiesis, cortical, focal		0	0	0	0	0	0	0	1
Macrovesicular vacuolation		0	0	0	0	0	0	1	1
AORTA		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		3	4	4	2	4	4	4	4
Mineralisation, adventitial, focal		1	0	0	2	0	0	0	0
BONE MARROW		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4
BRAIN		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4
CAECUM		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4

Reviewer: In the aorta, mineralization, adventitial, focal were noted in 2 HD-treated males (#13 and 16) vs. one male in the control. The animal #13 also was reported with liver necrosis (focal). The #16 was also noted with about two times higher level of ALP compared to the control animals.

Sponsor's Tables:

HISTOLOGICAL FINDINGS	GROUP	GROUP TOTALS							
		Males				Females			
		Grp 1	Grp 2	Grp 3	Grp 4	Grp 1	Grp 2	Grp 3	Grp 4
COLON		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4
DUODENUM		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4
EPIDIDYMIS		(4)	(4)	(4)	(4)				
No abnormality detected		4	4	3	4				
Atrophy, unilateral		0	0	1	0				
EYE		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4
FEMUR		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4

HISTOLOGICAL FINDINGS	GROUP	GROUP TOTALS							
		Males				Females			
		Grp 1	Grp 2	Grp 3	Grp 4	Grp 1	Grp 2	Grp 3	Grp 4
GALL BLADDER		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4
HEART		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	2	4	4	4	4
Granuloma/macrophage aggregates, epicardial, focal		0	0	0	1	0	0	0	0
Dilatation, lymphatic, localised		0	0	0	1	0	0	0	0
ILEUM		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4
JEJUNUM		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4
KIDNEY		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		3	3	3	3	4	4	4	4
Inflammatory cell infiltration, interstitial		1	0	1	1	0	0	0	0

HISTOLOGICAL FINDINGS	GROUP	GROUP TOTALS							
		Males				Females			
		Grp 1	Grp 2	Grp 3	Grp 4	Grp 1	Grp 2	Grp 3	Grp 4
KIDNEY		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
Mineral deposits, tubular		0	1	0	0	0	0	0	0
Oil red O stain positive for fat		2	1	2	2	4	4	4	4
Oil red O stain negative for fat		2	3	2	2	0	0	0	0
LARYNX		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4
LIVER		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		3	3	4	3	3	0	3	2
Inflammatory cell foci		1	1	0	1	1	4	1	2
Oil red O stain positive for fat		1	0	1	0	0	2	3	2
Oil red O stain negative for fat		3	4	3	4	4	2	1	2
Necrosis, focal		0	0	0	1	0	0	0	0
LUNG		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		3	4	4	4	3	2	2	4

HISTOLOGICAL FINDINGS	GROUP	GROUP TOTALS							
		Males				Females			
		Grp 1	Grp 2	Grp 3	Grp 4	Grp 1	Grp 2	Grp 3	Grp 4
LUNG		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
Inflammation, acute, polymorphonuclear leukocytic, focal		0	0	0	0	0	0	1	0
Inflammation, chronic, localised		0	0	0	0	1	0	0	0
Inflammatory cell foci		1	0	0	0	0	2	1	0
LYMPH NODE (MANDIBULAR)		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		3	3	1	4	3	2	3	2
Sinus histiocytosis		0	0	0	0	0	1	0	0
Pigmented macrophages		1	1	1	0	1	2	0	1
Erythrocytosis/erythrophagocytosis		0	0	2	0	0	0	1	1
LYMPH NODE (MEDIASTINAL)					(2)				
Erythrocytosis/erythrophagocytosis					2				
LYMPH NODE (MESENTERIC)		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		0	3	4	1	1	3	1	2
Erythrocytosis/erythrophagocytosis		4	1	0	3	3	1	3	2

HISTOLOGICAL FINDINGS	GROUP	GROUP TOTALS							
		Males				Females			
		Grp 1	Grp 2	Grp 3	Grp 4	Grp 1	Grp 2	Grp 3	Grp 4
LYMPH NODE (MESENTERIC)		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
Pigmented macrophages		0	0	0	0	0	0	0	1
LYMPH NODE (PANCREATIC)		(1)							
Erythrocytosis/erythrophagocytosis		1							
MAMMARY GLAND		(2)	(4)	(3)	(3)	(4)	(4)	(4)	(4)
No abnormality detected		2	4	3	3	4	4	4	4
OESOPHAGUS		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	3	4
Inflammatory cell foci, submucosal		0	0	0	0	0	0	1	0
OPTIC NERVE		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4

HISTOLOGICAL FINDINGS	GROUP	GROUP TOTALS							
		Males				Females			
		Grp 1	Grp 2	Grp 3	Grp 4	Grp 1	Grp 2	Grp 3	Grp 4
OVARY						(4)	(4)	(4)	(4)
No abnormality detected						4	4	4	4
PANCREAS (ENDOCRINE)		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4
PANCREAS (EXOCRINE)		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4
PARATHYROID GLAND		(3)	(4)	(3)	(2)	(3)	(4)	(4)	(4)
No abnormality detected		3	2	2	2	3	4	2	3
Cyst		0	2	1	0	0	0	2	1
PITUITARY GLAND		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	3	3	0	2
Inflammatory cell foci		0	0	0	0	1	0	0	0
Cyst		0	0	0	0	0	1	4	2

HISTOLOGICAL FINDINGS	GROUP	GROUP TOTALS							
		Males				Females			
		Grp 1	Grp 2	Grp 3	Grp 4	Grp 1	Grp 2	Grp 3	Grp 4
PROSTATE		(4)	(4)	(4)	(4)				
No abnormality detected		3	4	4	4				
Inflammation, chronic, interstitial, focal		1	0	0	0				
RECTUM		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4
SALIVARY GLAND (SUBMAXILLARY)		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	3	4	4	3	4
Inflammatory cell foci		0	0	0	1	0	0	1	0
SCIATIC NERVE		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4
SKELETAL MUSCLE		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4

HISTOLOGICAL FINDINGS	GROUP	GROUP TOTALS							
		Males				Females			
		Grp 1	Grp 2	Grp 3	Grp 4	Grp 1	Grp 2	Grp 3	Grp 4
SKIN AND SUBCUTIS		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	3	4	4	4	3	2	4
Inflammation, purulent, follicular, focal		0	1	0	0	0	0	0	0
Pyogranuloma, dermis		0	0	0	0	0	1	0	0
Dermatitis, granulomatous, localised		0	0	0	0	0	0	1	0
Inflammatory cell infiltration, dermis		0	0	0	0	0	0	1	0
Hyperkeratosis		0	1	0	0	0	0	0	0
SPINAL CORD		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4
SPLEEN		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4
STERNUM		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4

HISTOLOGICAL FINDINGS	GROUP	GROUP TOTALS							
		Males				Females			
		Grp 1	Grp 2	Grp 3	Grp 4	Grp 1	Grp 2	Grp 3	Grp 4
STOMACH		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	3	4
Inflammatory cell foci, perivascular, submucosal		0	0	0	0	0	0	1	0
TESTIS		(4)	(4)	(4)	(4)				
No abnormality detected		4	4	3	4				
Seminiferous epithelial degeneration		0	0	1	0				
THYMUS		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		3	4	3	3	4	3	2	3
Atrophy/involution		1	0	0	1	0	1	2	0
Cyst		0	0	1	0	0	0	0	1
THYROID GLAND		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4

HISTOLOGICAL FINDINGS	GROUP	GROUP TOTALS							
		Males				Females			
		Grp 1	Grp 2	Grp 3	Grp 4	Grp 1	Grp 2	Grp 3	Grp 4
TONGUE		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	3	4	4	4	4	4
Inflammatory cell foci, connective tissue		0	0	1	0	0	0	0	0
TRACHEA		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		4	4	4	4	4	4	4	4
URINARY BLADDER		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
No abnormality detected		3	4	3	4	4	3	4	4
Mineralisation, arterial		1	0	1	0	0	1	0	0
UTERUS						(4)	(4)	(4)	(4)
No abnormality detected						3	4	3	4
Cystic endometrial hyperplasia						1	0	0	0
Adenomyosis, localised						0	0	1	0

HISTOLOGICAL FINDINGS	GROUP	GROUP TOTALS							
		Males				Females			
		Grp 1	Grp 2	Grp 3	Grp 4	Grp 1	Grp 2	Grp 3	Grp 4
VAGINA						(4)	(4)	(4)	(4)
No abnormality detected						4	4	4	4

Figures in brackets represent the number of animals from which this tissue was examined microscopically

Pathology File Ref: PLAFOR_519026_MIC_LBE_KEEP1.SPL

Special Evaluation

None

Toxicokinetics

Systemic exposure to DHA and EPA was similar between males and females on Day 1 and Week 39, with the exception of systemic exposure to EPA being 2 to 3-fold greater on Day 1 in males than females at MD (Sponsor's Tables):

Text Table 13
Toxicokinetic Parameters Indicative of Systemic Exposure to EPA

Sex	Group	Dose (mg/kg/day)	Day/Week	Cmax (µg/mL)	Cmax/D* (µg/mL)/ (mg/kg/day)	Tmax (h)	AUC(0-t) (µg.h/mL)	AUC(0-t)/D* (µg.h/mL)/ (mg/kg/day)
Male	2	50	Day 1	34.9	1.03	3.75	619.0	18.31
			Week 39	72.7	2.15	1.00	1354	40.07
	3	300	Day 1	137	0.734	2.50	1546	8.312
			Week 39	65.0	0.349	5.50	1123	6.038
	4	1000	Day 1	194	0.313	12.00	3418	5.512
			Week 39	491	0.792	6.25	10260	16.55
Female	2	50	Day 1	37.1	1.10	1.25	501.6	14.84
			Week 39	67.8	2.01	2.00	1109	32.82
	3	300	Day 1	55.5	0.298	5.50	847.1	4.555
			Week 39	55.2	0.297	2.88	1017	5.470
	4	1000	Day 1	174	0.281	3.50	2638	4.255
			Week 39	582	0.938	5.00	9348	15.08

* Normalised based on estimated DHA dose

Text Table 14
Toxicokinetic Parameters Indicative of Systemic Exposure to DHA

Sex	Group	Dose (mg/kg/day)	Day/Week	Cmax (µg/mL)	Cmax/D* (µg/mL)/ (mg/kg/day)	Tmax (h)	AUC(0-t) (µg.h/mL)	AUC(0-t)/D* (µg.h/mL)/ (mg/kg/day)
Male	2	50	Day 1	73.1	6.14	1.50	1547	130.0
			Week 39	73.3	6.16	0.75	1471	123.6
	3	300	Day 1	101	1.54	7.25	1758	26.76
			Week 39	63.1	0.960	2.25	1295	19.71
	4	1000	Day 1	98.8	0.451	2.00	1883	8.597
			Week 39	222	1.01	1.25	4604	21.02
Female	2	50	Day 1	75.7	6.36	1.63	1538	129.2
			Week 39	85.2	7.16	0.50	1666	140.0
	3	300	Day 1	72.4	1.10	13.00	1442	21.94
			Week 39	87.8	1.34	0.13	1852	28.19
	4	1000	Day 1	88.7	0.405	3.50	1402	6.400
			Week 39	258	1.18	4.00	4395	20.07

* Normalised based on estimated DHA dose

Dosing Solution Analysis

No analysis was conducted for this study; stability analysis was previously performed for the test item extracted from the capsules.

7 Genetic Toxicology

Findings from genotoxicity studies suggested that omefas was not genotoxic or clastogenic in the Ames assay, the chromosomal aberration study and in the *in vivo* rat micronucleus study.

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Epanova: Testing for Mutagenic Activity with *Salmonella typhimurium* TA 1535, TA

100, TA 1537 and TA 98 and *Escherichia coli* WP2*uvr*A	
Study no.:	Test Facility No:789390; Report No: 31890
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 10th 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Drug: Epanova; Lot#: 36355 from capsules; Batch #: 143948; % purity: 100%

Key Study Findings

Epanova was not mutagenic in this test system.

Methods	
Strains:	TA1535, TA1537, TA98, TA100 and *E. coli* WP2 *uvrA*
Concentrations in definitive study:	160, 320, 640, 1280, 2560, 5000 g/plate
Basis of concentration selection:	Limit dose recommended by regulatory guidelines (concentrations: 17, 50, 167, 500, 1667 and 5000µg/plate)
Negative control:	DMSO with each strain (+S9 and –S9)
Positive control:	+S9: 2AAN and -S9: NaN3, 2-NF, ENNG, 9-AA
Metabolic activation system	Aroclor 1254-treated induced rat liver S9
Formulation/Vehicle:	Same as negative control
Incubation & sampling time:	The plate incorporation method was used (+S9 and –S9) with incubation at 37C for 3days.

Study Validity

Epanova was tested with positive controls and all positive controls gave the expected results. Therefore, the study was valid.

Results

Epanova was not mutagenic when was tested to a max concentration of 5000 ug/plate in the present of S9 (Sponsor's Tables):

Without metabolic activation

Strain	Test item	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts
TA 1535	**Epanova**	17 µg	*11.3*	*2.1*	*0.8*	13, 9, 12
		50 µg	*9.7*	*3.2*	*0.7*	6, 11, 12
		167 µg	*13.0*	*2.6*	*0.9*	16, 11, 12
		500 µg	*10.0*	*5.2*	*0.7*	7, 7, 16
		1667 µg	*12.0*	*2.6*	*0.9*	11 P, 15 P, 10 P
		5000 µg	*6.7*	*0.6*	*0.5*	7 P, 6 P, 7 P
	DMSO	-	*14.0*	*1.7*	-	12, 15, 15
TA 1537	**Epanova**	17 µg	*9.3*	*3.1*	*0.7*	6, 12, 10
		50 µg	*11.7*	*5.7*	*0.8*	18, 7, 10
		167 µg	*4.3*	*2.5*	*0.3*	4, 7, 2
		500 µg	*7.0*	*2.0*	*0.5*	7, 9, 5
		1667 µg	*5.7*	*1.5*	*0.4*	7 P ST, 6 P ST, 4 P ST
		5000 µg	*5.0*	*1.0*	*0.3*	5 P ST, 4 P ST, 6 P ST
	DMSO	-	*14.3*	*3.1*	-	17, 11, 15
TA 98	**Epanova**	17 µg	*22.7*	*2.3*	*0.8*	20, 24, 24
		50 µg	*21.3*	*3.1*	*0.8*	22, 24, 18
		167 µg	*21.0*	*5.6*	*0.8*	27, 20, 16
		500 µg	*18.7*	*6.4*	*0.7*	15, 26, 15
		1667 µg	*18.0*	*2.0*	*0.7*	18 P, 16 P, 20 P
		5000 µg	*23.3*	*6.8*	*0.8*	21 P, 31 P, 18 P
	DMSO	-	*27.7*	*6.5*	-	21, 28, 34
TA 100	**Epanova**	17 µg	*89.7*	*10.3*	*1.0*	87, 81, 101
		50 µg	*93.0*	*6.9*	*1.0*	89, 101, 89
		167 µg	*79.0*	*7.2*	*0.9*	87, 73, 77
		500 µg	*75.3*	*2.1*	*0.8*	76, 77, 73
		1667 µg	*69.0*	*18.7*	*0.8*	72 P, 86 P, 49 P
		5000 µg	*78.0*	*5.6*	*0.9*	79 P, 72 P, 83 P
	DMSO	-	*89.0*	*11.4*	-	76, 97, 94
WP2uvrA	**Epanova**	17 µg	*6.3*	*3.2*	*0.7*	4, 5, 10
		50 µg	*8.3*	*1.2*	*0.9*	7, 9, 9
		167 µg	*7.7*	*2.1*	*0.9*	10, 7, 6
		500 µg	*5.0*	*1.7*	*0.6*	4, 7, 4
		1667 µg	*5.7*	*2.9*	*0.6*	9 P, 4 P, 4 P
		5000 µg	*3.0*	*1.0*	*0.3*	4 P, 2 P, 3 P
	DMSO	-	*9.0*	*2.0*	-	9, 7, 11

Key to Plate Postfix Codes

P	Precipitate
ST	Slightly Thin Lawn

Without metabolic activation

Strain	Test item	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts
TA 1535	**NaN_3**	1 µg	*467.0*	*17.3*	*33.4*	487, 456, 458
TA 1537	**9AA**	80 µg	*4360.7*	*124.5*	*304.2*	4401, 4460, 4221
TA 98	**2NF**	1 µg	*542.0*	*73.9*	*19.6*	513, 487, 626
TA 100	**NaN_3**	1 µg	*1037.3*	*47.5*	*11.7*	1053, 1075, 984
WP2uvrA	**ENNG**	2 µg	*125.7*	*15.0*	*14.0*	130, 138, 109

Key to Positive Controls

NaN_3	Sodium Azide
9AA	9-Aminoacridine
2NF	2-Nitrofluorene
ENNG	N-Ethyl-N-Nitro-N-Nitrosoguanidine

With metabolic activation

Strain	Test item	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts
TA 1535	**Epanova**	17 µg	*15.0*	*1.7*	*1.4*	13, 16, 16
		50 µg	*6.7*	*0.6*	*0.6*	6, 7, 7
		167 µg	*14.7*	*4.0*	*1.3*	10, 17, 17
		500 µg	*12.7*	*3.1*	*1.2*	12, 16, 10
		1667 µg	*10.3*	*4.5*	*0.9*	6 P, 10 P, 15 P
		5000 µg	*11.0*	*2.6*	*1.0*	13 P, 12 P, 8 P
	DMSO	-	*11.0*	*0.0*	-	11, 11, 11
TA 1537	**Epanova**	17 µg	*17.0*	*1.7*	*0.9*	18, 18, 15
		50 µg	*18.3*	*2.3*	*1.0*	17, 21, 17
		167 µg	*22.0*	*5.3*	*1.2*	26, 24, 16
		500 µg	*13.0*	*2.0*	*0.7*	15, 11, 13
		1667 µg	*8.7*	*1.5*	*0.5*	9 P, 7 P, 10 P
		5000 µg	*6.3*	*2.1*	*0.3*	8 P, 7 P, 4 P
	DMSO	-	*18.7*	*2.9*	-	22, 17, 17
TA 98	**Epanova**	17 µg	*35.0*	*9.0*	*1.3*	35, 26, 44
		50 µg	*29.0*	*3.0*	*1.1*	32, 26, 29
		167 µg	*33.3*	*4.0*	*1.2*	37, 34, 29
		500 µg	*24.3*	*7.5*	*0.9*	32, 24, 17
		1667 µg	*27.7*	*4.0*	*1.0*	27 P, 32 P, 24 P
		5000 µg	*18.7*	*1.5*	*0.7*	20 P, 17 P, 19 P
	DMSO	-	*27.3*	*4.5*	-	32, 23, 27
TA 100	**Epanova**	17 µg	*100.0*	*2.6*	*1.0*	103, 99, 98
		50 µg	*87.3*	*11.2*	*0.8*	97, 75, 90
		167 µg	*91.0*	*3.6*	*0.9*	92, 87, 94
		500 µg	*75.3*	*3.5*	*0.7*	75, 79, 72
		1667 µg	*78.3*	*11.9*	*0.8*	82 P, 88 P, 65 P
		5000 µg	*94.7*	*6.5*	*0.9*	95 P, 88 P, 101 P
	DMSO	-	*104.0*	*16.4*	-	90, 122, 100
WP2uvrA	**Epanova**	17 µg	*9.7*	*5.0*	*1.9*	5, 15, 9
		50 µg	*5.7*	*1.5*	*1.1*	4, 6, 7
		167 µg	*8.0*	*2.6*	*1.6*	7, 11, 6
		500 µg	*10.3*	*4.5*	*2.1*	6, 10, 15
		1667 µg	*8.3*	*2.5*	*1.7*	11 P, 6 P, 8 P
		5000 µg	*3.7*	*3.1*	*0.7*	1 P, 7 P, 3 P
	DMSO	-	*5.0*	*2.6*	-	6, 2, 7

Key to Plate Postfix Codes

P	Precipitate

With metabolic activation

Strain	Test item	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts
TA 1535	**2AAN**	2 µg	*391.7*	*12.7*	*35.6*	406, 382, 387
TA 1537	**2AAN**	2 µg	*206.7*	*20.4*	*11.1*	198, 192, 230
TA 98	**2AAN**	0.5 µg	*229.3*	*16.8*	*8.4*	211, 233, 244
TA 100	**2AAN**	0.5 µg	*655.3*	*105.7*	*6.3*	560, 637, 769
WP2uvrA	**2AAN**	20 µg	*659.0*	*7.2*	*131.8*	665, 661, 651

Key to Positive Controls

2AAN	2-Aminoanthracene

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Appendix 3 Historical Positive and Negative Control Data

Ames Test Historical Vehicle and Positive Control Data 2005-2009

Vehicle Controls (Pooled) - Presence of S9 Mix						
Strain		TA 1535	TA 1537	TA 98	TA 100	WP2*uvrA*
Mean		15	17	32	94	9
Standard Deviation		6	7	9	17	4
Range	Min	4	2	13	59	1
	Max	31	35	62	160	24
No. of Plates		227	225	225	264	222

Vehicle Controls (Pooled) - Absence of S9 Mix						
Strain		TA 1535	TA 1537	TA 98	TA 100	WP2*uvrA*
Mean		15	13	25	92	9
Standard Deviation		5	6	7	19	4
Range	Min	5	1	10	60	1
	Max	30	31	44	163	23
No. of Plates		224	222	225	264	222

Positive Controls - Presence of S9 Mix						
Strain		TA 1535	TA 1537	TA 98	TA 100	WP2*uvrA*
Substance		2AAN	2AAN	2AAN	2AAN	2AAN
Concentration (µg per plate)		2	2	0.5	0.5	20
Mean		428	288	510	735	557
Standard Deviation		133	127	218	337	171
Range	Min	92	66	165	331	125
	Max	821	765	1646	2468	1103
No. of Plates		222	222	222	225	216

Positive Controls - Absence of S9 Mix						
Strain		TA 1535	TA 1537	TA 98	TA 100	WP2*uvrA*
Substance		NaN_3	9AA	2NF	NaN_3	ENNG
Concentration (µg per plate)		1	80	1	1	2
Mean		495	5727	958	1116	227
Standard Deviation		106	2102	474	397	122
Range	Min	263	152	331	551	45
	Max	882	10334	7084	3333	673
No. of Plates		222	222	225	225	222

Audited: (b) (4)
Date audited:
Date signed off:

7.2 *In Vitro* Assays in Mammalian Cells

Study title: Epanova: Chromosomal Aberrations Assay with Chinese Hamster Ovary Cell Cultures *In Vitro*	
Study no.:	Test Facility No:789406; Report No. 31957
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 9th 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Drug: Epanova; Lot#: 36355 from capsules; Batch #: 143948; purity: 100%

Key Study Findings

Epanova did not induce chromosome aberrations with or without of metabolic activation.

Methods	
Cell line	CHO
Concentrations in definitive study	Presence of S9 Mix: 5, 10, 15, 20, 22.5, 25, 27.5 and 30 µg/mL Absence of S9 Mix: 5, 10, 20, 40, 60, 80 and 100 µg/mL
Basis of concentration selection	Maximum dose level at short term and toxicity at long term
Negative control	DMSO
Positive control	+S9: cyclophosphamide (20-50ug/mL); - S9: methyl methanesulphonate (10-40ug/mL)

Formulation/Vehicle	Vehicle control

S9 Mix	Cultures Established	Test	Treatment Period	Recovery Period	Colcemid	Harvest
Presence of S9 mix	*ca* 20 h before exposure	Tests 1 and 2	0-6 h	6-22 h	22-24 h	24 h
Absence of S9 mix		Test 1 only				
		Test 2 only	0-22 h	none	22-24 h	24 h
				22-46 h	46-48 h	48 h

Study Validity

The experiments in this study were deemed to be valid because they fulfilled the following criteria:

There was no evidence of contamination
Cells in vehicle control cultures grew normally
The results of vehicle and positive control cultures were acceptable
There were 3 acceptable dose levels of the test item for assessment

Results

Epanova did not induce structural aberrations when tested with Chinese hamster ovary cell *in vitro*. Epanova induced polyploidy in cultures at 20 and 22.5 µg/mL in present of S9 (not in the absent of S9).

Reviewer: Increased polyploid cells usually showed the test article's potential to inhibit mitotic processes and to induce numerical chromosome aberrations including aneuploidy.

Sponsor's Tables.

Table 1 Aberration Data: Test 1, With S9 Mix, 6 h Treatment, 24 h Harvest

Treatment Group	Conc. (µg/mL)	Decoded Culture No.	No. of Cells Scored	Structural Aberrations										Aberration Frequency		Aberrant Cell Frequency				Numerical Aberrations		
				Chromatid			Chromosome			Complex			Multiple	Other	Lesions/Cell		Including Gaps		Excluding Gaps		% of Cells With		
				G	B	F	G	B	F	E	D	R				Judge	%	Judge	%	Judge	AE	ER	PP
Dimethyl-sulphoxide	1%	1	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	3	0
		2	100	1	0	0	0	0	0	0	0	0	0	0	0.01	-	1	-	0	-	1	0	0
Epanova	5	7	100	1	0	0	0	0	0	0	0	0	0	0	0.01	-	1	-	0	-	0	2	0
		8	100	1	0	0	0	0	0	0	0	0	0	0	0.01	-	1	-	0	-	1	1	0
	10	9	100	1	0	0	0	0	0	0	0	0	0	0	0.01	-	1	-	0	-	0	3	0
		10	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	1	1
	20	11	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	14	0
		12	100	2	0	1	0	0	0	0	0	0	0	0	0.03	-	3	-	1	-	0	8	0
Cyclophos-phamide	40	23	100	6	2	3	0	0	0	8	0	0	0	0	0.27	+	16	+	11	+	3	0	0
	50	24	100	5	5	0	0	0	0	5	0	0	0	0	0.20	+	13	+	9	+	2	0	0

Table 2 Aberration Data: Test 1, Without S9 Mix, 6 h Treatment, 24 h Harvest

Treatment Group	Conc. (µg/mL)	Decoded Culture No.	No. of Cells Scored	Structural Aberrations										Aberration Frequency		Aberrant Cell Frequency				Numerical Aberrations		
				Chromatid			Chromosome			Complex			Mult-iple	Other	Lesions/Cell		Including Gaps		Excluding Gaps		% of Cells With		
				G	B	F	G	B	F	E	D	R				Judge	%	Judge	%	Judge	AE	ER	PP
Dimethyl-sulphoxide	1%	25	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	0	0
		26	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	1	0	0
Epanova	20	27	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	0	0
		28	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	0	0
	39	29	100	1	0	0	0	0	0	0	0	0	0	0	0.01	-	1	-	0	-	0	0	0
		30	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	0	0
	78	31	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	0	0
		32	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	0	1
Methyl methane-sulphonate	30	47	100	1	1	1	0	0	0	0	0	0	0	0	0.03	-	3	-	2	-	2	0	0
	40	48	100	0	11	0	0	0	0	4	0	0	0	0	0.19	+	13	+	13	+	1	0	0

Table 3 Aberration Data: Test 2, With S9 Mix, 6 h Treatment, 24 h Harvest

Treatment Group	Conc. (µg/mL)	Decoded Culture No.	No. of Cells Scored	Structural Aberrations										Aberration Frequency		Aberrant Cell Frequency				Numerical Aberrations		
				Chromatid			Chromosome			Complex			Mult-iple	Other	Lesions/Cell		Including Gaps		Excluding Gaps		% of Cells With		
				G	B	F	G	B	F	E	D	R				Judge	%	Judge	%	Judge	AE	ER	PP
Dimethyl-sulphoxide	1%	49	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	0	0
		50	100	1	0	0	0	0	0	0	0	0	0	0	0.01	-	1	-	0	-	0	0	0
Epanova	15	55	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	2	1
		56	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	3	0
	20	57	100	2	1	0	0	0	0	0	0	0	0	0	0.03	-	3	-	1	-	0	3	0
		58	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	3	0
	22.5	59	100	0	3	0	0	0	0	0	0	0	0	0	0.03	-	2	-	2	-	0	5	0
		60	100	1	1	0	0	0	0	1	0	0	0	0	0.04	-	3	-	2	-	0	2	1
Cyclophos-phamide	30	68	100	1	7	1	0	0	0	1	0	0	0	0	0.11	+	8	+	7	+	0	0	0
	50	70	100	2	7	2	0	0	0	1	0	0	0	0	0.13	+	10	+	8	+	0	0	0

Table 4 Aberration Data: Test 2, Without S9 Mix, 22 h Treatment, 24 h Harvest

Treatment Group	Conc. (µg/mL)	Decoded Culture No.	No. of Cells Scored	Structural Aberrations										Aberration Frequency		Aberrant Cell Frequency				Numerical Aberrations		
				Chromatid			Chromosome			Complex			Mult-iple	Other	Lesions/Cell		Including Gaps		Excluding Gaps		% of Cells With		
				G	B	F	G	B	F	E	D	R				Judge	%	Judge	%	Judge	AE	ER	PP
Dimethyl-sulphoxide	1%	71	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	0	0
		72	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	1	0	0
Epanova	20	77	100	2	0	0	0	0	0	0	0	0	0	0	0.02	-	2	-	0	-	0	0	0
		78	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	0	0
	60	81	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	0	0
		82	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	0	0
	80	83	100	1	0	0	0	0	0	0	0	0	0	0	0.01	-	1	-	0	-	1	0	0
		84	100	3	2	0	0	0	0	0	0	0	0	0	0.05	+-	5	+-	2	-	0	0	0
Methyl methane-sulphonate	20	88	100	4	1	0	0	0	0	2	0	0	0	0	0.09	+	6	+-	3	+-	1	0	0
	30	89	100	5	8	0	0	0	0	7	0	0	0	0	0.27	+	16	+	14	+	0	0	0

Table 5 Aberration Data: Test 2, Without S9 Mix, 22 h Treatment, 48 h Harvest

Treatment Group	Conc. (µg/mL)	Decoded Culture No.	No. of Cells Scored	Structural Aberrations											Aberration Frequency		Aberrant Cell Frequency				Numerical Aberrations		
				Chromatid			Chromosome			Complex			Multiple	Other	Lesions/Cell		Including Gaps		Excluding Gaps		% of Cells With		
				G	B	F	G	B	F	E	D	R				Judge	%	Judge	%	Judge	AE	ER	PP
Dimethyl-sulphoxide	1%	91	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	0	0
		92	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	0	0
Epanova	10	95	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	1	0	0
		96	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	0	0
	40	99	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	0	0
		100	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	0	0
	60	101	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	0	0
		102	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	0	0	1
Methyl methane-sulphonate	30	109	100	0	0	0	0	0	0	0	0	0	0	0	0.00	-	0	-	0	-	1	0	1
	40	110	100	0	12	2	0	0	0	2	0	0	0	0	0.18	+	11	+	11	+	3	0	0

Table 6 Polyploid Data:
Test 2, With S9 Mix, 6 h Treatment, 24 h Harvest

Treatment Group	Conc. (µg/mL)	Decoded No.	No. of Diploid Cells	No. of Polyploid Cells		Frequency of Polyploid Cells	Judge
				Normal	Endoploid		
Dimethyl-sulphoxide	1%	49	300	1	1	0.66	-
		50	300	2	1	0.99	-
Epanova	15	55	300	0	3	0.99	-
		56	300	1	5	1.96	-
	20	57	300	0	14	4.46	+
		58	300	1	14	4.76	+
	22.5	59	300	0	18	5.66	+
		60	300	0	24	7.41	+

7 Polyploid Data:
Test 2, Without S9 Mix, 22 h Treatment, 48 h Harvest

Treatment Group	Conc. (µg/mL)	Decoded No.	No. of Diploid Cells	No. of Polyploid Cells		Frequency of Polyploid Cells	Judge
				Normal	Endoploid		
Dimethyl-sulphoxide	1%	91	300	0	0	0.00	-
		92	300	1	0	0.33	-
Epanova	10	95	300	0	0	0.00	-
		96	300	0	0	0.00	-
	40	99	300	2	0	0.66	-
		100	300	0	0	0.00	-
	60	101	300	0	0	0.00	-
		102	300	0	0	0.00	-

Appendix 11 Historical Negative and Positive Control Data

Negative Control Data

	Number of Records	Parameter	Confidence Levels for Negative Results			Mean and SD for each parameter	
			0-95%	>95-≤99%	>99%	Mean	SD
Structural Aberrations	1833	Lesions/cell	0.00-0.04	>0.04 -≤0.07	>0.07	0.01	0.02
	2157	Aberrant cell frequency including gaps (%)	0-4	>4 -≤6	>6	1.0	1.4
		Aberrant cell frequency excluding gaps (%)	0-2	>2-≤3	>3	0.3	0.7
Numerical Aberrations[1]	1805	AE (%)	0-3	>3-≤8	>8	0.6	1.4
	388	PP + ER (%)	0-1.96	>1.96-≤2.6	>2.6	0.77	0.65
Judgement of test item or positive control culture aberration values			Negative (-)	Suspicious (+-)	Positive (+)	NA	
QUALITY ASSURANCE	Last date data added to database: 07 May 2009 (b) (4)						

1 = Aneuploidy (AE) measured in 100 cells assessed for structural aberrations
Polyploidy (PP + ER) measured in approximately 300 cells assessed for polyploidy only.
95% confidence limits : 95% of values from negative controls fall on or within the values given.
99% confidence limits : 99% of values from negative controls fall on or within the values given.

Positive Control Data

	Number of Records	Parameter	Range
Structural Aberrations	1642	Lesions/cell	0.00-6.72
	1933	Aberrant cell frequency including gaps (%)	0-100
		Aberrant cell frequency excluding gaps (%)	0-100
Numerical Aberrations[1]	1610	AE (%)	0-52
QUALITY ASSURANCE	Last date data added to database: 07 May 2009 (b) (4)		

1 = Aneuploidy (AE) measured in 100 cells assessed for structural aberrations

Appendix 5 Toxicity Data:
Test 2, Without S9 Mix, 22 h Treatment, 48 h Harvest

Treatment Group	Conc. (µg/mL)	De-coded No.	Cell Count Data		Observations		Toxic Judge
			No. of Cells (x10^2)	Index	Culture	Slide	
Dimethyl-sulphoxide	1%	91	2.60	100	Nil toxicity	Nil toxicity	-
		92	2.60	100			-
Epanova	5	93	2.63	101			-
		94	2.68	103			-
	10	95	2.55	98			-
		96	2.65	102			-
	20	97	2.35	90	Cells look slightly grainy/fixed		t
		98	2.38	92			t
	40	99	2.33	90	Cells look grainy/fixed		t
		100	2.45	94			t
	60	101	1.85	71			t
		102	1.88	72			t
	80	103	0.08	3	Slightly rounded cells, look fixed	No metaphase cells	ttt
		104	0.00	0			ttt
	100	105	0.00	0	Rounded cells, look fixed		ttt
		106	0.00	0			ttt

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: Epanova: Micronucleus Test in Bone Marrow Cells of CD Rats: 0h+24h oral Dosing and 48 h sampling	
Study no.:	Test Facility No:789411; Report No: 31929
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 19th 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Epanova (Lot# 36355 from capsules Batch # 143948), 100%

Key Study Findings

Epanova at oral doses up to 2000mg/kg (2.2mL/kg) did not induce micronuclei in the *in vivo* rat micronucleus study.

Methods	
Doses in definitive study:	2.2 mL/kg or 2000mg/kg
Frequency of dosing:	at 0 h and 24 h with test or control
Route of administration:	Oral gavage
Dose volume:	2.2 mL/kg body weight
Formulation/Vehicle:	Corn oil (2.2ml/Kg)
Species/Strain:	CD rats (Crl:CD(SD))
Number/Sex/Group:	Epanova (7M/5F); Corn Oil (5/sex); Positive control (3M)
Satellite groups:	None
Basis of dose selection:	2000mg/kg/day; based on the highest dose level recommended in the OECD
Negative control:	Corn oil (2.2mL/kg)
Positive control:	Cyclophosphamide (10 mL/kg or 50 mg/kg)

Study Validity

The mean incidence of micronucleated polychromatic erythrocytes did not exceed 5/1000 polychromatic erythrocytes (0.5%) in the negative control, and the incidence of micronucleated polychromatic erythrocytes increased significantly in the positive control group. Therefore, the study was valid.

Results

There were no reports regarding the adverse clinical signs during the course of the study.

With the maximum recommended dose of 2000mg/kg/day, Epanova did not induce micronuclei in bone marrow cells after dosing (at 0, 24 hrs) and sampling (at 48hrs).

Table 2 Summary of Assessment Data

Treatment	Dose (h)	Sex	No. of Rats Scored	Erythrocytes				
				Normochromatic Cells (NCE)	Polychromatic Cells (PCE)			PCE/NCE
				No. of MN-NCE	PCE Analysed	No. of MN-PCE	% MN-PCE	Mean ± S.D.
Corn Oil 2.2 mL kg/day	0 + 24	M	5	3	10002	1	0.01	0.66 ± 0.13
		F	5	1	10002	1	0.01	0.63 ± 0.13
		M/F	10	4	20004	2	0.01	0.65 ± 0.13
Epanova 2.2 mL/kg/day (equivalent to 2000 mg/kg/day)	0 + 24	M	7	3	14000	1	0.01	0.60 ± 0.11
		F	7	4	14002	4	0.03	0.58 ± 0.07
		M/F	14	7	28002	5	0.02	0.59 ± 0.09
Cyclophosphamide 50 mg/kg/day	0 + 24	M	3	68α	6000	145	2.42Φ	0.35 ± 0.08

PCE = Polychromatic erythrocytes NCE = Normochromatic erythrocytes
MN-PCE = Micronucleated PCE MN-NCE = Micronucleated NCE
Φ = Positive response in PCE α = Evident response in NCE

Micronucleus Test in Bone Marrow of CD (Sprague Dawley) Rats Historical Negative and Positive Control Data (1997 - 2010)

Negative Control Data

Frequency of Micronucleated Polychromatic Erythrocytes (MN-PCE) in Vehicle and Untreated Male CD and Female CD Rats			
Mean		0.04%	
Standard Deviation		0.05%	
Ranges	Individual Rat	Group of 5-7 Rats	Group of 10-12 Rats
Min frequency	0.00%	0.01%	0.02%
Max frequency	0.20%	0.13%	0.11%
Number of Polychromatic Erythrocytes Assessed:		1068921	
Number of Rats Assessed:		539	

Positive Control Data

Frequency of Micronucleated Polychromatic Erythrocytes (MN-PCE) in Positive Control Male and Female Treated Rats	
Mean	2.20%
Standard Deviation	1.03%
Min - Max Frequencies	0.05-6.20%
Number of Polychromatic Erythrocytes Assessed:	398236
Number of Rats Assessed:	231

8 Carcinogenicity

The Sponsor conducted two carcinogenicity studies in rats (2-year) and transgenic mice (26-week). Regulatory background regarding the carcinogenicity studies summarized as follows:

1) A 104-week Rat Carcinogenicity Study was designed with Epanova at 100, 600, 2000 mg/kg/day (or 0.11, 0.65, and 2.2 mL/kg/day) by oral gavage. The SPA was not submitted for review to ECAC. The HD was selected due to tolerance of the HD in the subchronic and chronic studies in rats and available carcinogenicity data for approved fish oil, Lovaza. During the conduct of the study, the Sponsor requested guidance from the Agency as follows:

- On 1/5/2012, the Sponsor requested concurrence from the Agency for early termination of HD-treated females when the number of survivors reached 25 and if the number of the survivors in males at HD reached 25. On 2/5/2012, the Agency responded that the HD groups could be discontinued when the number of surviving animals reached 20; then, dosing should be discontinued. If the number of surviving animals fell to 15 before week 100, then all surviving members of this dose group should be sacrificed.

- On 11/9/2012, the Sponsor requested to terminate females at MD when survivors reached 15. Also, the Sponsor proposed to terminate all of the male groups when the number of survivors reached 15 at MD and HD groups prior to Week 100. On 11/12/2012, the Agency recommended that for females, LD continue till the end of the study (week 104), if possible. The ECAC noted that the deaths at MD and HD are dose related, so these groups can be terminated when the survivors reach n=15. On 20/11/2012, the Division agreed with the plan to stop LD groups, and the Division also stated that because the LD group is the only treatment group left in the study, the controls should be terminated as well.

2) A 26-week carcinogenicity study in transgenic mice was conducted twice with the approved dose levels from the Agency. The 1st study (01/21/2011) was seriously flawed (b) (4)

(b) (4) Therefore, the Sponsor submitted the 2nd transgenic study (4/15/2011), which was (b) (4) (b) (4) (b) (4) The Agency informed the sponsor that the proposed carcinogenicity study was not qualified and a DRF gavage study at the new facility was needed. Therefore, the Sponsor submitted results of a 2-week gavage dosing tolerability study with Epanova (2 and 4 g/kg/day) in wild type mice at (b) (4). ECAC accepted the 2-week dose-range study for the dose-selection of 0, 0.5, 1, 2, 4 g/kg/day. This study at (b) (4) continued for 26 weeks and the Sponsor requested guidance from the Agency during the study as follows: 1) The early termination of HD2- treated males (ECAC agreed); and 2) the early termination for HD2 -treated females when the number of survivors reached 15 mice (ECAC agreed).

A 104 Week Carcinogenicity Study of Epanova by Oral Gavage in Rats	
Study no.:	518911
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 1, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Drug: Omefas from Epanova Capsules; Lot No: 143948 (626100 ((b) (4)) 36355 (Omthera)); Density: 0.924 g/mL; Purity: 87.0%
CAC concurrence:	No.

Statistically Significant Neoplastic Findings:

Benign sex cord stromal tumors of the ovaries in the high dose (2000mg/kg/day) females were identified statistically significant by the CDER analyses for both trend (P=0.0005) and pairwise comparison (P=0.0054).

At HD, there is 5 fold to the MHRD (4g/day) based on a body surface area comparison.

The benign ovarian sex cord tumor in this study at HD exceeded concurrent control and historical controls and was drug-related.

Non-Neoplastic Findings:

- Due to a lower than expected survival rate, dosing was stopped early for all different groups (ECAC concurred). The study was less than 100 weeks.
- Mortality: Treatment-related mortality was statistically significant for the trend in dose and in the comparison among groups (CDER biostatistics Males: p≤ 0.0004, Females: p<0.0001).
- Microscopic findings: Dose-response gavage/reflux-related findings in the larynx (squamous metaplasia), lungs (bronchus-associated lymphoid tissues in males), nasal cavity (squamous metaplasia), and trachea. In addition, microscopic findings were reported in MD- and HD-treated animals in the kidneys (tubular dilatation); large and small intestine (lumen dilation and crypt hyperplasia); and liver (focal mononuclear cell inflammatory infiltrates).

Maximum Clinical Exposure:

TK parameters were not calculated; based on other Epanova non-clinical studies, Epanova at HD (2000mg/kg/day) is up to 5 fold human systemic exposure to MRHD of 4g/day (based on body surface area).

Adequacy of Carcinogenicity Study

ECAC concurred that the study was acceptable despite being suboptimal.

Appropriateness of Test Models

ECAC did not concur with dose selection. The sponsor selected doses based on MTD from the repeat-dose toxicity study and available data from another 2-year carci study with approved Lovaza.

Despite a lack of ECAC concurrence on dose selection, and early termination (with ECAC advice), this study was considered valid. The basis of this assessment is that tumors were observed, including statistically significant ovarian tumors following adjustment for mortality. This omega-3 product uses the free fatty acid form, and approved omega-3 products use an ester form. This may have contributed to the early mortality since the acid form is irritating, oily and low pH, contributing to the respiratory problems of gavaging relatively large volume substances.

Note: The rat is considered an appropriate test model for tumorigenicity of Epanova. Overall treatment was not well tolerated, supporting establishment of a MTD and the study was terminated prematurely.

Evaluation of Tumor Findings

In HD (2000mg/kg/day) treated females, there were significant tumor increases for benign sex cord stromal that was considered drug-related (at HD, there is 5 fold to MHRD for 4 g/day based on surface area)

Methods	
Doses:	0, 100, 600 or 2000 mg/kg/day
Frequency of dosing:	Once daily: males 84-97 weeks; females 66-95 weeks
Dose volume:	2.2, 0.11, 0.65 or 2.2 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Corn Oil
Basis of dose selection:	1. Based on MTD from the 13-week repeat-dose toxicity study in rats (mortality in this study was unremarkable). 2. *Based on available data from 2-year carcinogenicity study in rats from approved Lovaza (NDA 21-654) at 90, 540 and 1800 mg/kg/day (mortality in this study was unremarkable).
Species/Strain:	Rat, Sprague-Dawley (crl:CD(SD))
Number/Sex/Group:	60/sex/group
Age:	8 weeks
Animal housing:	**4 animals/cage/group of the same sex in the polycarbonate

	cages with stainless steel grid tops and solid bottoms
Paradigm for dietary restriction:	PMI Nutrition International Certified Rodent Diet No. 5CR4 (14% protein) was available *ad libitum*
Dual control employed:	No
Interim sacrifice:	No
Satellite groups:	TK: 5/sex/group
Deviation from study protocol:	Dosing was stopped prematurely and animals were removed from the study before the scheduled termination (ECAC notification).

Reviewer:
** Combinations of these two compounds DHA and EPA, with free fatty acid (Epanova) or ethyl ester (Lovaza) formulations along with a significant difference in ratio of these compounds probably make different in pharmacological properties of each formulation. In addition, based on nonclinical studies, AUC to DHA and EPA is ~ 1.6- to 2.6-fold greater for the Epanova formulation (form of free fatty acids) compared to Lovaza (form of ethyl esters). Therefore, the dose-selection for the 2-year carcinogenicity study with Lovaza was not valuable for Epanova in this study.*
***4animals/cage caused stress for animals.*

Observations and Results

Mortality

Mortality was statistical significant in both genders with both the CDER and the Sponsor analyses (Sponsor's Table):

Summary of survivorship

Group/sex	1M	2M	3M	4M	1F	2F	3F	4F
Dose level (mg/kg/day)	0	100	600	2000	0	100	600	2000
Total No. Animals	65	65	65	65	65	65	65	65
Found dead	11	12	21	13	8	5	12	11
Killed prematurely	26	39	29	37	40	45	38	39
Total No. of Decedents	37	51	50	50	48	50	50	50
% Survival	43	22	23	23	26	23	23	23

CDER analysis:
Statistical Significances of Tests of Homogeneity and Trend in Survival in Rats

Hypotheses	Males		Females	
	Logrank	Wilcoxon	Logrank	Wilcoxon
Homogeneity over all four groups	0.0004	0.0002	<0.0001	<0.0001
No Trend over all four groups	0.0004	<0.0001	<0.0001	<0.0001
No difference between high dose and vehicle	0.0003	<0.0001	<0.0001	<0.0001

Sponsor Tables:
In Males:

Peto fatal analysis of deaths before terminal sacrifice

Dosage level (mg/kg/day)		0	100	600	2000	Total	Trend
Unscheduled death							
	n	37	51	50	50	188	
	E	59.9353	51.8105	41.2861	34.9681	188.0000	
	E(2)		40.3898	36.0384	34.0894		
	ChiSq		4.8073	8.9952	12.0336	18.1959	12.7977
	P		0.0283 +	0.0027 ++	0.0005 +++	0.0004 ***	0.0003 +++

Peto fatal analysis of deaths before week 66

Died before week 66							
	n	9	15	18	27	69	
	E	19.0970	17.5747	16.9727	15.3557	69.0000	
	E(2)		11.4081	12.6813	16.0755		
	ChiSq		1.6083	3.4775	12.3613	14.7199	13.6249
	P		0.2047	0.0622 (+)	0.0004 +++	0.0021 **	0.0002 +++

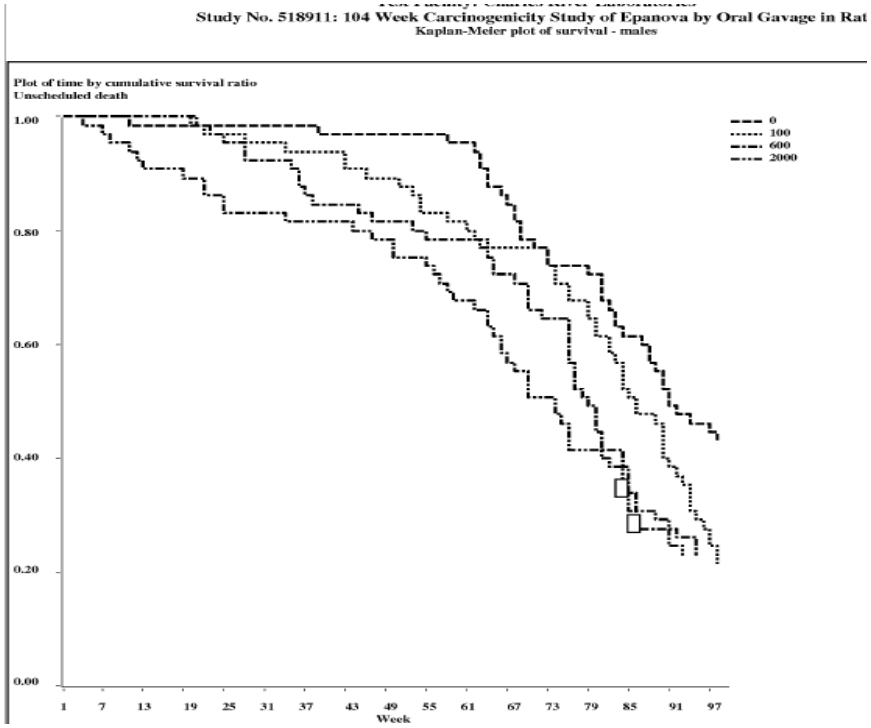
Test Facility: [redacted] b(4)

Study No. 518911: 104 Week Carcinogenicity Study of Epanova by Oral Gavage in Rats

Peto fatal analysis of deaths before week 84

Group		1	2	3	4		
Dosage level (mg/kg/day)		0	100	600	2000	Total	Trend
Died before week 84							
	n	25	31	40	42	138	
	E	39.9469	36.9059	32.8353	28.3119	138.0000	
	E(2)		26.7682	29.0394	28.1240		
	ChiSq		1.0120	6.9621	11.1821	15.0382	12.4758
	P		0.3144	0.0083 ++	0.0008 +++	0.0018 **	0.0004 +++

Sponsor Figure for survival males as a function of time:



In Females:

Peto fatal analysis of deaths before terminal sacrifice

Dosage level (mg/kg/day)		0	100	600	2000	Total	Trend
Unscheduled death							
	n	48	50	50	50	198	
	E	65.22	61.83	40.09	30.85	198.00	
	E(2)		47.54	36.67	32.05		
	ChiSq		0.16	7.91	15.88	23.25	20.98
	P		0.6872	0.0049 ++	0.0001 +++	0.0000 ***	0.0000 +++

Peto fatal analysis of deaths before week 66

Died before week 66							
	n	11	12	25	37	85	
	E	23.82	23.14	20.40	17.64	85.00	
	E(2)		11.32	16.62	20.37		
	ChiSq		0.01	7.07	22.73	35.25	33.97
	P		0.9402	0.0078 ++	0.0000 +++	0.0000 ***	0.0000 +++

Test Facility: [redacted] b(4)

Study No. 518911: 104 Week Carcinogenicity Study of Epanova by Oral Gavage in Rats

Peto fatal analysis of deaths before week 84

Group		1	2	3	4		
Dosage level (mg/kg/day)		0	100	600	2000	Total	Trend
Died before week 84							
	n	28	29	44	48	149	
	E	44.93	42.99	34.07	27.01	149.00	
	E(2)		27.79	30.67	29.06		
	ChiSq		0.04	9.63	19.68	31.13	28.24
	P		0.8485	0.0019 ++	0.0000 +++	0.0000 ***	0.0000 +++

Sponsor Figure for survival Females as a function of time:

Test Facility: [redacted] b(4)

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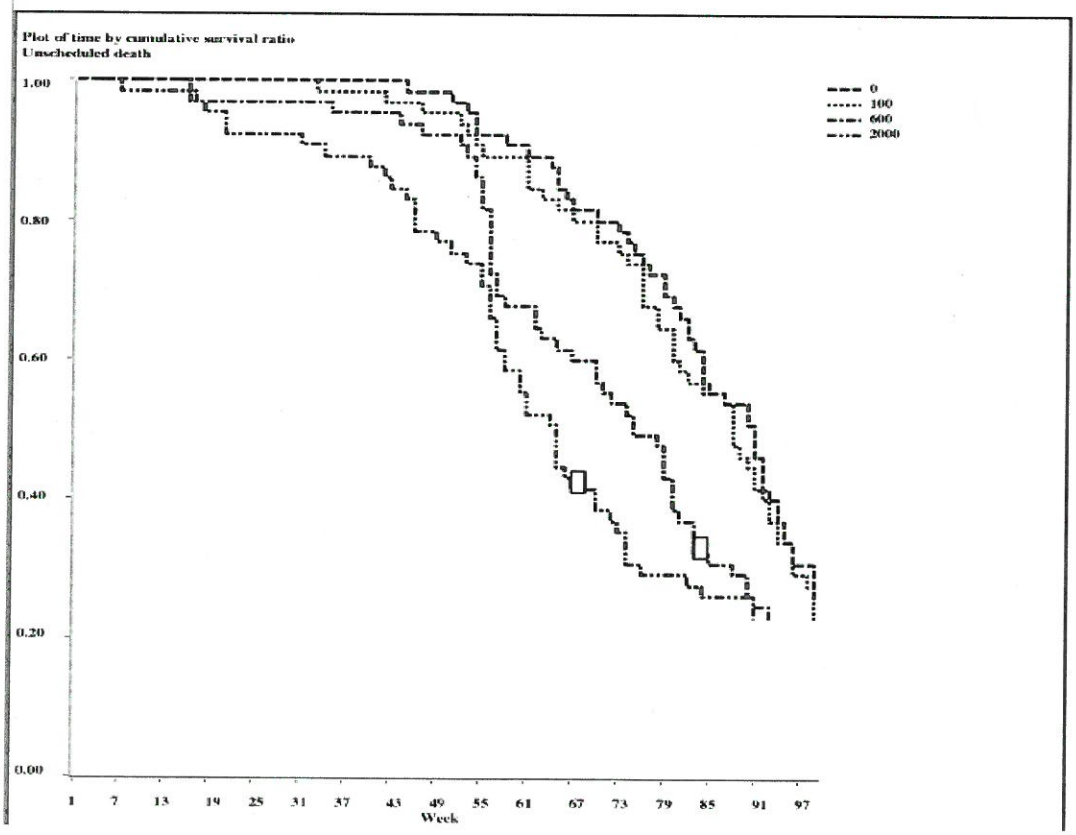
Kaplan-Meier plot of survival - females



Cause of Death:

Cause of death was non-neoplastic and was due to respiratory tract lesions based on clinical signs (excess salivation, and abnormal respiration) and gross / microscopic lesions findings in the respiratory tract.
Also, respiratory problems caused other stress-related issues in MD- and HD-treated animals based on stress-related microscopic findings in the adrenal glands (diffuse hypertrophy of the zona fasciculata), mesenteric lymph node (decreased size/lymphocyte density), spleen (decreased size/lymphocyte density), and thymus diffuse necrosis/loss of lymphocytes (Sponsor's Tables):

Incidence of treatment-related factors contributory to death

Sex	Male				Female			
Dosage level Epanova (mg/kg/day)	0	100	600	2000	0	100	600	2000
Number examined	25	32	43	45	12	13	26	38
Respiratory tract lesions	0	1	18	30	0	0	11	17

Incidence of treatment-related lesions indicative of stress

Sex	Male				Female			
Dosage level Epanova (mg/kg/day)	0	100	600	2000	0	100	600	2000
Adrenal cortex								
Number examined	24	31	40	43	12	13	26	38
Hypertrophy, zona fasciculata, diffuse	0	1	1	1	1	1	2	9
Lymph node: mesenteric								
Number examined	24	31	38	44	12	13	26	38
Decreased size/lymphocyte density, follicles	0	0	0	2	1	0	2	5
Decreased size/lymphocyte density, paracortex	0	0	2	4	1	0	3	6
Spleen								
Number examined	25	32	43	45	12	13	26	38
Decreased size/lymphocyte density, marginal zone	1	1	4	9	1	1	8	13
Decreased size/lymphocyte density, PALS	0	0	1	4	1	2	6	8
Decreased size/lymphocyte density, follicles	0	0	0	2	0	0	4	7
Necrosis, focal	0	0	2	3	1	1	0	0
Thymus								
Number examined	23	30	38	41	11	13	22	36
Necrosis/loss, lymphocytes, diffuse	1	0	1	7	0	0	2	5

Reviewer: Mortality was less in the Control- treated animals compared to the Epanova HD-treated animals despite the same volume of dosing. This difference might be due to the acidic formulation of Epanova that leads to irritative/reflux of dosing in the HD-treated animals.

Clinical Signs

An increased incidence of excess salivation, and abnormal respiration were observed in all Epanova treated animals in a dose-response. At HD, higher incidences of the fur staining

around the face/muzzle/nose, subdued behavior, hunched posture, piloerection, and eyes partially closed were observed (Sponsor's Table):

Group	:	1	2	3	4
Test Item	:	Control	----------	Epanova	----------
Dosage (mg/kg/day)	:	0	100	600	2000

Sex / Group	Males				Females			
	1	2	3	4	1	2	3	4
No. Animals	65	65	65	65	65	65	65	65
Terminal kill	28	14	15	15	17	15	15	15
Removals -								
Found dead	11	12	21	13	8	5	12	11
Killed prematurely	26	39	29	37	40	45	38	39
Excess salivation	1	1	25	64	2	0	8	65
Ploughing	1	0	22	63	0	0	20	65
Abnormal respiration	7	19	23	62	11	11	22	51
Subdued behaviour	13	22	27	27	18	19	27	42
Hunched posture	14	15	19	29	21	33	28	38
Piloerection	11	15	14	15	11	18	23	26
Eyes dark	1	2	6	18	1	3	2	7
Eyes partially closed/ closed	8	14	12	16	9	10	21	24
Weigh loss	14	17	18	19	11	22	17	22
Fur Stained around the face/muzzle/nose	18	26	22	47	16	19	19	46
Skin dark	0	0	1	4	0	0	2	1
Locomotion abnormalities	8	10	15	14	23	32	24	25

Body Weights

HD-treated animals showed reduce in mean body weights, significant for males from Week 24 and for females from Week 56 (Sponsor's Table and Figures):

Body Weights (g): Group Mean Values

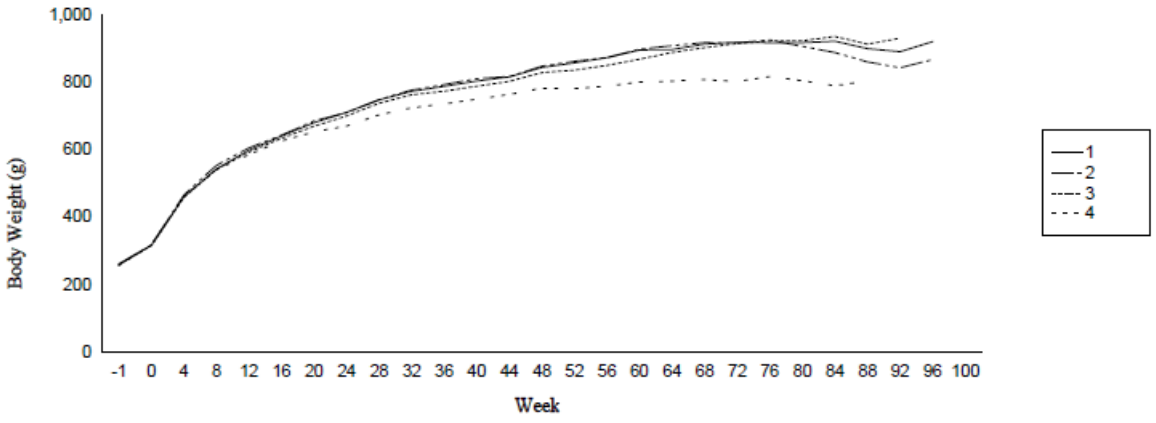
Group	: 1	2	3	4
Test Item	: Control	----------	Epanova	----------
Dosage (mg/kg/day)	: 0	100	600	2000

Group / sex		Week 0	91	92	93	94	Change 0 - 96
1M	Mean	317	919	919	918	917	615
	SD	26	114	114	113	111	95
	n	65	31	30	30	30	29
2M	Mean	316	851	845	856	843[a]	552
	SD	25	126	127	120	124	124
	n	65	23	23	20	19	16
3M	Mean	315	928	928	925	-	-
	SD	24	169	167	168	-	-
	n	65	17	17	17	-	-
4M	Mean	316	832[a]	-	-	-	-
	SD	22	87	-	-	-	-
	n	65	16	-	-	-	-

Group / sex		Week 0	89	Change 0 - 97
1F	Mean			
	SD	230	588	362
	n	18	140	126
		65	33	20
2F	Mean			
	SD	227	578	386
	n	16	141	131
		65	29	18
3F	Mean			
	SD	229	576	-
	n	17	140	-
		65	17	-
4F	Mean			
	SD	230	517	-
	n	18	117	-
		65	17	-

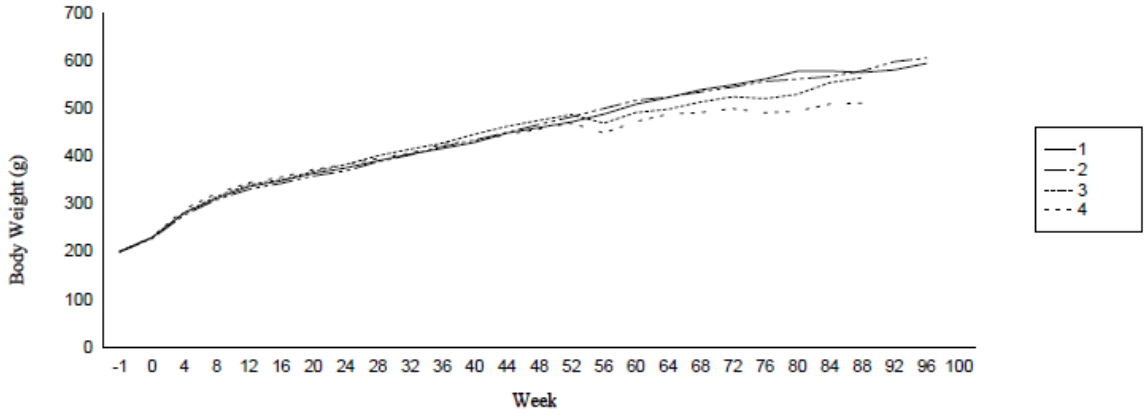
Body Weights (g): Group Mean Values: Males

Group	: 1	2	3	4
Test Item	: Control	----------	Epanova	----------
Dosage (mg/kg/day)	: 0	100	600	2000



Body Weights (g): Group Mean Values: Females

Group	:	1	2	3	4
Test Item	:	Control	----------	Epanova	----------
Dosage (mg/kg/day)	:	0	100	600	2000



Feed Consumption

No significant treatment-related effect.

Hematology

No significant treatment-related effect.

Gross Pathology

Gross pathology findings were reported as follows: decreases subcutaneous masses (in dose-response in both sexes), decrease incidence of enlargement of the adrenal gland (in dose-response in females), increase lesions in the respiratory tract (in dose-response in all groups), decrease adrenal glands (HD females), swelling of the gastro-intestinal tract, and abnormal content in the small intestine (males, MD and HD). In addition, injury-related to gavage treatment was reported as thickening of the diaphragm, adhesions in the lung, abnormal appearance and abnormal shape of the esophagus, abnormal consistency, discoloration and raised area of skeletal muscle, fluid accumulation, abnormal content and thickening in thoracic

cavity, mass and enlargement of thymus, and adhesions of trachea (Sponsor's Tables):

Summary Gross Pathology Findings – Unscheduled/Scheduled Euthanasia

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (mg/kg/day)	**0**	**100**	**600**	**2000**	**0**	**100**	**600**	**2000**
No. animals examined	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**
Caecum								
Distension	0	1	6	8	0	0	1	3
Colon								
Distension	0	1	4	3	0	0	0	3
Duodenum								
Distension	0	1	8	7	0	0	0	2
Abnormal content	0	1	2	7	2	0	1	1
Ileum								
Distension	0	1	6	7	0	0	0	2
Abnormal content	0	0	1	6	1	0	0	2

Summary Gross Pathology Findings – Unscheduled/Scheduled Euthanasia

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (mg/kg/day)	**0**	**100**	**600**	**2000**	**0**	**100**	**600**	**2000**
No. animals examined	**65**	**65**	**65**	**65**	**65**	**65**	**65**	**65**
Jejunum								
Distension	0	1	7	8	0	0	0	3
Abnormal content	0	2	2	6	1	0	2	1
Stomach								
Distension	0	0	7	13	1	0	0	4
Mass								
Subcutaneous mass(es)	21	13	14	10	47	38	36	15
Adrenal Gland								
Speckled	1	4	1	1	11	16	13	3
Enlargement	2	4	2	4	18	8	9	6
Lung								
Foci, pale	2	4	8	26	6	10	21	32
Failure to collapse	0	1	0	6	0	0	0	0
Abnormal consistency	0	0	0	2	0	0	1	3
Abnormal shape	0	0	0	0	0	0	0	1
Spongy	2	4	13	14	2	3	8	14
Dark	0	0	0	1	0	0	0	1
Firm	0	0	0	1	0	0	0	0
Small	0	1	0	6	0	0	1	0
Enlargement	0	1	2	2	0	0	0	1
Nasal Cavity								
Fluid accumulation	0	0	0	2	0	0	0	0
Abnormal content	0	0	0	1	0	0	0	0
Abnormal appearance	0	0	0	0	0	0	0	1

Organ Weights

Organ weights changes were summarized as follows:

- Thymus: Increased relative to body weight in HD-treated animals and also MD-treated females with no correlating histopathological findings (probably due to gavage treatment)
- Adrenal and pituitary gland: Increased relative to body weight in HD-treated males with gross pathology and microscopic findings (diffuse hypertrophy of the zona fasciculata). According to the Sponsor, this finding was non-specific secondary lesions due to stress-related for the treatment.

- Lung: Increased relative to body weight in HD-treated animals. Most animals had similar lung weights; however, 4 animals in both genders had very high values (probably due to gavage treatment).

Histopathology

Peer Review**:** yes

Neoplastic:

Ovaries:

Benign sex cord stromal tumors of the ovaries in the high dose (2000mg/kg/day) females were statistically significant by trend (P=0.0005) and pairwise comparison (P=0.0054):(control, 5/64; low dose, 4/62; mid dose, 6/62; and high dose,11/64) by both statistical analyses from the sponsor and the CDER. Moreover, 10 tumors were seen after dosing was stopped.

The benign ovarian sex cord tumor in this study at HD exceeded concurrent control and historical controls and was drug-related.

Reviewer: The sponsor did not submit the historical control database; however, based on the online historical control database ((b) (4) *Cri:CD(SD) rats; March2012), the incidence of this tumor for the control group was higher than the historical control database (7% in this study vs. 2% in the historical database). Moreover, the sex cord stromal tumors is about 8% of all ovarian tumors in humans; development of these tumors requires a high level of gonadotrophin stimulation (Dittrich et al., J cancer Res Clin Oncol 2001).*

Sponsor's Table:

Focal proliferative lesions in the ovaries

Dosage level Epanova (mg/kg/day)	0	100	600	2000
Number examined overall	64	62	62	64
Sex cord stromal tumours, benign				
Incidence	5	4	6	11
Hyperplasia, sex cord stromal, mixed				
minimal	24	21	24	22
slight	12	9	6	12
moderate	5	1	5	3
marked	1	1	1	0
Total	42	32	36	37
Animals with either hyperplasia or tumour				
Incidence	42	32	36	39
Number examined up to week 66	11	13	25	38
Sex cord stromal tumours, benign				
Incidence	0	0	0	1
Hyperplasia, sex cord stromal, mixed				
minimal	4	3	7	13
slight	0	0	2	3
moderate	0	0	0	1
Total	4	3	9	17
Animals with either hyperplasia or tumour				
Incidence	4	3	9	17

Statistical evaluation from Sponsor:

TEXT TABLE E: Ovarian – sex cord stromal tumours and focal hyperplasia

	Dose level (mg/kg/day)				Analysis[a]					
	0	100	600	2000	(1)	(5)	(4)	(3)	(2)	(6)
Benign sex cord stromal tumour										
n[b]	5	4	6	11[+]						
E[c]	7.29	6.82	6.83	5.06						
Trend p					0.0006[+++]	0.0003[+++]	0.0011[++]	0.0192[+]	0.1779	0.5402
Mixed sex cord stromal focal hyperplasia										
n	42	32	36	37						
E	40.88	38.89	35.15	32.09						
Trend p					0.0718[(+)]	0.0586[(+)]	0.0642[(+)]	0.0959[(+)]	0.1764	0.3650
Sex cord stromal tumour or focal hyperplasia										
n	43	32	37	39						
E	41.93	39.84	36.38	32.85						
Trend p					0.0236[+]	0.0269[+]	0.0387[+]	0.0781[(+)]	0.1676	0.3703

[a] For analyses (1), (5), (4), (3) and (2) corresponding half-life is infinite, 32, 16, 8 and 4 weeks. Analysis (6) ignores tumours seen in groups 3 and 4 after cessation of dosing. See methods section 2.1.9 for significance codes.

[b] n = number of animals with lesion.

[c] E = expected number assuming that age-specific lesion rates are independent of treatment.

Statistical evaluation from CDER:

	Tumor Incidence				Significant Levels			
Organ/Tumor	C	LD	MD	HD	Trend	HD vs C	MD vs. C	LD vs. C
Females: Number Evaluated	64	62	62	64				
Benign Sex Cord Stromal Tumour	5	4	6	11	0.0005	0.0054	0.2417	0.7172

Cause of death mostly was non -neoplastic in respiratory tract with no significant incidence of bronchial-alveolar neoplastic findings:

Statistical evaluation from CDER**:**

	Tumor Incidence				Significant Levels			
Organ/Tumor	C	LD	MD	HD	Trend	HD vs C	MD vs. C	LD vs. C
Males: Number Evaluated	64	62	62	64				
Bronchiolo-alveolar Adenoma	2	0	1	1	0.4201	0.7656	0.8069	1
Females: Number Evaluated	65	63	65	63				
Bronchiolo-alveolar Adenoma	0	0	1	0	0.379	-	0.4032	-

Statistical evaluation from Sponsor:

Statistical analysis of tumours ignoring cessation of dosing

1) Standard analysis - no change in trend by time						
Group	**1**	**2**	**3**	**4**		
Dosage level (mg/kg/day)	**0**	**100**	**600**	**2000**	**Total**	**Trend**
Lungs: bronchiolo-alveolar carcinoma:Females						
n	0	0	1	0	1	
Lungs: bronchiolo-alveolar adenoma:Males						
n	2	0	1	1	4	
2) Trend dose drops with half-life=4 weeks as dosing stops : Males						
Ex P						0.9345
3) Trend dose drops with half-life=8 weeks as dosing stops						
Ex P						0.9096
4) Trend dose drops with half-life=16 weeks as dosing stops						
Ex P						0.9096
5) Trend dose drops with half-life=32 weeks as dosing stops						
Ex P						0.9096
6) Ignoring tumours in groups 3 and 4 after dosing stops						
n	2	0	0	0	2	
E	1.33	0.67	0.00	0.00		
Ex P		0.8780	1.0000	1.0000		0.8780

(6) Ignoring tumours in groups 3 and 4 after dosing stops						
: Males						
	n	2	0	0	0	2
	E	1.33	0.67	0.00	0.00	
	Ex P		0.8780	1.0000	1.0000	0.8780
: Total						
	n	2	0	0	0	2
	E	1.33	0.67	0.00	0.00	
	Ex P		0.8780	1.0000	1.0000	0.8780

Pituitary gland: In LD-treated females, adenomas in the pars distalis was noted (p = 0.0418) with no incidence of focal hyperplasia. The historical control database was not submitted; however, this incidence is common in aged control rats, and significant finding at LD (~70%) in this study is within the online historical control database ((b) (4); Cri:CD(SD)rats; March2012; males:41% to 84% and females: 40% to 84%.)

Sponsor's Table:

Tumours of the pars distalis in the pituitary gland of females

Dosage level Epanova (mg/kg/day)	0	100	600	2000
Number examined overall	65	64	65	64
Adenoma, pars distalis				
Incidence	51	45	35	35
Number examined up to week 66	12	13	26	37
Adenoma, pars distalis				
Incidence	6	8	8	14

Statistical evaluation from CDER:

	Tumor Incidence				Significant Levels			
Organ/Tumor	*C	LD	MD	HD	Trend	HD vs C	MD vs. C	LD vs. C
Males: Number Evaluated	65	65	63	64				
Par Distalis Adenoma	38	37	25	28	0.4764	0.5723	0.8742	0.6108
Females: Number Evaluated	65	64	65	64				
Par Distalis Adenoma	51	45	35	35	0.604	0.8226	0.9525	0.8897

*C=Negative Control

Skin: squamous cell papilloma was reported with a positive-dose related trend in males and for sexes combined (p<0.01; sponsor's analysis). This incidence was 1/controls, 1/MD and 6/HD.

This finding occurs in aged control rats and incidence of 9.3% at HD is within the historical control database range for males (online; (b) (4); Cri:CD(SD)rats; March2012).

Sponsor's Table:

TEXT TABLE H: Skin (extra section) – squamous cell papillomas

		Dose level (mg/kg/day) 0	100	600	2000	Trend[a]
Males	n[b]	1	0	0	4	
	E[c]	1.31	1.33	1.25	1.11	0.0070^{++}
Females	N	0	0	1	0	
Sexes combined	N	1	0	1	4	
	E	1.52	1.47	1.58	1.44	0.0045^{++}

[a] Assuming a half-life of 16 weeks. See methods section 2.1.9 for significance codes.
[b] n = number of animals with lesion.
[c] E = expected number assuming that age-specific lesion rates are independent of treatment.

Statistical evaluation from CDER:

	Tumor Incidence				Significant Levels			
Organ/Tumor	*C	LD	MD	HD	Trend	HD vs C	MD vs. C	LD vs. C
Males: Number Evaluated	65	65	65	65				
Squamous cell Papilloma	1	0	0	4	0.0060	0.0759	1	1
Females: Number Evaluated	65	65	65	65				
Squamous cell Papilloma	0	0	1	0	0.3793	-	0.4032	-

*C=Negative Control

Mammary gland tumors were not statistically significant (Sponsor's Table):

TEXT TABLE D: Mammary gland tumours

Sex	Tumour type	Dose level (mg/kg/day) 0	100	600	2000	Trend p[a]
Male	Fibroadenoma	1	0	1	3	0.0552$^{(+)}$
	Adenoma	1	0	0	0	
	Any benign tumour	2	0	1	3	0.0552$^{(+)}$
	- Analysis (6)[b]	2	0	1	2	0.0734$^{(+)}$
Female	Adenocarcinoma	19	16	16	8	0.1438
	Adenocarcinoma in fibroadenoma	7	10	7	2	0.4063
	Malignant mixed tumour	0	1	1	0	
	Any malignant tumour	22	21	19	8	0.0895$^{(-)}$
	- Analysis (6)[b]	22	21	11	2	0.3182
	Fibroadenoma	26	21	13	6$^{(-)}$	0.1457
	Adenoma	1	2	0	0	0.4969
	Fibroadenoma with atypia	8	4	6	3	0.5321
	Any benign tumour	32	25	16	8^{--}	0.1070
	- Analysis (6)[b]	32	25	10	3^{-}	0.2277
	Any tumour	46	38	33	15^{--}	0.0170^{-}
	- Analysis (6)[b]	46	38	20	4^{-}	0.0467^{-}
Sexes combined	Fibroadenoma	27	21	14	9	0.6567
	Adenoma	2	2	0	0	0.4424
	Any benign tumour	34	25	17	11$^{(-)}$	0.4888
	- Analysis (6)[b]	34	25	11	5	0.7955
	Any tumour	48	38	34	18^{-}	0.0997$^{(-)}$
	- Analysis (6)[b]	48	38	21	6	0.2288

[a] Assuming a half-life of 16 weeks. See methods section 2.1.9 for significance codes.
[b] Ignoring tumours seen in groups 3 and 4 after cessation of dosing.

Statistical evaluation from CDER:

	Tumor Incidence				Significant Levels			
Mammary gland tumors	*C	LD	MD	HD	Trend	HD vs C	MD vs. C	LD vs. C
Males: Number Evaluated	65	64	62	64				
Fibroadenoma	1	0	1	3	0.0284	0.1569	0.6513	1
Fibroadenoma/Adenoma	2	0	1	3	0.0633	0.2889	0.7975	1
Females: Number Evaluated	65	64	65	64				
Fibroadenoma	26	21	13	6	0.9883	0.9933	0.9350	0.7624
Fibroadenoma with Atypia	8	4	6	3	0.5532	0.8146	0.5297	0.9170
Fibroad./Adenocarc./ Adenoma	46	37	32	15	0.9970	0.9992	0.8794	0.8989

*C=Negative Control

Non Neoplastic

Non-neoplastic findings were reported for animals that were dosed for the same period of treatment (males: up to 84 weeks and females up to 66 weeks). Dose-response gavage/reflux-related non neoplastic findings in the larynx (squamous metaplasia), lungs (bronchus-associated lymphoid tissues in males), nasal cavity (squamous metaplasia), and trachea. Additional non-neoplastic findings were noted in MD and HD-treated animals in the kidneys (tubular dilatation); large and small intestine (lumen dilation and crypt hyperplasia); and liver (focal mononuclear cell inflammatory infiltrates). Sponsor's Tables:

Treatment-related non-neoplastic findings in the kidneys

Sex	Male				Female			
Dosage level Epanova (mg/kg/day)	0	100	600	2000	0	100	600	2000
Number examined	25	32	43	45	12	13	26	38
Dilatation, tubular, bilateral								
minimal	0	1	6	5	0	0	5	6
slight	0	0	0	1	0	0	2	2
Total	0	1	6	6	0	0	7	8

Treatment-related non-neoplastic findings in the large intestine

Sex	Male				Female			
Dosage level Epanova (mg/kg/day)	0	100	600	2000	0	100	600	2000
Number examined: caecum	25	31	40	44	12	13	26	38
Number examined: colon	25	32	43	45	12	13	26	38
Number examined: rectum	25	31	40	44	12	13	26	38
Dilatation, lumen								
Caecum	0	0	1	6	0	0	0	0
Colon	0	0	0	3	0	0	0	0
Rectum	0	0	0	1	0	0	0	0
Hyperplasia, crypts								
Caecum	0	0	2	2	0	1	1	6
Colon	0	0	1	1	0	0	1	4
Rectum	0	0	0	0	0	0	1	3

Treatment-related non-neoplastic findings in the larynx

Sex	Male				Female			
Dosage level Epanova (mg/kg/day)	0	100	600	2000	0	100	600	2000
Number examined	25	30	40	44	12	13	26	37
Exudate, inflammatory/mucous, lumen								
minimal	1	2	6	10	0	0	1	1
slight	0	0	2	1	0	0	0	0
severe	0	0	1	0	0	0	0	0
Total	1	2	9	11	0	0	1	1
Inflammation, lamina propria, acute								
minimal	0	0	2	7	0	0	1	2
slight	0	0	4	2	0	0	0	3
marked	0	0	1	0	0	0	0	0
Total	0	0	7	9	0	0	1	5

Treatment-related non-neoplastic findings in the larynx

Sex	Male				Female			
Dosage level Epanova (mg/kg/day)	0	100	600	2000	0	100	600	2000
Number examined	25	30	40	44	12	13	26	37
Necrosis/atrophy, epithelial								
minimal	0	0	1	3	0	0	2	1
slight	0	0	2	1	0	0	3	1
moderate	0	0	2	4	0	0	0	1
marked	0	0	3	3	0	0	1	3
severe	0	0	2	2	0	0	0	1
Total	0	0	10	13	0	0	6	7
Metaplasia, squamous								
minimal	2	5	8	17	0	1	5	6
slight	0	0	1	6	0	0	1	5
moderate	0	0	2	1	0	0	1	1
marked	0	0	0	1	0	0	0	1
Total	2	5	11	25	0	1	7	13

Treatment-related non-neoplastic findings in the liver

Sex	Male				Female			
Dosage level Epanova (mg/kg/day)	0	100	600	2000	0	100	600	2000
Number examined	25	32	43	45	12	13	26	38
Infiltrate, inflammatory, mononuclear cell, focal								
minimal	0	1	4	3	0	2	0	2
slight	0	0	0	1	0	0	0	2
Total	0	1	4	4	0	2	0	4

Treatment-related non-neoplastic findings in the lungs

Sex	Male				Female			
Dosage level Epanova (mg/kg/day)	0	100	600	2000	0	100	600	2000
Number examined	24	32	43	44	12	13	26	35
Bronchus-associated lymphoid tissue, prominent								
minimal	0	2	3	6	0	1	0	1
slight	0	0	1	1	0	0	0	0
Total	0	2	4	7	0	1	0	1

Treatment-related non-neoplastic findings in the lungs

Sex	Male				Female			
Dosage level Epanova (mg/kg/day)	0	100	600	2000	0	100	600	2000
Number examined	24	32	43	44	12	13	26	35
Inflammation, bronchiolo-alveolar								
minimal	0	5	6	12	0	2	0	5
slight	0	0	3	8	0	0	4	3
moderate	0	0	11	10	0	0	5	2
marked	0	1	3	4	0	0	3	1
severe	0	0	4	7	0	0	0	11
Total	0	6	27	41	0	2	12	22
Inflammation, bronchiolo-alveolar: type								
Chronic with fibrosis	0	6	17	34	0	2	8	16
Acute with necrosis	0	0	18	18	0	0	8	10
Acute, suppurative	0	1	4	9	0	1	1	7
Areas of underinflation/collapse								
minimal	0	3	6	6	0	0	5	2
slight	0	0	2	5	0	0	2	1
moderate	0	0	0	1	0	0	0	0
Total	0	3	8	12	0	0	7	3

Macrophages, alveolar, aggregations								
minimal	11	19	16	14	3	7	10	13
slight	0	0	8	14	0	1	4	11
moderate	0	0	2	3	0	0	1	6
marked	0	0	0	1	0	0	1	1
Total	11	19	26	32	3	8	16	31
Macrophages, alveolar, pigmented, focal								
minimal	5	5	12	18	0	0	3	4
slight	0	3	2	3	0	0	0	0
Total	5	8	14	21	0	0	3	4
Basophilic (mucous) material, airways								
minimal	0	0	2	8	0	1	1	3
slight	0	0	0	0	0	0	0	0
Total	0	0	2	8	0	1	1	3
Hyperplasia, bronchiolo-alveolar, bronchiolisation								
minimal	1	0	5	9	0	1	3	5
slight	0	0	0	0	0	0	2	0
Total	1	0	5	9	0	1	5	5

Treatment-related non-neoplastic findings in the lungs

Sex	Male				Female			
Dosage level Epanova (mg/kg/day)	0	100	600	2000	0	100	600	2000
Number examined	24	32	43	44	12	13	26	35
Oedema, intra-alveolar								
minimal	3	3	4	1	1	1	1	0
slight	0	1	3	3	0	0	4	1
moderate	0	0	1	0	0	0	2	2
marked	0	0	0	0	0	0	0	1
Total	3	4	8	4	1	1	7	4
Bronchiectasis								
minimal	0	0	3	5	0	0	1	0
slight	0	0	1	4	0	0	0	0
Total	0	0	4	9	0	0	1	0
Emphysema, focal								
minimal	0	0	0	0	0	0	1	2

Text Table 24
Treatment-related non-neoplastic findings in Nasal cavity: Section 3

Sex	Male				Female			
Dosage level Epanova (mg/kg/day)	0	100	600	2000	0	100	600	2000
Number examined	24	30	40	36	12	13	26	35
Increased size/lymphocyte density, NALT								
minimal	5	4	10	14	1	2	1	8
slight	0	0	0	7	0	0	0	0
Total	5	4	10	21	1	2	1	8
Exudate, inflammatory/mucous, lumen								
minimal	0	1	11	4	0	1	7	8
slight	0	0	2	9	0	0	4	3
moderate	0	0	3	9	0	0	1	11
marked	0	0	0	2	0	0	0	1
severe	0	0	1	1	0	0	0	0
Total	0	1	17	25	0	1	12	23
Inflammation, lamina propria								
minimal	0	0	2	9	0	0	1	3
slight	0	0	1	6	0	0	1	2
moderate	0	0	0	0	0	0	0	1
marked	0	0	0	1	0	0	0	0
Total	0	0	3	16	0	0	2	6
Necrosis/atrophy, epithelial								
minimal	0	0	0	2	0	0	1	3
slight	0	0	6	2	0	0	2	4
moderate	0	0	1	6	0	0	2	6
marked	0	0	0	8	0	0	2	6
severe	0	0	2	2	0	0	2	3
Total	0	0	9	20	0	0	9	22
Location, inflammatory & degenerative lesions								
Ventral region, bilateral	0	0	5	10	0	0	6	7
Diffuse, bilateral	0	0	3	13	0	0	3	17
Metaplasia, respiratory								
minimal	0	0	0	1	0	0	0	1
slight	0	0	0	3	0	0	0	1
moderate	0	0	0	1	0	0	0	0
Total	0	0	0	5	0	0	0	2
Synechiae, turbinates								
minimal	0	0	0	6	0	0	1	9
slight	0	0	0	4	0	0	2	5
moderate	0	0	0	1	0	0	0	0
marked	0	0	0	0	0	0	0	1
Total	0	0	0	11	0	0	3	15

Treatment-related non-neoplastic findings in Nasal cavity: Section 3

Sex	Male				Female			
Dosage level Epanova (mg/kg/day)	0	100	600	2000	0	100	600	2000
Number examined	24	30	40	36	12	13	26	35
Inflammation, lamina propria								
minimal	0	0	2	9	0	0	1	3
slight	0	0	1	6	0	0	1	2
moderate	0	0	0	0	0	0	0	1
marked	0	0	0	1	0	0	0	0
Total	0	0	3	16	0	0	2	6
Necrosis/atrophy, epithelial								
minimal	0	0	0	2	0	0	1	3
slight	0	0	6	2	0	0	2	4
moderate	0	0	1	6	0	0	2	6
marked	0	0	0	8	0	0	2	6
severe	0	0	2	2	0	0	2	3
Total	0	0	9	20	0	0	9	22

Treatment-related non-neoplastic findings in Nasal cavity: Section 4

Sex	Male				Female			
Dosage level Epanova (mg/kg/day)	0	100	600	2000	0	100	600	2000
Number examined	24	31	40	36	12	13	26	35
Exudate, inflammatory/mucous, lumen								
minimal	3	2	7	15	0	0	6	8
slight	0	0	8	7	0	0	3	5
moderate	0	0	1	4	0	0	2	1
marked	0	0	1	2	0	0	1	1
Total	3	2	17	28	0	0	12	15

Treatment-related non-neoplastic findings in Nasal cavity: Section 4

Sex	Male				Female			
Dosage level Epanova (mg/kg/day)	0	100	600	2000	0	100	600	2000
Number examined	24	31	40	36	12	13	26	35
Inflammation, lamina propria								
minimal	0	0	1	7	0	0	3	5
Slight	0	0	2	7	0	0	1	2
moderate	0	0	0	0	0	0	1	0
marked	0	0	1	1	0	0	0	0
Total	0	0	4	15	0	0	5	7
Necrosis/atrophy, epithelial								
slight	0	0	1	1	0	0	0	2
moderate	0	0	1	3	0	0	0	1
marked	0	0	2	0	0	0	3	2
severe	0	0	6	7	0	0	7	7
Total	0	0	10	11	0	0	10	12
Metaplasia, squamous								
minimal	0	0	0	3	0	1	0	3
Slight	0	0	2	1	0	0	0	0
moderate	0	0	1	4	0	0	2	8
marked	0	0	0	5	0	0	0	4
severe	0	0	0	1	0	0	0	1
Total	0	0	3	14	0	1	2	16

Treatment-related non-neoplastic findings in the larynx

Sex	Male				Female			
Dosage level Epanova (mg/kg/day)	0	100	600	2000	0	100	600	2000
Number examined	25	30	40	44	12	13	26	37
Necrosis/atrophy, epithelial								
minimal	0	0	1	3	0	0	2	1
slight	0	0	2	1	0	0	3	1
moderate	0	0	2	4	0	0	0	1
marked	0	0	3	3	0	0	1	3
severe	0	0	2	2	0	0	0	1
Total	0	0	10	13	0	0	6	7
Metaplasia, squamous								
minimal	2	5	8	17	0	1	5	6
slight	0	0	1	6	0	0	1	5
moderate	0	0	2	1	0	0	1	1
marked	0	0	0	1	0	0	0	1
Total	2	5	11	25	0	1	7	13

Treatment-related non-neoplastic findings in the trachea

Sex	Male				Female			
Dosage level Epanova (mg/kg/day)	0	100	600	2000	0	100	600	2000
Number examined	24	31	39	44	12	13	26	38
Exudate, inflammatory/mucous, lumen								
minimal	0	0	2	8	0	0	1	2
slight	0	0	0	1	0	0	0	1
Total	0	0	2	9	0	0	1	3
Inflammation, lamina propria								
minimal	0	0	6	8	0	1	4	2
slight	0	0	1	2	0	0	0	1
Total	0	0	7	10	0	1	4	3

Treatment-related non-neoplastic findings in the trachea

Sex	Male				Female			
Dosage level Epanova (mg/kg/day)	0	100	600	2000	0	100	600	2000
Number examined	24	31	39	44	12	13	26	38
Necrosis/atrophy, epithelial								
minimal	0	0	0	1	0	0	0	0
slight	0	0	0	0	0	0	1	1
moderate	0	0	0	0	0	0	1	0
marked	0	0	0	3	0	0	1	2
severe	0	0	9	10	0	0	4	5
Total	0	0	9	14	0	0	7	8
Hyperplasia, epithelial								
minimal	0	0	3	5	0	1	0	1
slight	0	0	1	4	0	0	1	6
moderate	0	1	0	1	0	0	0	0
Total	0	1	4	10	0	1	1	7

Toxicokinetics

TK parameters were not calculated; samples were collected at several time points to measure the plasma concentration of EPA and DHA. Findings of these data suggested that at LD level, both EPA and DHA levels increased in all treated animals over time. However, at MD and HD, saturation for both EPA and DHA was reported for all treated animals. In females, both compounds levels increased from Day 1 to Week 13 and then stayed at the same level. In males, both compounds levels stayed in the same levels at all-time points. Sponsor's Table:

Mean concentrations (µg/mL) of EPA and DHA[a]

	Group/dose level (mg/kg/day)							
	1M (0)	2M (100)	3M (600)	4M (2000)	1F (0)	2F (100)	3F (600)	4F (2000)
EPA								
Day 1	43.8	89.0	860	956	15.8	59.0	263	403
Week 13	27.6	150	1143	813	22.1	222	877	725
Week 26	23.6	276	1019	522	33.0	414	779	719
DHA								
Day 1	173	107	506	555	83.9	82.2	183	249
Week 13	105	149	604	465	97.1	231	496	405
Week 26	124	220	514	308	150	364	442	464

[a] Blood samples collected from the same 3 animals/group on each occasion , where possible

Dosing Solution Analysis:

Epanove was extracted every day from the capsules.

Study title: Epanova: 26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 Mice	
Study no.:	AD29PL.7G8R.BTL
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	19 July, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Epanova, lot#: 3130616 with batch number:36355; Purity: NA
CAC concurrence:	Yes

Key Study Findings

Statistically Significant Neoplastic Findings:
None

Non-Neoplastic Findings:
- HD (4000mg/kg/day) treated animals were removed from the study on Day 73 (Week 10) with 50% surviving. There was an increase in mortality in males (in all LD, MD and HD) and females (in MD and HD) with no evidence of an increase in incidence of tumors in either sex. Cause of death was due to respiratory system injury.
- Body weights (gain) decreased in all animals at 2000 and 4000 mg/kg/day.
- Microscopic findings were observed for hyperplasia in the non-glandular portion of the stomach and for inflammatory lesions in the nasal cavity, trachea, and lungs.

Maximum Clinical Exposure:

TK parameters were not calculated. Exposure multiples for transgenic studies are not typically included in labeling.

Adequacy of Carcinogenicity Study

The Committee concurred that the study was adequate.

Appropriateness of Test Models

The test model was appropriate to assess the carcinogenic potential of Epanova. Positive control animals exhibited the expected results

Evaluation of Tumor Findings

There were no tumor increases in any Epanova treatment group that were considered treatment-related (ECAC concurred).

Methods	
Doses:	0 (water), 500, 1000, 2000, and 4000 mg/kg/day 1000 mg/kg/day for urethane (positive control)
Frequency of dosing:	Daily for 26 weeks
Dose volume:	4.4 (Water; negative control), 10.0 (urethane, positive control), 0.55, 1.1, 2.2 and 4.4 mL/kg/day (Epanova)
Route of administration:	Oral gavage except for urethane formulated (3 i.p. injections on Days 1, 3, and 5)
Formulation/Vehicle:	Sterile Water for Injection, USP
Basis of dose selection:	ECAC concurrence and was based on 2-week non-GLP pilot study and maximum feasible dose at HD in mice.
Species/Strain:	Hemizygous Tg.rasH2 mice
Number/Sex/Group:	Epanova/30 mice/sex/group Positive control (Urethane in Saline) /20 mice/sex/group
Age:	5 to 6 weeks
Animal housing:	Individually housed in polycarbonate cages
Paradigm for dietary restriction:	Harlan TEKLAD Global Diet: #2018CM (Certified 18% Protein Rodent Diet, Harlan TEKLAD, Madison WI) in meal form, in stainless steel rodent feeders, *ad libitum.*
Dual control employed:	There were Positive and negative control groups
Interim sacrifice:	No
Satellite groups:	8/sex/Epanova groups
Deviation from study protocol:	Because of mortality and sings of toxicity in HD-treated males, surviving males, were sacrificed on Day 73.

Observations and Results

Mortality

There was an increased incidence of dose-response mortality in both genders. HD (4000mg/kg/day) treated animals were removed from the study on Day 73 (Week 10) with 50% surviving. Mortality was higher in males than females and at HD, was higher than the positive Control (urethane).

Cause of death was due to aspiration of the test article based on pathological findings in the respiratory system (nasal cavity, trachea, lungs).

Positive control animals showed expected mortality (6/20 males and 7/20 females).
Sponsor's Table:

Text Table 1: Summary of Survival

Nominal Dose	0	PC	500	1000	2000	4000
Males						
Number At Initiation	30	20	30	30	30	30
Number Early Deaths	0	6	5	3	14	15
Number At Terminal Sacrifice	30	14[A]	25	27	16	15[A]
% Surviving to Terminal Sacrifice	100.0%	70.0%	83.3%	90.0%	53.3%	50.0%
Females						
Number At Initiation	30	20	30	30	30	30
Number Early Deaths	1	7	6	5	10	15
Number At Terminal Sacrifice	29	13[A]	24	25	20	15
% Surviving to Terminal Sacrifice	96.7%	65.0%	80.0%	83.3%	66.7%	50.0%

[A]= 4000 mg/kg/day males scheduled termination was on Day 73; Positive Control (PC) scheduled termination was on Day 122 (males) and Day 120 (females).

CDER statistical analysis:

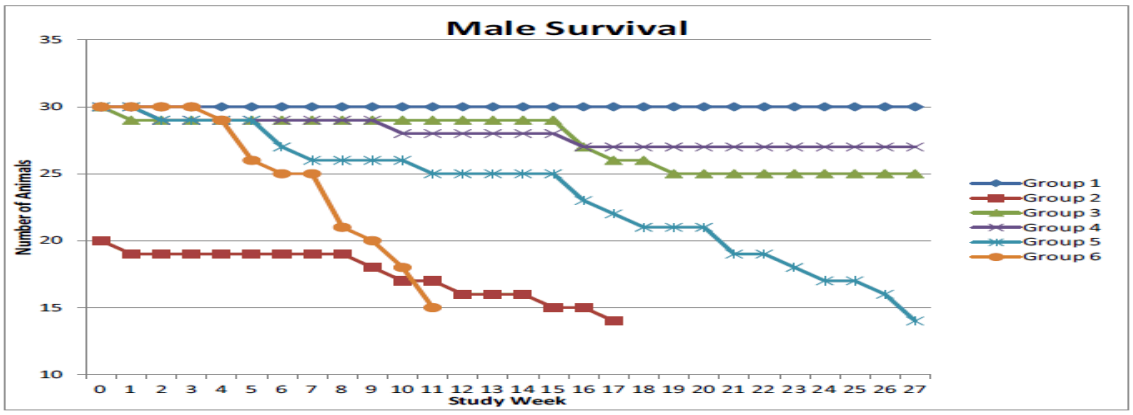
Survival Times in Male Tg.rasH2 Mice

Dose Group	Dosage	Survival Time in Days	
1. Water	0		*183(30)
2. Urethane	1000	4, 58, 66, 83,101,115,	*122 (14)
3. Low	0.55	5,109,113,116,134,	*184(25)
4. Low-Med.	1.1	10, 69,113,	*184(27)
5. High-Med.	2.2	14, 38, 40, 45, 76, 112,113,117,118,143,145,161,163, 179,	*183(16)
6. High	4.4	27, 31, 36, 36, 38, 44, 45, 48, 48, 54, 59, 62, 71, 71, *73(16)	

Table 5. Survival Times in Female Tg.rasH2 Mice

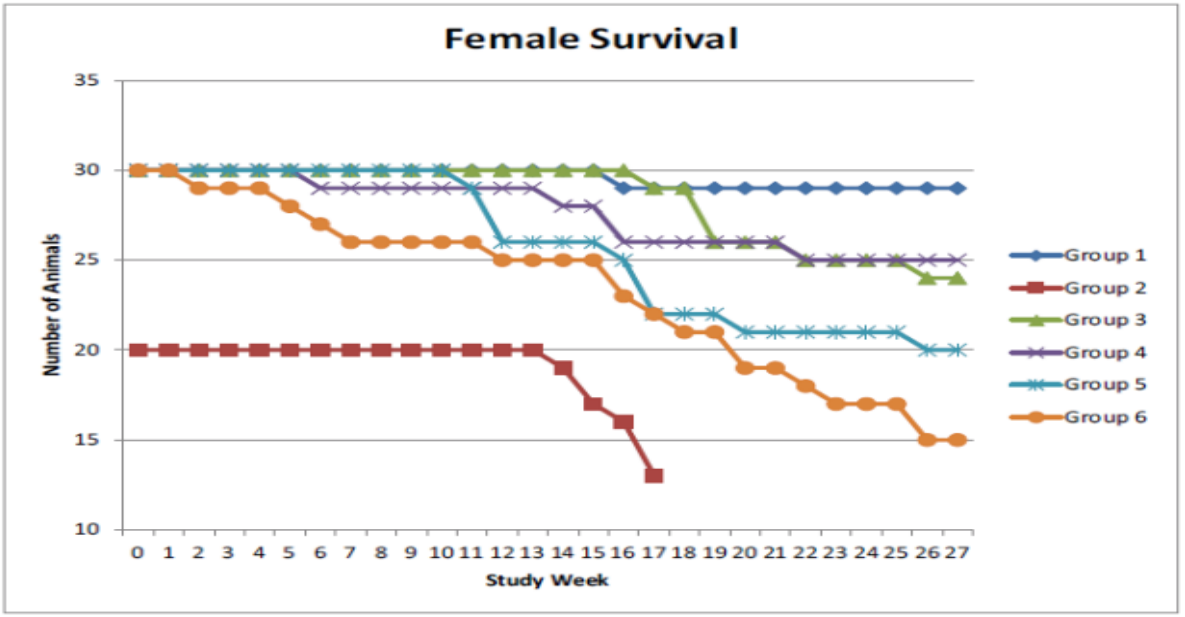
Dose Group	Dosage	Survival Time in Days	
1. Water	0	113,	*183(29)
2. Urethane	1000	93,103,106,112,117,118,120,	*120 (13)
3. Low	0.55	117,128,132,132,154,179,	*184(24)
4. Low-Med.	1.1	49, 95,107,111,150,	*184(25)
5. High-Med.	2.2	73, 80, 83, 84,110,114,114,116,137,175,	*183(20)
6. High	4.4	15, 34, 41, 49, 80,110,113,117,126,140,141,153,157,174,176,	*183(16)

Sponsor's Figures:



Group 1 - 0 mg/kg/day (Negative Control) Group 2 - 1000 mg/kg/day (Positive Control)
Group 3 - 500 mg/kg/day Group 4 - 1000 mg/kg/day Group 5 - 2000 mg/kg/day
Group 6 - 4000 mg/kg/day

FEMALE SURIVIVAL - MAIN STUDY



Clinical Signs

Clinical signs of hypothermia, thinness, decreased motor activity, ruffled fur, hunched or prostrate (rarely) posture, and labored or rapid and shallow breathing were seen in a dose-response in Epanova treated animals.

Positive control animals were reported for expected clinical signs of decrease motor activity, thinness, hunched posture, ruffled fur and masses; hypothermia and rapid and shallow breathing.

Body Weights

Animals were treated at MD and HD showed loss of body weight gain as follows:

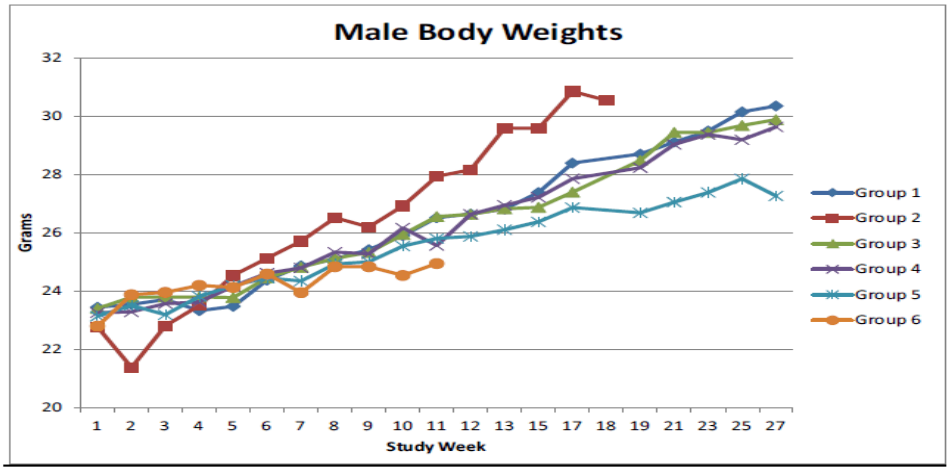
In males: On Day 73 (termination), at 4000mg/kg/day, the mean body weight gain from the first Day was 30% lower that the control group; and on Day 183 (scheduled termination), at 2000 mg/kg/day, the mean body weight gain from the first day was 44% lower than the control group (ss on Days 127, 141 and 183).

In females: On Day 183 (scheduled termination), at 4000mg/kg/day, the mean body weight gain was 64% lower than the control group (ss from Day 57); and at 2000mg/kg/day, the mean body weight gains from the first day was 35% lower than the control group (ss from Day 155).

Positive Control: Body weight means decreased significantly from Day 8 due to decreased motor activity, and caused increased body weights toward the end of the study due to the development of lung and spleen tumors.

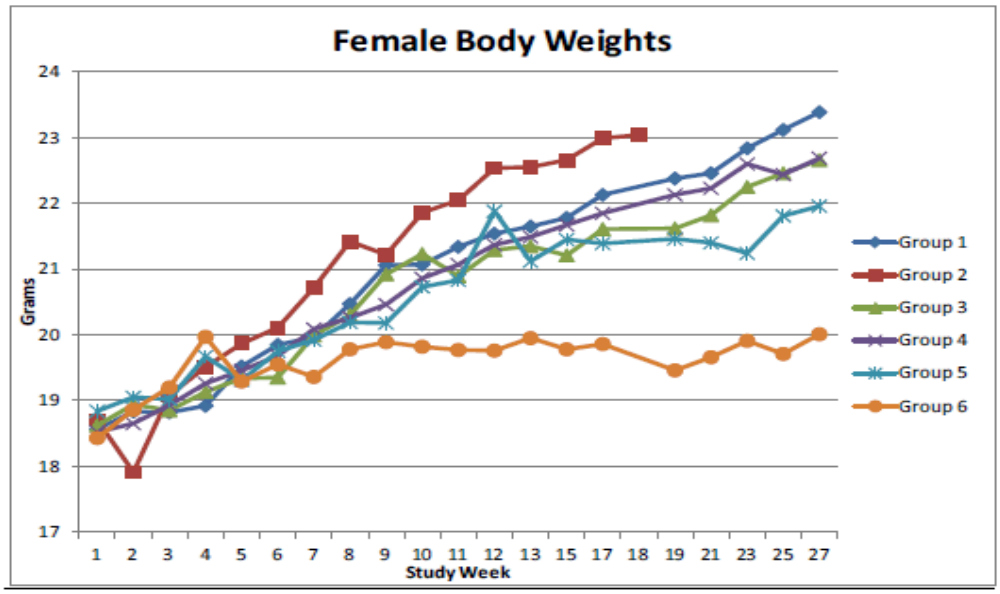
Sponsor's Figures:

MALE MEAN BODY WEIGHTS - MAIN STUDY



Group 1 - 0 mg/kg/day (Negative Control) Group 2 - 1000 mg/kg/day (Positive Control)
Group 3 - 500 mg/kg/day Group 4 - 1000 mg/kg/day Group 5 - 2000 mg/kg/day
Group 6 - 4000 mg/kg/day

FEMALE MEAN BODY WEIGHTS - MAIN STUDY



Group 1 - 0 mg/kg/day (Negative Control) Group 2 - 1000 mg/kg/day (Positive Control)
Group 3 - 500 mg/kg/day Group 4 - 1000 mg/kg/day Group 5 - 2000 mg/kg/day
Group 6 - 4000 mg/kg/day

Feed Consumption

Changes in food consumption were not in a dose-response. Food consumption was lower (ss) for HD-treated females compared to control from Day 64 to day 113.

Gross Pathology

Only positive control-treated animals were observed with pulmonary and splenic lesions as expected for urethane treatment.

Organ Weight

Sponsor's Table below shows all changes for organ weight; these changes were not correlated with any gross or microscopic lesions.

Text Table 3: Absolute and Relative Organ Weights

Parameter	Males Group No.*	Significant Difference Compared to Group 1 (%)
Brain Weight	5	↓ (3.8%)
Kidneys Weight	5	↓ (12.5%)
Liver Weight	5	↓ (12.7%)
Relative Heart Weight	5	↑ (12.5%)
Relative Spleen Weight	5	↑ (14.3%)
Parameter	**Females Group No.**	**Significant Difference Compared to Group 1 (%)**
Brain Weight	6	↓ (8.6%)
Relative Brain Weight	6	↑ (6.4%)
Kidneys Weight	6	↓ (9.6%)
Relative Kidneys Weight	3, 4, 6	↑ (6.1%), ↑ (6.0%), ↑ (5.6%)
Liver Weight	5, 6	↓ (9.9%), ↓ (15.3%)
Relative Liver Weight	5	↓ (4.1%)
Relative Spleen Weight	3	↑ (23.3%)

↑ = Statistically significant ($p < 0.05$) increase, compared to Group 1.
↓ = Statistically significant ($p < 0.05$) decrease, compared to Group 1.
(%) = Percent difference from the control group.
* = Group 6 males were terminated on Day 73, without a concurrent control.
Dose: Group 1 - 0 mg/kg/day Group 3 - 500 mg/kg/day Group 4 - 1000 mg/kg/day
Group 5 - 2000 mg/kg/day Group 6 - 4000 mg/kg/day

According to the Sponsor, the decrease in absolute organ weight of liver was due to glycogen depletion of liver noted in animals in this group.

Histopathology

Peer Review

Yes

Neoplastic

In female mice, the test of trend for the alveolar-bronchiolar adenoma of the lungs was identified statistical significant by the CDER biostatistics ($p = 0.009$); however, the comparison between Epanova treated groups to the negative control group was not significant (Sponsor's Table):

Text Table 3: Lung Tumors

MALE							
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	HCR
Number Examined	30	20	30	30	30	30	
Adenoma, single	1	0	2	1	1	0	0-6
Adenoma, multiple	0	19	0	0	0	0	0-1
Carcinoma	0	8	1	0	0	0	0-2
All Lung Tumors[1]	1	19	3	1	1	0	0-7
FEMALE							
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	HCR
Number Examined	30	20	30	30	30	30	
Adenoma, single	0	0	1	0	3	3	0-6
Adenoma, multiple	0	20	0	0	0	0	0-1
Carcinoma	1	14	1	1	0	0	0-1
All Lung Tumors[1]	1	20	2	1	3	3	0-6

Group 1 - 0 mg/kg/day Group 2 – positive control, urethane Group 3 - 500 mg/kg/day
Group 4 - 1000 mg/kg/day Group 5 - 2000 mg/kg/day Group 6 - 4000 mg/kg/day
[1] Number of tumor bearing animals.
HCR: Historical control range

All incidences of multiple adenomas, carcinomas, and the combined incidences of all tumors in the vehicle control and Epanova treated animals were not statistically significant by trend and/or pairwise (Sponsor's Tables):

MALE						
	Group 1	Group 3	Group 4	Group 5	Group 6	HCR
Number Examined	30	30	30	30	30	
Spleen	4	0	1	0	1	0-4
Ear[1]	0	1	0	0	0	NR
Kidney	0	1	0	0	0	NR
Lung	0	2	0	0	0	0-1
Testes[1]	0	0	1	0	0	0-1
Skull	0	1	0	0	0	NR
Total Tumors	4	5	2	0	1	0-4
FEMALE						
	Group 1	Group 3	Group 4	Group 5	Group 6	HCR
Number Examined	30	30	30	30	30	
Spleen	1	1	0	1	0	0-4
Multi-centric	1	0	0	0	0	0-1
Mammary Gland	0	0	0	1	0	0-1
Salivary Gland	0	2	0	0	0	NR
Skin	0	0	0	0	1	0-1
Uterus	0	1	1	0	0	0-2
Total Tumors	2	4	1	2	1	0-5

Group 1 - 0 mg/kg/day Group 3 - 500 mg/kg/day Group 4 - 1000 mg/kg/day
Group 5 - 2000 mg/kg/day Group 6 - 4000 mg/kg/day
[1] A hemangioma was diagnosed for this organ. For all other organs, a hemangiosarcoma was diagnosed.
NR: Not recorded in (b) (4) Historical Control Database.
HCR: Historical control range

MALE						
	Group 1	Group 3	Group 4	Group 5	Group 6	HCR
Number Examined	30	30	30	30	30	
Harderian Gland, adenoma	2	2	0	0	0	0-2
Harderian Gland, carcinoma	0	0	0	1	0	NR
Liver, adenoma	1	0	0	0	0	0-1
Stomach, papilloma	0	0	0	1	0	0-1
Skin, lymphangioma	0	1	0	0	0	NR
FEMALE						
	Group 1	Group 3	Group 4	Group 5	Group 6	HCR
Number Examined	30	30	30	30	30	
Nasal Cavity, sarcoma	0	1	0	0	0	NR
Harderian Gland, adenoma	1	1	0	0	0	0-4
Harderian Gland, carcinoma	1	0	0	0	0	0-2
Heart, sarcoma	0	1	0	0	0	NR
Mandibular Lymph node, lymphangioma	0	0	0	1	0	NR
Mammary Gland, lymphangioma	0	1	0	0	0	0-1
Stomach, papilloma	1	0	0	1	0	0-1

Group 1 - 0 mg/kg/day Group 3 - 500 mg/kg/day Group 4 - 1000 mg/kg/day
Group 5 - 2000 mg/kg/day Group 6 - 4000 mg/kg/day
NR: Not recorded in (b) (4) Historical Control Database.
HCR: Historical control range

Tumor Summary: Males

				Number of Animals with Tumor (a)					
ORGAN	TUMOR	DAY	CONTEXT	Control	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day	Positive Control
EAR	HEMANGIOMA (B)	109	F/M	0	1	0	0	0	0
HARDERIAN GLANDS	ADENOMA (B)	1-EOS	I	0/0	0/5	0/3	0/14	0/30	0/0
		Term	I	2/30	2/25	0/27	0/16	0/0	0/0
	CARCINOMA (M)	1-EOS	I	0/0	0/5	0/3	0/14	0/30	0/0
		Term	I	0/30	0/25	0/27	1/16	0/0	0/0
	CARCINOMA/ADENOMA	1-EOS	I	0/0	0/5	0/3	0/14	0/30	0/0
		Term	I	2/30	2/25	0/27	1/16	0/0	0/0
KIDNEYS	HEMANGIOSARCOMA (M)	1-EOS	I	0/0	0/5	0/3	0/14	0/30	0/0
		Term	I	0/30	1/25	0/27	0/16	0/0	0/0
LIVER	HEPATOCELLULAR ADENOMA (B)	1-EOS	I	0/0	0/5	0/3	0/14	0/30	0/0
		Term	I	1/30	0/25	0/27	0/16	0/0	0/0
LUNGS WITH BRONCHI	ALVEOLAR-BRONCHIOLAR ADENOMA (B)	Inter	I	0/0	0/0	0/0	0/0	0/0	14/14
		1-EOS	I	0/0	0/5	0/3	0/14	0/30	1/2
		Term	I	1/30	2/25	1/27	1/16	0/0	0/0
		58	F/M	0	0	0	0	0	1
		66	F/M	0	0	0	0	0	1
		83	F/M	0	0	0	0	0	1
		101	F/M	0	0	0	0	0	1
	ALVEOLAR-BRONCHIOLAR CARCINOMA (M)	Inter	I	0/0	0/0	0/0	0/0	0/0	7/14
		1-EOS	I	0/0	0/4	0/3	0/14	0/30	1/6
		Term	I	0/30	0/25	0/27	0/16	0/0	0/0
		116	F/M	0	1	0	0	0	0
	ALVEOLAR-BRONCHIOLAR CARCINOMA/ADENOMA	Inter	I	0/0	0/0	0/0	0/0	0/0	14/14
		1-EOS	I	0/0	0/4	0/3	0/14	0/30	1/2

Context - Context of tumor for statistical analysis: I = Incidental; F/M = Fatal or Mortality Independent
(a) I: Number of animals with tumor/Number of Animals examined in the time interval
F/M: Number of animals with tumor at specified study day
Inter = Intermittent Sacrifice; Term = Terminal Sacrifice
EOS = end of study (up to terminal sacrifice) (B) - Benign (M) - Malignant

ORGAN	TUMOR	DAY	CONTEXT	Number of Animals with Tumor (a) Control	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day	Positive Control
LUNGS WITH BRONCHI	ALVEOLAR-BRONCHIOLAR CARCINOMA/ADENOMA	Term	I	1/30	2/25	1/27	1/16	0/0	0/0
		58	F/M	0	0	0	0	0	1
		66	F/M	0	0	0	0	0	1
		83	F/M	0	0	0	0	0	1
		101	F/M	0	0	0	0	0	1
		116	F/M	0	1	0	0	0	0
	HEMANGIOSARCOMA (M)	Inter	I	0/0	0/0	0/0	0/0	0/0	4/14
		1-EOS	I	0/0	0/4	0/3	0/14	0/30	0/6
		Term	I	0/30	1/25	0/27	0/16	0/0	0/0
		113	F/M	0	1	0	0	0	0
MULTIPLE ORGANS	HEMANGIOSARCOMA/HEMANGIOMA	Inter	I	0/0	0/0	0/0	0/0	0/0	14/14
		1-EOS	I	0/0	0/3	0/3	0/14	1/30	1/5
		Term	I	4/30	3/25	2/27	0/16	0/0	0/0
		101	F/M	0	0	0	0	0	1
		109	F/M	0	1	0	0	0	0
		113	F/M	0	1	0	0	0	0
SKIN (MAMMARY AREA)	LYMPHANGIOMA (B)	1-EOS	I	0/0	1/5	0/3	0/14	0/30	0/0
		Term	I	0/30	0/25	0/27	0/16	0/0	0/0
SKULL CAP	HEMANGIOSARCOMA (M)	Term	I	0/0	1/1	0/0	0/0	0/0	0/0
SPLEEN	HEMANGIOSARCOMA (M)	Inter	I	0/0	0/0	0/0	0/0	0/0	14/14
		1-EOS	I	0/0	0/5	0/3	0/14	1/30	1/5
		Term	I	4/30	0/25	1/27	0/16	0/0	0/0
		101	F/M	0	0	0	0	0	1
STOMACH	PAPILLOMA (B)	1-EOS	I	0/0	0/5	0/3	1/14	0/30	0/0
		Term	I	0/30	0/25	0/27	0/16	0/0	0/0

Context - Context of tumor for statistical analysis: I = Incidental; F/M = Fatal or Mortality Independent
(a) I: Number of animals with tumor/Number of Animals examined in the time interval
F/M: Number of animals with tumor at specified study day
Inter = Intermittent Sacrifice; Term = Terminal Sacrifice
EOS = end of study (up to terminal sacrifice) (B) - Benign (M) - Malignant

ORGAN	TUMOR	DAY	CONTEXT	Number of Animals with Tumor (a) Control	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day	Positive Control
TESTES	HEMANGIOMA (B)	1-EOS	I	0/0	0/5	0/3	0/14	0/30	0/0
		Term	I	0/30	0/25	1/27	0/16	0/0	0/0

Tumor Summary: Females

ORGAN	TUMOR	DAY	CONTEXT	Number of Animals with Tumor (a) Control	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day	Positive Control
BONE, STERNUM	ALVEOLAR-BRONCHIOLAR CARCINOMA (M)	1-EOS	I	0/1	0/6	0/4	0/10	0/15	0/0
		Term	I	0/29	0/24	0/25	0/20	0/15	0/0
		150	F/M	0	0	1	0	0	0
CAVITY, NASAL	SARCOMA (M)	1-EOS	I	0/1	0/6	0/5	0/10	0/15	0/0
		Term	I	0/29	1/24	0/25	0/20	0/15	0/0
HARDERIAN GLANDS	ADENOMA (B)	1-EOS	I	0/1	0/6	0/5	0/10	0/15	0/0
		Term	I	1/29	1/24	0/25	0/20	0/15	0/0
	CARCINOMA (M)	1-EOS	I	0/1	0/6	0/5	0/10	0/15	0/0
		Term	I	1/29	0/24	0/25	0/20	0/15	0/0
	CARCINOMA/ADENOMA	1-EOS	I	0/1	0/6	0/5	0/10	0/15	0/0
		Term	I	2/29	1/24	0/25	0/20	0/15	0/0
HEART	SARCOMA (M)	1-EOS	I	0/1	0/6	0/5	0/10	0/15	0/0
		Term	I	0/29	1/24	0/25	0/20	0/15	0/0
LUNGS WITH BRONCHI	ALVEOLAR-BRONCHIOLAR ADENOMA (B)	Inter	I	0/0	0/0	0/0	0/0	0/0	13/13
		1-EOS	I	0/1	1/6	0/5	0/10	1/15	0/0
		Term	I	0/29	0/24	0/25	3/20	2/15	0/0
		93	F/M	0	0	0	0	0	1
		103	F/M	0	0	0	0	0	1
		106	F/M	0	0	0	0	0	1
		112	F/M	0	0	0	0	0	1
		117	F/M	0	0	0	0	0	1
		118	F/M	0	0	0	0	0	1
		120	F/M	0	0	0	0	0	1
	ALVEOLAR-BRONCHIOLAR CARCINOMA (M)	Inter	I	0/0	0/0	0/0	0/0	0/0	11/13
		1-EOS	I	0/1	0/6	0/4	0/10	0/15	0/4
		Term	I	1/29	1/24	0/25	0/20	0/15	0/0

Context - Context of tumor for statistical analysis: I = Incidental; F/M = Fatal or Mortality Independent
(a) I: Number of animals with tumor/Number of Animals examined in the time interval
F/M: Number of animals with tumor at specified study day
Inter = Intermittent Sacrifice; Term = Terminal Sacrifice
EOS = end of study (up to terminal sacrifice) (B) - Benign (M) - Malignant

ORGAN	TUMOR	DAY	CONTEXT	Number of Animals with Tumor (a) Control	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day	Positive Control
LUNGS WITH BRONCHI	ALVEOLAR-BRONCHIOLAR CARCINOMA (M)	112	F/M	0	0	0	0	0	1
		117	F/M	0	0	0	0	0	1
		120	F/M	0	0	0	0	0	1
		150	F/M	0	0	1	0	0	0
	ALVEOLAR-BRONCHIOLAR CARCINOMA/ADENOMA	Inter	I	0/0	0/0	0/0	0/0	0/0	13/13
		1-EOS	I	0/1	1/6	0/4	0/10	1/15	0/0
		Term	I	1/29	1/24	0/25	3/20	2/15	0/0
		93	F/M	0	0	0	0	0	1
		103	F/M	0	0	0	0	0	1
		106	F/M	0	0	0	0	0	1
		112	F/M	0	0	0	0	0	1
		117	F/M	0	0	0	0	0	1
		118	F/M	0	0	0	0	0	1
		120	F/M	0	0	0	0	0	1
		150	F/M	0	0	1	0	0	0
	HEMANGIOSARCOMA (M)	Inter	I	0/0	0/0	0/0	0/0	0/0	4/13
		1-EOS	I	0/1	0/6	0/5	0/10	0/15	0/7
		Term	I	0/29	0/24	0/25	0/20	0/15	0/0
LYMPH NODE, MANDIBULAR	LYMPHANGIOMA (B)	1-EOS	I	0/1	0/6	0/5	1/10	0/15	0/0
		Term	I	0/29	0/24	0/25	0/20	0/15	0/0
MAMMARY GLAND	HEMANGIOSARCOMA (M)	1-EOS	I	0/1	0/6	0/5	0/9	0/15	0/0
		Term	I	0/29	0/24	0/25	0/20	0/15	0/0
		114	F/M	0	0	0	1	0	0
	LYMPHANGIOMA (B)	1-EOS	I	0/1	0/6	0/5	0/10	0/15	0/0
		Term	I	0/29	1/24	0/25	0/20	0/15	0/0
MULTICENTRIC	HEMANGIOSARCOMA (M)	Inter	I	0/0	0/0	0/0	0/0	0/0	0/13

Context - Context of tumor for statistical analysis: I = Incidental; F/M = Fatal or Mortality Independent
(a) I: Number of animals with tumor/Number of Animals examined in the time interval
F/M: Number of animals with tumor at specified study day
Inter = Intermittent Sacrifice; Term = Terminal Sacrifice
EOS = end of study (up to terminal sacrifice) (B) - Benign (M) - Malignant

ORGAN	TUMOR	DAY	CONTEXT	Number of Animals with Tumor (a) Control	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day	Positive Control
MULTICENTRIC	HEMANGIOSARCOMA (M)	1-EOS	I	0/0	0/6	0/5	0/10	0/15	0/7
		Term	I	0/29	0/24	0/25	0/20	0/15	0/0
		113	F/M	1	0	0	0	0	0
MULTIPLE ORGANS	HEMANGIOSARCOMA/HEMANGIOMA	Inter	I	0/0	0/0	0/0	0/0	0/0	12/13
		1-EOS	I	0/0	0/5	0/5	0/9	0/14	0/0
		Term	I	1/29	3/24	1/25	1/20	0/15	0/0
		93	F/M	0	0	0	0	0	1
		103	F/M	0	0	0	0	0	1
		106	F/M	0	0	0	0	0	1
		112	F/M	0	0	0	0	0	1
		113	F/M	1	0	0	0	0	0
		114	F/M	0	0	0	1	0	0
		117	F/M	0	0	0	0	0	1
		118	F/M	0	0	0	0	0	1
		120	F/M	0	0	0	0	0	1
		140	F/M	0	0	0	0	1	0
		154	F/M	0	1	0	0	0	0
SALIVARY GLANDS	HEMANGIOSARCOMA (M)	1-EOS	I	0/1	0/5	0/5	0/10	0/15	0/0
		Term	I	0/29	1/24	0/25	0/20	0/15	0/0
		154	F/M	0	1	0	0	0	0
SKIN	HEMANGIOSARCOMA (M)	1-EOS	I	0/1	0/0	0/0	0/0	0/0	0/0
		140	F/M	0	0	0	0	1	0
SPLEEN	HEMANGIOSARCOMA (M)	Inter	I	0/0	0/0	0/0	0/0	0/0	12/13
		1-EOS	I	0/1	0/6	0/5	0/10	0/15	0/0
		Term	I	1/29	1/24	0/25	1/20	0/15	0/0
		93	F/M	0	0	0	0	0	1
		103	F/M	0	0	0	0	0	1
		106	F/M	0	0	0	0	0	1
		112	F/M	0	0	0	0	0	1

Context - Context of tumor for statistical analysis: I = Incidental; F/M = Fatal or Mortality Independent
(a) I: Number of animals with tumor/Number of Animals examined in the time interval
F/M: Number of animals with tumor at specified study day
Inter = Intermittent Sacrifice; Term = Terminal Sacrifice
EOS = end of study (up to terminal sacrifice) (B) - Benign (M) - Malignant

ORGAN	TUMOR	DAY	CONTEXT	Number of Animals with Tumor (a) Control	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day	Positive Control
SPLEEN	HEMANGIOSARCOMA (M)	117	F/M	0	0	0	0	0	1
		118	F/M	0	0	0	0	0	1
		120	F/M	0	0	0	0	0	1
STOMACH	PAPILLOMA (B)	1-EOS	I	0/1	0/6	0/5	1/10	0/15	0/0
		Term	I	1/29	0/24	0/25	0/20	0/15	0/0
UTERUS	HEMANGIOSARCOMA (M)	1-EOS	I	0/1	0/6	0/5	0/10	0/15	0/0
		Term	I	0/29	1/24	1/25	0/20	0/15	0/0

Non Neoplastic

Treatment-related non-neoplastic lesions were observed in a dose-response for hyperplasia of non-glandular portion of the stomach (probably due to the irritation from treatment with no tumors) and for inflammatory lesions in the nasal cavity, trachea, and lungs (due to aspiration of the test article) (Sponsor's Tables):

Text Table 7: Non-Glandular Stomach Hyperplasia

MALE					
	Group 1	Group 3	Group 4	Group 5	Group 6
Number Examined	30	30	30	30	30
Minimal	0	1	2	5	5
Mild	0	0	1	1	3
Moderate	0	1	0	0	3
Marked	0	0	1	0	0
FEMALE					
	Group 1	Group 3	Group 4	Group 5	Group 6
Number Examined	30	30	30	30	30
Minimal	0	0	0	3	2
Mild	0	1	0	2	0
Moderate	0	0	0	0	1

Group 1 - 0 mg/kg/day Group 3 - 500 mg/kg/day Group 4 - 1000 mg/kg/day
Group 5 - 2000 mg/kg/day Group 6 - 4000 mg/kg/day

Reviewer: The hyperplasia of non-glandular stomach in group 6 was reported with no tumors in stomach; however, these animals were removed from the study earlier due to the survival rate.

Text Table 8: Nasal Cavity Lesions

MALE					
	Group 1	Group 3	Group 4	Group 5	Group 6
Number Examined	30	30	30	30	30
Submucosa, inflammation					
Minimal	8	8	12	11	21
Mild	0	2	9	1	3
Exudative, inflammation					
Minimal	1	1	3	4	4
Mild	0	3	1	8	8
Moderate	0	1	3	6	6
Marked	0	0	0	1	2
FEMALE					
	Group 1	Group 3	Group 4	Group 5	Group 6
Number Examined	30	30	30	30	30
Submucosa, inflammation					
Minimal	22	11	21	18	25
Mild	3	6	4	5	3
Exudative, inflammation					
Minimal	0	1	2	4	5
Mild	0	0	5	10	15
Moderate	0	1	4	6	8
Marked	0	0	0	0	1

Group 1 - 0 mg/kg/day Group 3 - 500 mg/kg/day Group 4 - 1000 mg/kg/day
Group 5 - 2000 mg/kg/day Group 6 - 4000 mg/kg/day

Text Table 9: Inflammatory Tracheal Lesions

MALE					
	Group 1	Group 3	Group 4	Group 5	Group 6
Number Examined	30	30	30	30	30
Minimal	0	1	0	1	0
Mild	0	1	0	4	0
Moderate	0	0	0	0	0
Marked	0	1	1	2	0
FEMALE					
	Group 1	Group 3	Group 4	Group 5	Group 6
Number Examined	30	30	30	30	30
Minimal	0	0	0	0	0
Mild	0	0	0	1	4
Moderate	0	1	1	1	1
Marked	0	1	1	4	3

Group 1 - 0 mg/kg/day Group 3 - 500 mg/kg/day Group 4 - 1000 mg/kg/day
Group 5 - 2000 mg/kg/day Group 6 - 4000 mg/kg/day

Text Table 10: Inflammatory Lung Lesions in Bronchus

MALE					
	Group 1	Group 3	Group 4	Group 5	Group 6
Number Examined	30	30	30	30	30
Minimal	0	0	0	1	0
Mild	0	0	0	1	0
Moderate	0	0	0	1	0
Marked	0	1	0	2	0
FEMALE					
	Group 1	Group 3	Group 4	Group 5	Group 6
Number Examined	30	30	30	30	30
Minimal	0	0	0	0	0
Mild	0	0	0	0	0
Moderate	0	1	1	2	2
Marked	0	1	0	2	0

Group 1 - 0 mg/kg/day Group 3 - 500 mg/kg/day Group 4 - 1000 mg/kg/day
Group 5 - 2000 mg/kg/day Group 6 - 4000 mg/kg/day

According to the Sponsor, “The lesions in the trachea of moderate to marked intensity were characterized by necrosis of the tracheal epithelium, accumulation of necrotic debris and degenerate neutrophils in the lumen. The lesions of minimal to mild intensity were characterized by attenuation of tracheal epithelium and infiltration of mixed inflammatory cells in the proliferating fibrous tissue that caused fronds or papillary projections to protrude in the lumen of the trachea.” “Lesions in the lungs were mostly present in the primary bronchi at the bifurcation as the trachea enters the lungs. The lesions in the bronchi were similar to those noted in the trachea and were mostly of moderate to marked intensity, with only a few being of mild or less intensity.”

Reviewer: The lack of tracheal lesions and inflammatory lung lesions in the HD Epanova-treated males probably were due to early termination of this group.

Other histopathology findings in those animals that were removed early because of either natural death or moribund sacrifice were involution of thymus (stress-related) and necrosis of lymphoid tissue (in thymus, mandibular lymph nodes, mesenteric lymph nodes, and spleen). According to the Sponsor, depletion of glycogen in the liver was considered by lack of vacuolation of hepatocytes that would be seen normally. Sponsor’s Table:

Text Table 11: Miscellaneous Lesions

MALE					
	Group 1	Group 3	Group 4	Group 5	Group 6
Number Examined	30	30	30	30	30
Duodenum infiltration pigmented macrophages	0	4	11	9	1
Mesenteric Lymph Node infiltration pigmented macrophages	0	1	5	15	0
Thymus Involution	0	2	2	5	7
Thymus Necrosis	0	0	0	3	4
Spleen Necrosis	0	0	3	8	7
Mandibular Lymph Node Necrosis	0	0	1	3	2
Mesenteric Lymph Node Necrosis	1	1	1	12	1
Liver Glycogen Depletion	0	4	4	14	13
FEMALE					
	Group 1	Group 3	Group 4	Group 5	Group 6
Number Examined	30	30	30	30	30
Duodenum infiltration pigmented macrophages	0	14	10	12	13
Mesenteric Lymph Node infiltration pigmented macrophages	0	5	9	18	20
Thymus Involution	3	4	3	11	13
Thymus Necrosis	0	0	2	4	2
Spleen Necrosis	0	2	3	3	11
Mandibular Lymph Node Necrosis	0	0	1	2	3
Mesenteric Lymph Node Necrosis	0	1	1	9	8
Liver Glycogen Depletion	0	5	5	10	13

Group 1 - 0 mg/kg/day Group 3 - 500 mg/kg/day Group 4 - 1000 mg/kg/day
Group 5 - 2000 mg/kg/day Group 6 - 4000 mg/kg/day

In the positive control groups, there were incidences of tumors in the lung and spleen of both males and females, indicating that the model was sensitive to the induction of tumors.

Toxicokinetics

TK parameters were not calculated; samples were collected (Day 1 and 29) to measure plasma EPA and DHA concentrations (Sponsor's Table):

Text Table 2: Summary of Bioanalytical Results

Gender	Study Day	Dose (mg/kg/day)	DHA (µg/mL)		EPA (µg/mL)	
			Mean	SD	Mean	SD
Male	1	0*	261.7	17.62	16.9	2.12
		500	268.3	25.32	122.7	30.60
		1000	309.3	55.51	265.7	119.68
		2000	235.7	45.39	171.4	80.94
		4000	399.0	21.66	449.7	111.38
	29	0*	242.3	39.27	16.8	1.15
		500	416.0	125.03	346.7	163.69
		1000	375.7	66.79	347.0	136.72
		2000	422.7	110.35	452.3	217.01
		4000	480.0	94.73	659.0	187.49
Female	1	0*	181.3	6.66	15.3	0.96
		500	130.7	7.77	88.7	9.95
		1000	179.3	15.14	172.3	17.01
		2000	194.7	27.15	139.4	39.97
		4000	303.0	97.41	379.7	125.17
	29	0*	160.7	14.05	12.5**	3.32
		500	231.3	6.66	159.7	33.84
		1000	352.3	141.55	377.3	224.45
		2000	365.3	85.78	420.3	121.40
		4000	394.3	138.07	546.3	315.01

* = DHA and EPA are endogenous compounds in mice.
** = The value for one of the animals was below the limit of quantitation (10 µg/mL) and was thus excluded from the mean.
DHA: Docosahexaenoic Acid; EPA: Eicosapentaenoic Acid

Dosing Solution Analysis:

Epanove was extracted every day from the capsules.

Submitted historical database Tables:

(b) (4)

Historical Control Database of rasH2 Mouse 6 Month Studies

Vehicle (Negative) Control TgrasH2 Mice	Male		
Study Numbers	Total	%	Range
Number of Animals Examined	600	100.0	
Lungs			
Lungs, adenoma; single	57	9.5	0-6
Lungs, adenoma; multiple	8	1.3	0-1
Lungs, carcinoma	4	0.7	0-2
Combined incidence of lung tumors			0-7
Spleen			
Spleen, hemangiosarcoma	19	3.2	0-4
Multiple organs Hemangiosarcoma other than spleen			
Testes	4	0.7	0-1
Liver	1	0.2	0-1
Lungs	1	0.2	0-1
Seminal vesicles	1	0.2	0-1
Nasal cavity	1	0.2	0-1
Subcutis	1	0.2	0-1
Bone Marrow, Sternum	1	0.2	0-1
Epididymides	1	0.2	0-1
Multiple organs Hemangioma			
Liver	1	0.2	0-1
Lymph node	1	0.2	0-1
Penis	1	0.2	0-1
Combined incidence of hemangiosarcoma and hemangioma in all organs			0-4
Other Tumors			
Spleen, lymphoma	1	0.2	0-1
Skin, papilloma	2	0.3	0-1
Harderian glands, adenoma	8	1.3	0-2
Stomach, nonglandular, papilloma	2	0.3	0-1
Stomach, nonglandular, squamous cell carcinoma	2	0.3	0-1
Skin, sarcoma	1	0.2	0-1
Prostate, transitional cell carcinoma	1	0.2	0-1
Multiple organ, mesothelioma	2	0.3	0-1
Jaw, Sarcoma	1	0.2	0-1
Liver, adenoma	1	0.2	0-1
Thyroid gland, adenoma	1	0.2	0-1
Multi-centric, sarcoma	1	0.2	0-1
Madible, squamous cell carcinoma	1	0.2	0-1
Nasal Cavity, adenoma	3	0.5	0-2

(b) (4)

Historical Control Database of rasH2 Mouse 6 Month Studies

Vehicle (Negative) Control TgrasH2 Mice	Female		
Study Numbers	Total	%	Range
Number of Animals Examined	600	100.0	
Lungs			
Lungs, adenoma; single	38	6.3	0-6
Lungs, adenoma; multiple	5	0.8	0-1
Lungs, carcinoma	4	0.7	0-1
Combined incidence of lung tumors			0-6
Spleen			
Spleen, hemangiosarcoma	22	3.7	0-4
Multiple organs Hemangiosarcoma other than spleen			
Mammary glands	1	0.2	0-1
Skin (multiple sites)	3	0.5	0-1
Uterus	9	1.5	0-2
Lungs	1	0.2	0-1
Kidney	1	0.2	0-1
Bone	1	0.2	0-1
Ovary	2	0.3	0-1
Subcutis	1	0.2	0-1
Multi-centric	1	0.2	0-1
Vagina	1	0.2	0-1
Combined incidence of hemangiosarcoma in all organs			0-5
Other Tumors			
Spleen, lymphoma	4	0.7	0-2
Spleen, leukemia	2	0.3	0-1
Liver, leukemia	1	0.2	0-1
Harderian glands, adenoma	17	2.8	0-4
Harderian glands, carcinoma	3	0.5	0-2
Stomach, nonglandular, papilloma	3	0.5	0-1
Stomach, nonglandular, squamos cell carcinoma	1	0.2	0-1
Lymphoma, multiple organ	3	0.5	0-1
Skin; squamos cell carinoma	1	0.2	0-1
Nasal cavity, adenocarcinoma	5	0.8	0-1
Ovaries; teratoma	1	0.2	0-1
Ovaries; leiomyosarcoma	1	0.2	0-1
Multiple organ, mesothelioma	2	0.3	0-1
Thymus, thymoma	2	0.3	0-1
Salivary glands, mesothelioma	1	0.2	0-1
Multi-centric, lymphangioma	1	0.2	0-1
Multi-centic, mesothelioma	1	0.2	0-1
Stomach; adenocarcinoma	1	0.2	0-1

9 Reproductive and Developmental Toxicology

The Sponsor conducted a full ICH S5 battery of reproductive toxicology with omefas.

9.1 Fertility and Early Embryonic Development

A GLP-compliant fertility study was conducted in the rat at 0 (corn oil), 100, 600, or 2000 mg/kg/day. The study report was summarized below.

Study title: The Effects on Fertility and Early Embryonic Development to Implantation of Epanova in Rats Dosed by Oral Gavage	
Study no.:	495655
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 24, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Drug: Epanova; Lot#: 36355 (API); 143948; Purity: not provided, used as supplied

Key Study Findings

No treatment effects on reproductive performance or early embryonic development in treated rats with Epanova up to 2000mg/kg/day. NOAEL was established at HD (2000mg/kg/day); 5 fold to MHRD of 4 g/day (based on systemic exposure).

Methods	
Doses:	0 (corn oil control), 100, 600 and 2000 mg/kg/day
Frequency of dosing:	Once a day
Dose volume:	2.2, 0.11, 0.65 and 2.2 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Corn Oil
Species/Strain:	Sprague-Dawley rats
Number/Sex/Group:	24/sex/group
Satellite groups:	None
Study design:	Males and females were dosed before mating up to the time of implantation (males:4 weeks prior mating, killed after 9 weeks; females:2 weeks prior mating until GD6), C-section on GD 14, 15, or 16.
Deviation from study protocol:	None to effect study outcome

Observations and Results

Mortality

None

Clinical Signs

Excess salivation was noted after dosing in the HD-treated animals (males; 24/24; females: 15/24) and in the MD-treated animals (males: 17/24; females: 3/24). No salivation at LD- or control-treated animals.

Body Weight and Feed Consumption

Unremarkable

Toxicokinetics

NA

Dosing Solution Analysis

Dosing formulations were extracted from the capsules and administered as supplied. No dosing analysis was submitted.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

There were no treatment related changes with treatment of Epanova up to 2000mg/kg/day (Sponsor's Tables):

1 Control 0 | 2 ---------- 100 | 3 Epanova 600 | 4 ---------- 2000

Stages of Oestrus	Group/Dose level (mg/kg/day)			
	1 (0)	2 (100)	3 (600)	4 (2000)
Pro-oestrus	3.5 ± 0.8	3.3 ± 0.8	3.2 ± 1.1	3.5 ± 0.7
Oestrus	3.5 ± 0.8	3.2 ± 0.9	3.4 ± 0.5	3.3 ± 0.8
Di-Oestrus	7.1 ± 1.0	7.5 ± 1.0	7.4 ± 1.2	7.0 ± 1.0
Met-oestrus	0.0 ± 0.0	0.0 ± 0.2	0.0 ± 0.2	0.1 ± 0.3
Cycle length (days)	4.1 ± 0.2	4.0 ± 0.2	4.0 ± 0.2	4.0 ± 0.1

Pregnancy Performance

Group : 1 | 2 | 3 | 4
Test Item : Control | ---------- | Epanova | ----------
Dosage (mg/kg/day) : 0 | 100 | 600 | 2000

	Group/Dose Level (mg/kg/dose.)			
	1 (0)	2 (100)	3 (600)	4 (2000)
Number of animals mated	24	24	24	24
Number pregnant	24	23	24	24
Number of premature decedents	0	0	0	0
Number pregnant at necropsy	24	23	24	24
Pregnancy frequency as %	100	96	100	100
Total corpora lutea graviditatis	385	365	392	387
Total number of implants	371	356	376	360
Pre-implantation loss as %	4	2	4	7
Total live implants (%)	347 (94)	340 (96)	348 (93)	340 (94)
Total dead implants (%)	24 (6)	16 (4)	28 (7)	20 (6)
Total early embryonic deaths (%)	24 (6)	15 (4)	27 (7)	20 (6)
Total late embryonic deaths (%)	0	1 (0.3)	1 (0.3)	0
Mean corpora lutea graviditatis	16.0 ± 1.9	15.9 ± 1.3	16.3 ± 1.6	16.1 ± 2.6
Mean implants	15.5 ± 1.8	15.5 ± 1.7	15.7 ± 1.8	15.0 ± 3.4
Mean live implants	14.5 ± 2.4	14.8 ± 2.1	14.5 ± 2.0	14.2 ± 3.3
Mean dead implants	1.0 ± 1.3	0.7 ± 0.9	1.2 ± 1.1	0.8 ± 0.9
Mean early embryonic deaths	1.0 ± 1.3	0.7 ± 0.9	1.1 ± 1.2	0.8 ± 0.9
Mean late embryonic deaths	0	0.04 ± 0.2	0.04 ± 0.2	0

Means are given ± Standard Deviation

Necropsy

No treatment related changes were observed in males and females at scheduled necropsy.

Organ Weights

No treatment related changes were observed in male organ weights.

Histopathological changes:

A section of each epididymis and testis were evaluated microscopically and no drug-related effects were noted (Sponsor Table):

Summary of Histopathology Findings

Group	:	1	2	3	4
Test Item	:	Control	----------	Epanova	----------
Dosage (mg/kg/day)	:	0	100	600	2000

Histopathology Summary Incidence
Male

Dose level: Epanova (mg/kg/day)	**0**	**100**	**600**	**2000**
number of animals	24	24	24	24
EPIDIDYMIDES				
number examined	24	-	-	24
Focal mononuclear cell infiltration				
- minimal	3	-	-	7
Serosal granuloma				
- mild	1	-	-	0
Intratubular degenerate spermatozoa				
- minimal	0	-	-	1
TESTES (H&E AND PAS)				
number examined	24	-	-	24
Bilateral germinal epithelial atrophy				
- mild	0	-	-	2
Unilateral germinal epithelial atrophy				
- minimal	1	-	-	1
Dystrophic tubular mineralisation				
present	0	-	-	1

None of these observations had an effect on male endpoints.

9.2 Embryonic Fetal Development

The effect of Epanova on prenatal development was investigated in rats and rabbits and on embryo-fetal development in rats.

Study title: Epanova: A Development Toxicity Study of Epanova by Oral Gavage in Rats.	
Study no.:	495634
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 6, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Epanova, 36355 (API); 143948 (capsules); purity not provided used as supplied (Density: 0.924g/mL)

Key Study Findings

No maternal or fetal toxicity was observed in treated rats up to 2000mg/kg/day. NOAEL was established for maternal and for embryo-fetal development at MD (500mg/kg/day); 2.4 fold equivalent to MHRD of 4g/day based on a body surface area comparison based on increased late embryonic deaths (2%), and various variations (ribs sternebrae and pelvis) at HD.

Methods	
Doses:	0, 100, 500, 2000 mg/kg/day
Frequency of dosing:	Daily
Dose volume:	2.2, 0.11, 0.65, 2.2 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Corn oil
Species/Strain:	Sprague-Dawley (Crl: CD®(SD))
Number/Sex/Group:	20/females/group
Satellite groups:	None
Study design:	Animals dosed on Days 6-16 of gestation, all animals were euthanized on GD 20
Deviation from study protocol:	None

Observations and Results

Mortality

None

Clinical Signs

- At HD, 5/20 animals was reported with salivation for after dosing
- Abnormal red discharge around the vagina (*ca* Day 15 of gestation) was reported (LD, 1/20; MD,1/20; HD, 5/20). This finding did not correlate to the pregnancy performance data (similar within groups).

Body Weight

Unremarkable

Feed Consumption

Unremarkable

Toxicokinetics

NA

Pregnancy Performance and Foetal Weights

Pregnancy performance was unremarkable within groups; foetal weights were reported slightly lower (nss) at HD.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)
No treatment related changes were observed in viable fetuses, corpora lutea, resorptions, pre- and post-implantation losses and fetal body weight (Sponsor's Table):

Pregnancy Performance and Foetal Weights

	Group/Dose Level (mg/kg/day)			
	1 (0)	2 (100)	3 (600)	4 (2000)
Number of animals mated	20	20	20	20
Number pregnant	18	19	17	18
Number of premature decedents	0	0	0	0
Number pregnant at Day 20 necropsy	18	19	17	18
Pregnancy frequency as %	90	95	85	90
Total corpora lutea graviditatis	265	280	259	275
Total number of implants	258	269	246	267
Pre-implantation loss as %	3	4	5	3
Total live implants (%)	243 (94)	257 (96)	234 (95)	250 (94)
Total dead implants (%)	15 (6)	12 (4)	12 (5)	17 (6)
Total early embryonic deaths (%)	15 (6)	11 (4)	12 (5)	15 (6)
Total late embryonic deaths (%)	0	1 (0.4)	0	2 (1)
Total dead foetuses (%)	0	0	0	0
Mean corpora lutea graviditatis	14.7 ± 1.7	14.7 ± 2.2	15.2 ± 1.4	15.3 ± 1.8
Mean implants	14.3 ± 2.1	14.2 ± 2.6	14.5 ± 1.4	14.8 ± 2.1
Mean live implants	13.5 ± 2.1	13.5 ± 2.4	13.8 ± 1.5	13.9 ± 2.6
Mean dead implants	0.8 ± 0.8	0.6 ± 0.7	0.7 ± 0.9	0.9 ± 1.2
Mean early embryonic deaths	0.8 ± 0.8	0.6 ± 0.7	0.7 ± 0.9	0.8 ± 1.0
Mean late embryonic deaths	0	0.1 ± 0.2	0	0.1 ± 0.3
Mean dead foetuses	0	0	0	0
Total live male foetuses (%)	111 (46)	108 (42)	97 (41)	137 (55)
Total live female foetuses (%)	132 (54)	149 (58)	137 (59)	113 (45)
Live foetal sex ratio (M:F)	1:1.19	1:1.38	1:1.41	1:0.82
Mean total uterus weight (g)	85 ± 12	84 ± 14	84 ± 9	85 ± 14
Mean litter mean foetal weight (g) †	3.87 ± 0.34	3.88 ± 0.25	3.84 ± 0.33	3.75 ± 0.21

Means are given ± Standard Deviation
† = Statistically analysed; no statistical significance achieved (P<0.001)

Offspring (Malformations, Variations, etc.)

At HD, slightly higher malformation was reported for foetuses with incidences of cervical remnant of thymus, tendinous region of diaphragm (locally thinned with minimal lump of liver lobe), and the costal cartilages of ribs (asymmetrically aligned). According to the Sponsor, these incidences were within the current background range (data not submitted). See Sponsor's Tables:

Parameter	Group/Dose Level (mg/kg/day)			
	1 (0)	2 (100)	3 (600)	4 (2000)
	Incidence of Foetuses (Litters)			
Skeletal				
Sutural bone. Cranial bone(s) linear ossification irregularity/ies. Jugal(s) connected/fused to zygomatic process of squamosal. Cervical vertebral arch(es) connected. Cervical and thoracic vertebral arch(es) asymmetrically aligned. Rib(s) partially fused. Rib(s) costal cartilage shortened, Rib(s) costal cartilages not attached to sternum. Rib(s) costal cartilages connected. Sternebrae connected and/or flattened.	0	1(1)	0	0
Small discrete/discrete unossified/incompletely ossified area(s) cranial bone(s)	3(2)	1(1)	0	0
Additional ossification between cranial bones	2(2)	0	0	0
Cervical rib(s)	0	2(2)	1(1)	0
Thoracic vertebra hemicentric	0	1(1)	0	0
Rib(s) partially fused	0	1(1)	0	0
Rib(s) minimally kinked	0	3(2)	2(2)	1(1)
Rib(s) incompletely ossified	2(1)	2(1)	1(1)	1(1)
Additional ossified area arising from sternebra	1(1)	0	0	2(2)
Rib(s) costal cartilages asymmetrically aligned	2(2)	4(2)	1(1)	6(6)
Unilateral/bilateral rib 7 costal cartilage not attached to sternum	0	0	2(2)	1(1)
Pelvic girdle cranial displacement :				
Bilateral	0	0	0	1(1)
Pelvic girdle caudal displacement :				
Unilateral	0	1(1)	0	0
Bilateral	1(1)	0	0	0
Number with minor abnormality/variant	11(7)	14(8)	6(5)	12(10)
Total number examined skeletally	121(18)	129(19)	118(17)	125(18)

Parameter	Group/Dose Level (mg/kg/day)			
	1 (0)	2 (100)	3 (600)	4 (2000)
	Incidence of Foetuses (Litters)			
Number of ribs				
12 complete ribs	0	0	0	1(1)
13th vestigial rib(s)	0	0	0	1(1)
13th reduced rib(s)	2(2)	1(1)	1(1)	2(2)
13 complete ribs	107(18)	117(19)	114(17)	114(18)
Vestigial supernumerary rib(s) on 1st lumbar vertebra	12(8)	11(5)	3(3)	7(4)

Reviewer: No TK data was submitted; therefore, no data to see if pregnancy alters after exposure.

Study title: Epanova: Development Toxicity Study in Rabbits Dosed by oral Gavage	
Study no.:	495660
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	January 20, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Epanova, 36355 (API); 143948 (capsules); purity not provided used as supplied (Density: 0.924g/mL)

Key Study Findings

- Maternal toxicity was established at HD (750mg/kg/day) based on mortality (3/20) on GD Days 19 to 23 due to abortion, increased incidence of clinical signs, lower weight gains during treatment, and reduced feed consumption during dosing period.
- Embryofetal toxicity was observed at HD for increased incidences fetuses with incomplete/reduced ossification of the hyoid, epiphyses of the fore/hind limb, and of sternebrae, and with rib(s) costal cartilage not attached to sternum.
- NOAEL was established for maternal at MD (500mg/kg/day) about 2.4 fold to MHRD of 4g/day (based on surface area) because of mortality and fetal skeletal variation at HD.
- NOAEL was established for embryo-fetal development at LD (100mg/kg/day) about 0.5 fold to MHRD of 4g/day (based on surface area) because of skeletal malformation and ossification effects (variations) as well as visceral variations at 500 mg/kg/day.

Methods	
Doses:	0, 100, 500, 750 mg/kg/day
Frequency of dosing:	Daily
Dose volume:	0.81, 0.11, 0.54,0.81 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Corn oil
Species/Strain:	female New Zealand White rabbits
Number/Sex/Group:	20/females/group
Satellite groups:	None
Study design:	Dosed on Days 6-18 of gestation, all animals were euthanized on GD 29
Deviation from study protocol:	None

Observations and Results

Mortality

There were 6 premature decedents (2/control; 4/HD). At HD, cause of death was treatment-related for three animals based on evidence of abortion (red lumps/fetuses). Cause of death for other animals (2/Control; 1/HD) was due to the dosing procedure based on mechanical damage findings at necropsy in lungs, trachea blood and month/nose.

Clinical Signs

Not remarkable
At HD, decreased and altered fecal appearance was noted more than other groups, which correlates with the reduced feed consumption.

Body Weight

At HD, lower group mean body weight gains (nss) were reported at different GD (Sponsor's Table):

Day of Gestation	Dose Group/Dose Level (mg/kg/day)			
	1 (0)	2 (100)	3 (500)	4 (750)
4	3.43 ± 0.20	3.37 ± 0.21	3.33 ± 0.19	3.37 ± 0.27
6	3.45 ± 0.22	3.35 ± 0.22	3.32 ± 0.19	3.40 ± 0.25
9	3.45 ± 0.25	3.39 ± 0.21	3.35 ± 0.18	3.42 ± 0.25
12	3.54 ± 0.27	3.46 ± 0.21	3.42 ± 0.18	3.45 ± 0.27
15	3.59 ± 0.27	3.53 ± 0.21	3.45 ± 0.18	3.47 ± 0.27
19	3.63 ± 0.27	3.58 ± 0.21	3.50 ± 0.24	3.48 ± 0.25
22	3.72 ± 0.24	3.63 ± 0.22	3.56 ± 0.22	3.55 ± 0.26
26	3.81 ± 0.25	3.73 ± 0.21	3.64 ± 0.21	3.65 ± 0.27
29	3.88 ± 0.28	3.81 ± 0.21	3.72 ± 0.23	3.73 ± 0.29
Weight Gain Days 6-19†	0.16 ± 0.19	0.23 ± 0.14	0.19 ± 0.16	0.07 ± 0.16
% of Control	-	144	119	44

† = Statistically analysed; no statistical significance achieved (P<0.001)

Feed Consumption

Lower food consumptions were reported at HD, which was correlated to decrease and alter fecal appearance at high dose.

Toxicokinetics

NA

Dosing Solution Analysis

Epanova was used as supplied (density of 0.924 g/ml).

Necropsy

Necropsy findings were primarily noted in animals that were killed prematurely (Sponsor's Table):

Necropsy Finding	Dose Group/Dose Level (mg/kg/day)			
	1 (0)	2 (100)	3 (500)	4 (750)
Liver – Pale	0	0	0	1
Liver – Pale foci	0	0	0	1
Liver – Prominent lobulation	0	0	0	2
Lungs – Dark foci	1	1	0	2
Lungs – Mottled	1	0	0	0
Lungs – Pale	0	0	0	1
Lungs – Spongy	2	0	0	1
Skin – Hairloss (dorsal neck)	0	1	0	1
Skin – Scab(s)	0	2	0	0
Skin – Staining (ventral abdomen/ tail)	0	0	0	2
Trachea – Blood/ red-fluid filled	2	0	0	1
Trachea - Frothy	2	0	0	0
Trachea – Surrounding soft tissue reddened	1	0	0	0
Uterus – Right horn contained thick green viscous material	0	0	1	0
Uterus – Right horn wall thickened; contents abnormal, solid brown material present adhered to mucosa. Many pale raised areas on whole horn	1	0	0	0
Placenta/ embryonic remains in cage	0	0	0	3
Found dead	1	0	0	0
Killed prematurely	1	0	0	4
Number of Females	20	20	20	20

Pregnancy Performance and Foetal Weights

No treatment-related findings

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)
No treatment related changes in viable fetuses, corpora lutea, resorptions, pre- and postimplantation losses and fetal weight were observed (Sponsor's Table):

	Dose Group/Dose Level (mg/kg/day)			
	1 (0)	2 (100)	3 (500)	4 (750)
Number of animals mated	20	20	20	20
Number pregnant	17	20	19	18
Number of premature decedents	2	0	0	4
Number of pregnant premature decedents	2	0	0	4
Number pregnant at Day 29 necropsy	15	20	19	14
Pregnancy Frequency as %	85	100	95	90
Total corpora lutea graviditatis	159	214	210	151
Total number of implants	146	198	196	146
Pre-implantation loss as %	8	7	7	3
Total live implants (%)	129 (88)	183 (92)	179 (91)	135 (92)
Total dead implants (%)	17 (12)	15 (8)	17 (9)	11 (8)
Total early embryonic deaths (%)	6 (4)	4 (2)	8 (4)	9 (6)
Total late embryonic deaths (%)	9 (6)	8 (4)	7 (4)	1 (1)
Total foetal deaths (%)	2 (1)	3 (2)	2 (1)	1 (1)
Mean corpora lutea graviditatis	10.6 ± 2.2	10.7 ± 2.0	11.1 ± 1.8	10.8 ± 1.9
Mean implants	9.7 ± 2.6	9.9 ± 2.7	10.3 ± 2.1	10.4 ± 2.1
Mean live implants	8.6 ± 2.5	9.2 ± 2.4	9.4 ± 2.2	9.6 ± 1.9
Mean dead implants	1.1 ± 1.2	0.8 ± 1.1	0.9 ± 1.5	0.8 ± 1.1
Mean early embryonic deaths	0.4 ± 0.8	0.2 ± 0.4	0.4 ± 0.8	0.6 ± 1.0
Mean late embryonic deaths	0.6 ± 0.9	0.4 ± 0.8	0.4 ± 1.0	0.1 ± 0.3
Mean foetal deaths	0.1 ± 0.4	0.2 ± 0.5	0.1 ± 0.3	0.1 ± 0.3
Total live male foteuses (%)	64 (50)	93 (51)	95 (53)	66 (49)
Total live female foetuses (%)	65 (50)	90 (49)	84 (47)	69 (51)
Live foetal sex ratio (male:female)	1:1.02	1:0.97	1:0.88	1:1.05
Mean total uterus weight (g)	539 ± 130	556 ± 108	550 ± 83	547 ± 92
Mean litter mean foetal weight (g) †	40.5 ± 4.1	40.4 ± 4.1	39.8 ± 4.9	38.6 ± 6.0

Means are given ± Standard Deviation
Note: premature decedents excluded below double line
† = Statistically analysed; no statistical significance achieved (P<0.001)

Reviewer: Based on ICH, n=16 pregnant animals should be in each group at C-section. The Control and HD group had fewer animals.

Offspring (Malformations, Variations, etc.)

1. No drug-related increase in malformations or in the incidence of visceral anomalies at 100mg/kg/day less than therapeutic exposure
2. At HD, foetuses with rib(s) costal cartilage not attached to sternum was higher than control (17% vs. 9% in controls)
3. Increased incidence of incomplete/reduced ossification of the hyoid, epiphyses of the fore/hind limb, and of sternebrae at the HD (42% vs. 24% of control)

Sponsor's Tables:

Group Incidence of Major Foetal Abnormalities

Abnormality	Group/Dose Level (mg/kg/day)			
	1 (0)	2 (100)	3 (500)	4 (750)
	Incidence of Foetuses (Litters)			
Exencephaly, brain exposed with eye(s) open. Major abnormalities including cranial bone(s) absent/markedly reduced (in size). Omphalocele. Hindpaw digit reduced (in size) with claw absent. Forepaw and hindpaw digit(s) claw absent/reduced (in size)	0	1(1)	0	0
One additional cervical vertebra and paired rib with/without cervical rib long	0	2(1)	0	0
Right subclavian artery retro-oesophageal	0	2(1)	0	0
Thoracic hemivertebra with absent rib	0	1(1)	0	0
Thoracic hemivertebra with absent rib. Partial rib between ribs. Thoracic vertebral centrum bipartite with vertebral hemicentre fused to thoracic vertebral centrum	0	0	1(1)	0
Omphalocele. Aortic arch interrupted. Cranial bones fused. Thoracic vertebral centrum absent with thoracic vertebral arches connected and/or reduced (in size)	1(1)	0	0	0
Insertion of hemivertebra, thoracic/lumbar region	1(1)	1(1)	0	0
Omphalocele	0	1(1)	0	0
Meningocele lumbar region with vertebral arches open	0	1(1)	0	0
Forepaw digits absent	0	0	1(1)	0
Number with major abnormality	2(2)	9(7)	2(2)	0
Total number examined	129(15)	183(20)	179(19)	135(14)

Table 7
Group Incidence of Minor Foetal Abnormalities and Variants

Abnormality/Variant	Group/Dose Level (mg/kg/day)			
	1 (0)	2 (100)	3 (500)	4 (750)
	Incidence of Foetuses [as %] (Litters)			
Visceral				
Brain ventricles minimally dilated	0	0	1 [0.6] (1)	0
Eye(s) iridial haemorrhage	1 [0.8] (1)	4 [2] (4)	3 [2] (2)	3 [2] (2)
Pinna reduced(in size)	0	1 [0.5] (1)	0	0
Upper incisors not erupted	1 [0.8] (1)	0	0	0
Tongue protruding and reddened	0	1 [0.5] (1)	0	0
Cervical remnant of thymus	6 [5] (4)	4 [2] (4)	11 [6] (9)	6 [4] (5)
Variation in origin of arteries arising directly from aortic arch	6 [5] (4)	8 [4] (6)	7 [4] (4)	9 [7] (5)
Gall bladder reduced (in size)	0	1 [0.5] (1)	1 [0.6] (1)	0
Gall bladder contents clear	0	2 [1] (2)	0	1 [0.7] (1)
Spleen pale colouration	0	0	1 [0.6] (1)	0
Forelimb minimal flexure	0	0	2 [1] (1)	0
Small foetus	0	2 [1] (2)	0	0
Number with minor visceral abnormality/variant	13(7)	23(13)	25(14)	19(11)
Total number examined	129(15)	183(20)	179(19)	135(14)

Table 7 (continued)
Group Incidence of Minor Foetal Abnormalities and Variants

Abnormality/Variant	Group/Dose Level (mg/kg/day)			
	1 (0)	2 (100)	3 (500)	4 (750)
	Incidence of Foetuses [as %] (Litters)			
Skeletal				
Cranial bone(s) unossified/incompletely ossified area(s)	0	1 [0.5] (1)	1 [0.6] (1)	1 [0.7] (1)
Cranial bone(s) small linear/linear ossification irregularity/ies	1 [0.8] (1)	7 [4] (5)	4 [2] (4)	0
Sutural bone/sutural deviation	0	1 [0.5] (1)	3 [2] (3)	0
Additional ossified area within suture	0	0	1 [0.6] (1)	0
Jugal connected/fused to zygomatic process of maxilla	0	1 [0.5] (1)	2 [1] (2)	0
Tympanic bulla incompletely ossified	1 [0.8] (1)	0	0	0
Greater horn of hyoid bent outwards	1 [0.8] (1)	0	0	1 [0.7] (1)
Greater horn of hyoid incompletely ossified	1 [0.8] (1)	0	0	0
Cervical vertebral arch(es) incompletely ossified	0	1 [0.5] (1)	0	0
Cervical rib(s)	3 [2] (2)	1 [0.5] (1)	5 [3] (1)	0
Cervical rib/cervical rib long with costal cartilage attached to sternum	0	2 [1] (1)	0	0
Sternebrae fused/connected/flattened and misshapen	6 [5] (4)	1 [0.5] (1)	3 [2] (2)	4 [3] (3)
Additional ossified area/centre/sternebra cranial to or between sternebra with/without fusion to sternebra	2 [2] (2)	2 [1] (1)	0	1 [0.7] (1)
Rib(s) thickened area	1 [0.8] (1)	2 [1] (2)	4 [2] (3)	1 [0.7] (1)
Thoracic vertebra hemicentric with thoracic vertebral centrum misshapen	0	1 [0.5] (1)	0	0
Thoracic vertebral centra connected	0	1 [0.5] (1)	0	0
Thoracic/lumbar vertebral arches asymmetrically aligned	0	2 [1] (2)	1 [0.6] (1)	0

Table 7 (continued)
Group Incidence of Minor Foetal Abnormalities and Variants

Abnormality/Variant	Group/Dose Level (mg/kg/day)			
	1 (0)	2 (100)	3 (500)	4 (750)
	Incidence of Foetuses [as %] (Litters)			
Skeletal (cont.)				
Rib with costal cartilage attached to sternum	0	0	2 [1] (2)	0
Rib(s) costal cartilages cranially/caudally displaced	1 [0.8] (1)	1 [0.5] (1)	1 [0.6] (1)	0
Rib(s) costal cartilage(s) connected at point of attachment to sternum	1 [0.8] (1)	0	1 [0.6] (1)	0
Rib(s) costal cartilage(s) asymmetrically aligned at point of attachment to sternum	3 [2] (2)	3 [2] (3)	0	1 [0.7] (1)
Rib(s) costal cartilage(s) bifurcated at point of attachment to sternum	0	2 [1] (1)	0	0
Rib(s) costal cartilage(s) not attached to sternum	12 [9] (5)	8 [4] (6)	19 [11] (9)	23 [17] (7)
Xiphoid cartilage bifurcated	0	1 [0.5] (1)	0	2 [1] (2)
Pelvic girdle caudal displacement :				
Unilateral	4 [3] (4)	8 [4] (6)	5 [3] (5)	5 [4] (5)
Bilateral	20 [16] (10)	65 [36] (16)	49 [27] (12)	27 [20] (9)
Astragalus incompletely ossified/unossified	1 [0.8] (1)	4 [2] (4)	0	8 [6] (4)
Distal caudal vertebrae reduced (in size)/misaligned	7 [5] (6)	2 [1] (2)	4 [2] (4)	3 [2] (3)
Number with minor abnormality/variant	55(14)	93(19)	89(18)	60(13)
Total number examined skeletally	129(15)	183(20)	179(19)	135(14)
Number of Ribs				
12 complete ribs	45 [35] (12)	46 [25] (14)	63 [35] (17)	65 [48] (12)
Vestigial supernumerary rib(s) on 1st lumbar vertebra	9 [7] (9)	14 [8] (10)	14 [8] (10)	16 [12] (10)
Reduced supernumerary rib(s) on 1st lumbar vertebra	14 [11] (11)	18 [10] (9)	10 [6] (8)	8 [6] (6)
Complete supernumerary rib(s) on 13th thoracic vertebra	61 [47] (13)	105 [57] (19)	92 [51] (19)	46 [34] (13)

Table 8
Group Incidence of Skeletal Ossification Parameters

Parameter	Group/Dose Level (mg/kg/day)			
	1 (0)	2 (100)	3 (500)	4 (750)
	Incidence of Foetuses [as %] (Litters)			
Incomplete ossification:				
Skull bone(s)	0	2[1](1)	0	0
Hyoid	9 [7](5)	8[4](3)	14[8](8)	15[11](8)
Odontoid process	2[2](2)	4[2](3)	3[2](3)	1[0.7](1)
Cervical centrum/a	1[0.8]((1)	2[1](2)	3[2](3)	3[2](2)
Thoracic centrum/a	0	1[0.5](1)	0	0
Pubis(es)	3[2](3)	5[3](4)	4[2](2)	3[2](3)
Reduced/unossified:				
All 8 epiphyses of fore and hindlimbs	1[0.8](1)	11[6](6)	3[2](2)	3[2](3)
Up to 7 epiphyses of fore and hindlimbs	59[46](14)	93[51](19)	115[64](19)	81[60](13)
Metacarpal and/or phalanx on pollex/pollices	4[3](3)	11[6](6)	10[6](5)	5[4](3)
Unossified 2nd phalanx on 2nd, 4th, 5th digit(s) of forepaw(s)	31[24](9)	38[21](13)	32[18](13)	16[12](8)
Unossified 2nd phalanx on 3rd, 4th digit(s) of hindpaw(s)	0	3[2](3)	0	3[2](2)
Ossified:				
Olecranon(s)	0	8[4](5)	3[2](3)	1[0.7](1)
Number of sternebrae incompletely ossified				
0	85[66](14)	139[76](20)	122[68](19)	73[54](14)
1	31[24](11)	36[20](12)	45[25](15)	57[42](13)
2	12[9](6)	7[4](6)	10[6](7)	5[4](4)
>2	1[0.8](1)	1[0.5](1)	2[1](2)	0
Total number examined skeletally	129(15)	183(20)	179(19)	135(14)

Reviewer: there are two issues with this study:

- *No TK data was submitted to know if pregnancy alters exposure and how exposure compares to that seen at similar dosages in other species.*
- *The number of control and high dose animals evaluated by scheduled C-section is less than the desired number of at least 16 litters and differs considerably from the number of litters/fetuses evaluated in the low and mid dose groups. Raises questions about the true incidence of anomalies in the control and high dose groups given that, there are somewhere around 25% fewer litters and 30% fewer fetuses that were evaluated.*

9.3 Prenatal and Postnatal Development

Effects of Epanova on prenatal/postnatal development were investigated with the GLP-compliant study in rats.

Study title: Epanova: Pre and Post Natal Oral (Gavage) Study in Rats	
Study no.:	495440
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	January 19, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Epanova, 36355 (API); 143948 (capsules); purity not provided; used as supplied

Key Study Findings

F0 dams:

Mortality was reported at HD (2000mg/kg/day) for 9/24 animals due to difficulties during or shortly after parturition. These animals had lower body weight gain/food consumption. The necropsy of these animals revealed abnormal stomach and/or intestinal contents and glandular mucosa abnormalities. As a result, there were fewer live litters able to be evaluated at this dosage. Furthermore, there were fewer pups surviving to day 4 at the HD.

F1 generation:

Although there were no effects on growth or development of the F1 animals or on their ability to initiate and maintain a pregnancy, there was an increased incidence of pup (F2) mortality at the mid and high dosages, with the majority occurring on day 4 or later following birth. In all groups, including controls, there were 1 to 3 litters that lost 1 or 2 pups each. However, the proportion of litters in which 3 or more pups died was slightly higher at the MD and HD groups (13%, 17%, 22%, and 21% at C, LD, MD, and HD, respectively).

NOAEL for the treated F0 generation was at 600 mg/kg/day (1.5x to MRHD), based on issues with parturition and F1 pup survival.

NOAEL for the F1 animals was at 100 mg/kg/day (0.3 fold to MRHD) based on a decrease in survival of the F2 generation pups during lactation.

Reviewer: The administration of Epanova clearly affects parturition and pup viability as demonstrated by difficulties with parturition and reduced pup survival. However, there is no explanation in this study for the poor survival rate in F2 generation. Findings from the reproductive studies with the Lovaza (approved fish oil) also showed effects on lower live birth index and F1 postnatal survival; however, there was no indication that the F2 was affected based on evaluation of embryofetal viability at a mid-gestation C-section.

Methods	
Doses:	0 (corn oil), 100, 600 and 2000 mg/kg/day
Frequency of dosing:	Once daily
Dose volume:	2.2, 0.11, 0.65 and 2.2 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Corn oil

Species/Strain:	Mated female Sprague Dawley rats
Number/Sex/Group:	24/group
Satellite groups:	None
Study design:	Mated females were dosed from Day 6 of gestation until the end of lactation and weaning of their litters (weaned at Day 21 of lactation).
Deviation from study protocol:	None that affected study outcome

Observations and Results

F0 generation (directly treated with test article)

Survival

At HD, 9/24 dams were killed early or found dead due to difficulties during the parturition process. Antemortem and postmortem signs are summarized in the Sponsor Table below:

Clinical Observations and Necropsy Findings of Premature Decedents

Animal	Day	Clinical Signs at/around Time of Death	Parturition Status	Necropsy Findings
76	Day 21 Gestation	Body hunched, eyes closed, piloerection, skin cold, walking on tip toes	Animal did not give birth to litter	Stomach contents abnormal (hard and dry). Intestine contents watery/yellow*, live foetuses in uterus
79	Day 1 of lactation (Animal found dead)	Found dead – all pups found cold and unclean	Animal gave birth to 12 pups	One dead foetus in uterus. Stomach: dark focus glandular mucosa. Intestine contents watery/yellow*. Liver, pale focus
81	Day 22 Gestation	Body hunched, walking on tip toes, red discharge from vagina, piloerection, subdued – Litter unclean and scattered	Animal gave birth to litter on day of sacrifice	Intestine contents watery/yellow* Spleen: small.
83	Day 1 of Lactation	Killed prematurely (due to overall condition, live pups were uncleaned, few teats present in dam)	Animal gave birth to litter	Stomach had green/watery content, glandular mucosa dark focus and reddened. Intestine contents watery/green. Duodenum ruptured, depressed focus. Liver, pale focus. Uterus, 1 placenta in right horn.
86	Day 1 of lactation	Abnormal vocalisation in hand, intermittent, red discharge from vagina, litter scattered around cage and uncleaned	Animal gave birth to litter	Duodenum distended by gas. Intestine contents watery/yellow*. Stomach, thickened non-glandular mucosa. Liver pale focus.
87	Day 21 Gestation	Hunched, eye partially closed, skin cold, yellow faeces, piloerection, staggering, subdued.	Animal did not give birth	Intestine contents watery/yellow*. Kidneys pale, liver pale focus. Uterus, 16 live foetuses present
89	Day 22 Gestation	Hunched, eyes partially closed, thin, walking on toes, abnormal discharge from vagina, piloerection, slow respiration, staggering, subdued	Animal gave birth to 2 live and 10 dead pups	Stomach, depressed focus. Ileum contents watery/green
92	Day 22 Gestation	Hunched, cold skin, eyes small, walking on tip toes, piloerection, loose body tone, wheezing respiration, subdued	Animal did not give birth	Stomach contents abnormal (hard and dry). Intestine contents watery/green. Liver lobes pale. Uterus, 12 live foetuses
95	Day 2 of Lactation	Hard area ventral thorax, irregular respiration, dam had few teats and pups scattered and cold	Animal gave birth to litter	Liver, dark focus. Intestine contents dark/dry. Stomach, depressed focus non-glandular mucosa, abnormal contents. Mammary prominent

*Note: The test formulations were yellow in colour and may at least in part be reflective of yellow contents

These deaths were considered treatment related as the administration of omega 3 fatty acids to rats has been associated with prolonged/impaired parturition likely resulting from altered

prostaglandin synthesis (refer to the sponsor response to question 2 in the regulatory background).

Clinical Signs

Salivation, was noted in all HD-treated animals and 4/24 animals (on single days) at the MD.

Clinical signs for HD-treated animals that were killed prematurely were: body hunched, walking on tiptoes and red discharge from vagina, skin cold and piloerection. At MD, one animal (1/24) was observed with hunched and piloerection at the time of parturition. This animal had a total litter loss with no necropsy findings at the schedule necropsy.

Body Weight

Unremarkable for all treated animals except for the premature decedent animals at HD; these animals were reported with reduced weight gains.

Feed Consumption

Unremarkable for all treated animals except for the premature decedent animals at HD; these animals were reported with reduced food consumptions.

Reproductive Performance on Preweaning Survival

There were no effects on the number of animals pregnant. However, because of difficulties with deliveries, multiple HD animals were euthanized/found dead during or shortly after parturition. Therefore, there were fewer litters with pups at this dosage available for remaining study activities (23, 24, 24, and 14 litters at Control, LD, MD and HD, respectively).

For animals that did deliver successfully (ie, therefore not including those that were killed or found dead during parturition or shortly thereafter), there were no effects on gestation length. In this same population of animals, there also were no effects on the mean number of pups/litter, the number of implant sites/litter (as determined at their necropsies), or sex ratio.

Pup loss during lactation did occur in each group, including controls. When it did occur, it was typically a loss of multiple pups from a few litters rather than the loss of a few pups from multiple litters. In the C, L, and M dose groups, there were 4/23, 2/24, and 2/24 litters, respectively, that lost 4 or more pups during the lactation phase, including 3, 1, and 1 litter in each of these respective groups with total litter loss. At the HD, in addition to the 9 litters with total litter loss resulting from parturition difficulties or death, 1 additional dam lost her entire litter. In the majority of cases across groups, the deaths occurred prior to day 4. At HD, the mean number of pups/litter was lower than controls by day 4, and overall survival during the weaning period (mean number of pups/litter at day 21 ÷ mean number of pups/litter at day 0) was slightly lower as a result (96%, 95%, 97%, and 91% at C, L, M, and H dosages, respectively) although the observed number of pups/litter remained within the historical range of the test facility (see sponsor response to question 1 of the information request in the Appendix). These data are summarized in the sponsor table below:

Table 4
F0 Generation: Duration of Gestation and Overall Litter Performance

	Group/Dose Level (mg/kg/day)			
	1 (0)	2 (100)	3 (600)	4 (2000)
Number Pregnant	23	24	24	23
Duration of Gestation (Days)				
21	9	16	10	7
22	14	8	14	16
Mean Duration	21.6	21.3	21.6	21.7
Number of females producing a live litter	23	24	24	14*
Gestation index as %	100	100	100	61*
Mean number of implant sites[a] per pregnancy ± standard deviation	13.4 ± 1.2	14.2 ± 2.0	13.0 ± 2.9	13.5 ± 1.9**
Mean total number of pups[a] born per litter	12.6 ± 1.6	12.8 ± 1.6	11.5 ± 2.8	12.8 ± 1.8
Mean number of live pups[a] per litter ± standard deviation:				
Day 0 of lactation	12.6 ± 1.6	12.8 ± 1.6	11.5 ± 2.8	12.8 ± 1.8
Day 1 of lactation	12.4 ± 1.7	12.6 ± 1.6	11.4 ± 2.7	11.8 ± 2.0
Day 4 of lactation	12.3 ± 1.7	12.2 ± 2.4	11.3 ± 2.6	11.7 ± 2.0
Day 7 of lactation	12.1 ± 1.9	12.2 ± 2.4	11.2 ± 2.7	11.7 ± 2.0
Day 14 of lactation	12.1 ± 2.0	12.2 ± 2.4	11.2 ± 2.7	11.7 ± 2.0
Day 21 of lactation	12.1 ± 2.0	12.1 ± 2.4	11.2 ± 2.7	11.7 ± 2.0
Total number of males[a] on Day 1 of lactation (%)	133 (54)	131 (47)	130 (49)	74 (48)
Total number of females[a] on Day 1 of lactation (%)	115 (46)	147 (53)	133 (51)	80 (52)

a = Excludes litters where all pups died or animals killed prematurely
* Please see Appendix 6, all premature decedents were considered not to have produced a live litter due to the problems observed during parturition
**Number implants 13.2 ± 3.4 when premature decedents included

Reviewer: In the control group, 4/23 litters lost approximately half or more of their offspring before the completion of weaning. Although the overall viability during the weaning period is within historical range, the high incidence of pup loss in a few litters raises questions about the population of animals used.

Necropsy Observations

Postmortem observations were unremarkable. The only animals with significant findings were those in the HD that were terminated early or found dead. The postmortem observations of these animals were previously summarized in the Mortality section above.

F1 Generation Growth, Physical, and Functional Development

As a result of the F0 mortality and litter loss occurring amongst the various groups, pups from 20, 23, 23, and 13 litters in the Control, LD, MD, and HD groups (respectively) were available for use in assessing growth and development. No treatment-related effects were noted as summarized in the table below:

F_1 Generation	
Survival:	No-treatment effect
Clinical signs:	No-treatment effect
Body weight:	No-treatment effect
Feed consumption:	No-treatment effect
Physical development:	No-treatment effect

Neurological assessment:	No-treatment effect
Reproduction:	No-treatment effect
Necropsy	No-treatment effect

F1 Generation Reproductive Performance

There were no apparent effects on the numbers of animals for mating, the time to mate, or gestation length. Although 2, 4, and 1 pairings in the Control, LD, and MD groups (respectively), did not result in a pregnancy. As a result, there were 18, 19, 22, and 13 pregnancies in the Control, LD, MD, and HD groups (respectively). Sponsor's Table:

Table 17
F1 Generation: Mating Performance and Fertility Indices

Number of Nights to Positive Mating Sign	Group/Dose Level (mg/kg/day)			
	1 (0)	2 (100)	3 (600)	4 (2000)
	Number of Animals (Number of these not becoming pregnant)			
1	7	8	5(1)	1
2	2	6	7	0
3	3(2)	9(4)	6	4
4	8	0	5	6
No clear indication of mating	0	0	0	2
Median number of nights to positive mating sign	3	2	2	4
Number passing one oestrus	0	0	0	0
Number of males paired	20	23	23	13
Number of siring males	18	19	22	13
Male Fertility Index (%)	90	83	96	100
Number of females paired	20	23	23	13
Number pregnant	18	19	22	13
Female Fertility Index (%)	90	83	96	100

Reviewer: The sponsor did not collect estrous cycle data or evaluate sperm parameters of F1 animals so it is not possible to ascertain the reason for the unsuccessful matings. However, given that the highest incidence was at the low dose while no effect was seen at the high dose, the reason for these infertile pairings is not considered drug-related.

There were no effects on the number of implant sites/litter, the number of pups born/litter, or sex ratio. These data are shown in the Sponsor Table below (modified by reviewer to only show these data:

Table 18
F1 Generation: Duration of Gestation and Overall Litter Performance

	Group/Dose Level (mg/kg/day)			
	1 (0)	2 (100)	3 (600)	4 (2000)
Number Pregnant	18	19	22	13
Mean number of implant sites[a] per pregnancy ± standard deviation	16.1 ± 2.3	15.6 ± 1.8	16.0 ± 2.2	16.2 ± 2.1
Mean total number of pups[a] born per litter	15.2 ± 2.4	15.2 ± 1.9	15.0 ± 2.1	15.3 ± 2.3
Total number of males[a] on Day 1 of lactation (%)	141 (53)	150 (53)	152 (49)	100 (51)
Total number of females[a] on Day 1 of lactation (%)	127 (47)	134 (47)	160 (51)	96 (49)

a = Excludes litters where all pups died

F2 Generation Survival

Pup mortality occurred in all groups, although the number of litters affected was lower in the drug-treated groups than in controls. In all groups (including controls), there were multiple animals that lost 3 or more pups during the 14 day observation period which demonstrated a dose response in terms of proportion affected, although the fewer number of litters at the HD somewhat confounds the interpretation. These data are summarized in the reviewer Table below:

Offspring Survival				
	Control	LD	MD	HD
Number of pups found dead or killed prematurely / number of litters affected	31 / 9	40 / 6	46* / 8*	30 / 6
Number litters losing ≥3 pups / number of litters	3/18 17%	4/19 21%	5*/22 23%	4/13 31%
* Includes 1 animal with total litter loss				

In the Control and LD groups, most pup loss occurred within days 0 - 4 postnatally while in the MD group the loss occurred later in the postnatal phase; at HD, pup deaths occurred throughout the postnatal period, with most occurring after Day 7. Data are summarized in the reviewer table below:

Viability Index				
Number litters losing ≥3 pups	Control (3)	LD (4)	MD (5)	HD (4)
Days 0 - 4	2	4	1	3*
Days 4 - 14	1	0	4	2*
* Includes 1 animal with a loss of greater than 3 pups both before day 4 and a second time after day 7				

The increased proportion of litters with higher incidence of mortality had no effect on the mean number of live pups/litter at various ages as shown in the sponsor table (Table modified by reviewer to show only the litter size data) below:

Table 18
F1 Generation: Duration of Gestation and Overall Litter Performance

	Group/Dose Level (mg/kg/day)			
	1 (0)	2 (100)	3 (600)	4 (2000)
Number Pregnant	18	19	22	13
Mean number of live pups[a] per litter ±standard deviation:				
Day 0 of lactation	15.1 ± 2.6	15.1 ± 1.9	15.0 ± 2.1	15.2 ± 2.3
Day 1 of lactation	14.9 ± 2.7	14.9 ± 1.8	14.9 ± 2.2	15.1 ± 2.1
Day 4 of lactation	13.8 ± 3.6	13.2 ± 4.0	14.8 ± 2.3	13.7 ± 2.2
Day 7 of lactation	13.8 ± 3.6	13.1 ± 4.0	14.7 ± 2.3	13.6 ± 2.1
Day 14 of lactation	13.4 ± 3.3	13.0 ± 3.9	13.6 ± 2.9	13.0 ± 2.4
Total number of males[a] on Day 1 of lactation (%)	141 (53)	150 (53)	152 (49)	100 (51)
Total number of females[a] on Day 1 of lactation (%)	127 (47)	134 (47)	160 (51)	96 (49)

a = Excludes litters where all pups died

Reviewer: Although there appeared to be an increase in pup mortality at the mid and high dosages during the post-weaning observational period, the observed number of pups/litter remained within the historical range of the test facility (see sponsor response to question 1 of the information request in the regulatory background).

The sponsor was requested to explain the increased mortality (see sponsor response to question 3 of the information request under regulatory background). It was suggested the combination of high mortality in few litters, postmortem exams revealing no milk in pup stomach along with gas distention in the stomach, and large litters leading to weaker pups not being able to compete for nursing were responsible which led to their interpretation that this effect was incidental. However, this explanation is in contrast to the conclusion in the report which identifies the low dosage as the NOAEL based on the mortality of the F2 occurring at the mid and high dosages. The data do not also fully support this interpretation as there were also larger litters in the various groups in which there was no pup loss, there were no obvious effects on litter weight, and data regarding the presence of milk in stomach was not collected except as a necropsy observation in the few pups evaluated.

Regardless of the absence of an effect on litter size at the various ages, the increased mortality occurring during the last week of the observation period at the mid and high dosages led to the identification of the low dose as the NOAEL by the sponsor. At this point the sponsor has not

identified a mechanism to account for the mortality. This reviewer agrees with the identification of the NOAEL as the low dose.

F2 Generation Clinical Signs, Body Weight, and Necropsy Observations

Clinical signs were noted in some of the F2 pups leading to a decision to necropsy selected pups. At the H dose, 7 pups from 3 litters were reported with respiration irregularities and distended intestines from ca Day 8 of lactation (similar to F0). Necropsy findings of these animals included intestines distended with gas and abnormal (yellow) stomach contents.

At the M dose, a total 16 pups from 6 litters were killed prematurely (7/16) or found dead (9/16) from ca Day 10 of lactation with clinical signs of slow /irregular breathing, swollen abdomen and darkened skin. Necropsy findings from selected animals revealed swollen abdomen distended by contents (yellow) and stomach distended by gas.

At the L dose a single pup was killed prematurely (Day 17 of lactation) due to irregular breathing, lump on abdomen, cold to touch, and appeared unfed. This pup had no necropsy findings.

There were no effects on body weight during the 14 day observation period.

Reviewer, issues with the study: Some typical study parameters were not included in the report and/or protocol that may have helped identify potential reasons for some of the observations. For example, the protocol indicated F1 and F2 pups will be evaluated for the presence of milk in the stomach but these data were not provided in the report, estrous cycle evaluations of F1 females would have provided info on the reproductive readiness, and it appears that necropsies were only performed on selected F2 pups.

The low number of F1 animas at the HD may have masked potential drug-related effects on growth and development. The low number of F1 animals at HD may also have affected the magnitude of the observations on the F2 generation.

***Note:** Based on the preliminary review of the reproductive studies, an information request was sent to the sponsor asking for additional information. The questions and sponsor responses are rovided below:*

Question: Regarding the Pre and Post Natal Oral (Gavage) study in Rats (Study NO. 495440), please provide:

Question 1: Historical control data for F1 and F2 survival rates

Response:

Historical control data at [redacted] (b) (4) with F0 and F1 generational survival data, are presented in *Table 1* and *Table 2*, respectively.

Table 1: F0 Generation Survival Data

Parameter	Mean	Minimum	Maximum
Litter mean values (F0 generation)			
Implants	13.9	13.0	15.0
F1 Pups born	13.0	12.2	14.6
F1 Live pups Day 0	12.9	12.2	14.1
F1 Live pups Day 1	12.6	12.0	13.3
F1 Live pups Day 4	12.2	11.4	12.8
F1 Live pups Day 7	12.1	11.1	12.8
F1 Live pups Day 14	12.1	11.2	12.8
F1 Live pups Day 21	12.1	11.1	12.8
Birth index (%)	92.4	87.0	98.0
Live birth index (%)	98.1	95.0	100.0
Viability index (%)	90.1	73.0	98.0
Lactation index (%)	98.9	95.0	100.0
F1 Overall Survival (% birth-Day	88.3	72.0	96.0

Table 2: F1 Generation Survival Data

Parameter	Mean	Minimum	Maximum
Litter mean values (F1 generation)			
Implants	15.6	14.9	16.3
F2 Pups born	14.5	13.6	15.4
F2 Live pups Day 0	14.3	13.5	15.3
F2 Live pups Day 1	14.1	13.3	15.1
F2 Live pups Day 4	13.7	12.4	14.8
F2 Live pups Day 7	13.7	12.4	14.8
F2 Live pups Day 14	13.6	12.4	14.8
Birth index (%)	93.1	89.0	95.0
Live birth index (%)	99.1	97.0	100.0
Viability index (%)	93.5	86.0	98

Question 2: Explain why 2000 mg/kg/day treated F0 dams had the parturition difficulties.

Response:

Administration of omega-3 fatty acids to rats has been demonstrated to prolong/impair parturition in rats (*Leaver et al, Prog Lipid Research, 1986*) resulting in increases in fetal mortality likely secondary to altered prostaglandin synthesis. The Leaver paper demonstrates marked reductions in uterine and renal PG E2 concentrations. Rats typically deliver within 2-4 hours and prolongation of parturition is associated with increased stillborn pups and fetal deaths.

Question 3: Explain the reason for the reduce survival in F2 generation pups.

Response:

The reason for reduced survival of F2 generation pups is not clear. However, pup survival was excellent in most F2 litters at all doses. The decreased survival at 600 and 2000 mg/kg was driven by poor condition of some pups in a few dams (e.g. F1 dam 271 and 267 from 600 mg/kg F0 groups and F1 dams 281, 284 and 285 from the 2000 mpk F0 group).

Notably, the F1 dams were not dosed so any effects due to Epanova are highly unlikely. In addition, the reproductive performance of F1 dams and the litter size, litter and pup weights and fetal survival at day 1 of lactation in F2 litters were normal in all groups and the affected litters.

The common findings in premature decedent pups were stomach distended with gas or no milk in stomach suggesting that poor condition was secondary to poor nutrition in these pups. The fact that the poor condition developed primarily in the second week of lactation in affected pups is also consistent with poor nutritional status in pups competing for milk. It is not uncommon that some weaker pups may not survive when large litters are competing for milk. The F2 litters in this study were not culled which may have resulted in the death of some pups in dams with limited milk production. Since F1 dams were not dosed with Epanova and no adverse effects were observed on any parameter in the F1 generation or F2 litters on day 1 of lactation, the impaired survival of pups in a limited number of litters is likely incidental.

Question 4: What was the reason for F1 generation being allowed to deliver and raise F2 generation for up to 3 weeks?

Response:

This is the standard design of peri/postnatal development studies since reproductive performance of the F1 generation is evaluated by assessing fertility, pregnancy outcomes, and lactation (rat pups are weaned by 3 weeks).

Reviewer: Regarding Response 4, peri/postnatal studies typically include a mid-gestation C-section of F1 animals (eg, pregnancy status, the numbers of live and dead fetuses) rather than allowing them to deliver and nurse the F2 offspring for a period of time.

10 Special Toxicology Studies

None

11 Integrated Summary and Safety Evaluation

Most Common Toxicity findings	Species	NOAEL (mg/kg) M/F	Safety Margin Based on BSA*
None	Mice (4-week)	4000	5 fold
Liver: ↑ ALT; ↑ AP	Rat (4-week)	1,000	2.5 fold
Liver: ↑ ALT ;↑ AP; ↑ AST; microscopic cholangiohepatitis with widespread biliary proliferation and necrosis Kidney: ↑basophilic cortical tubules	Rat (13-week)	600	1.5 fold
Liver: ↑ALP Mortality at higher exposure level	Rat (26-week)	600	1.5 fold
Liver: ↑ AP and ↑ liver weight	Dog (4-week)	1000	8 fold
Live: ↑ ALP, ↑AST↑ and focal necrosis Heart: Focal granuloma /macrophage aggregates, epicardial Aorta: Focal mineralization, adventitial	Dog (39-weeks)	300	2.4 fold

*Based on a body surface area comparison and maximum daily dose of 4 g/day with a mean weight of 60 kg

Background

The Sponsor proposes Epanova soft gelatin capsules (omefas) for the treatment of severe hypertriglyceridemia (≥500 mg/dL) under NDA205060. Epanova is a novel Omega-3, mixture of polyunsaturated free fatty acids, with active components of EPA (55%), DHA (20%), and DPA ((b) (4)%) in their free fatty acid forms from fish oil. The proposed clinical dose is for 2 g/day (2 capsules) and (b) (4) 4 g/day (4 capsules; MRHD) (b) (4) .

Epanova (Omega-3 fatty acid) has a higher absorption of EPA and DHA compared to the approved Lovaza® (Omega-3 ethyl esters; IND (b) (4); NDA 21-654 AP 2004) with EPA ((b) (4)%) and DHA ((b) (4)%). Lovaza requires pancreatic lipases to change to the omega-3 fatty acid.

Fish oil (mixture of EPA/DHA) has been used as dietary supplements for a long time in both the United States and the European Union. In addition, EPA is an essential omega-3 fatty acid, which is consumed with fish, fish oil and nuts/seeds. Also, Menhaden oil (fish oil with multiple fatty acids as including EPA/DHA) is established as GRAS by the FDA with a dose of 3g/day.

To support approval of Epanova, the Sponsor conducted pivotal nonclinical studies in mice, rats, dogs, a full panel of genotoxicity, two carcinogenicity, and a full ICH S5 battery of

reproductive toxicology. Oral (gavage) administration was conducted in rodent with omefas (extracted from Epanova soft gel capsules) and in dogs with oral Epanova soft gel capsules.

Pharmacology: Based on available data, long chain polyunsaturated fatty acids (PUFAs) are absorbed from the small intestine and transported by the lymph to systemic distribution. Fatty acids are incorporated into the cell and can affect the fluidity of the membranes, regulate cellular signaling, and alter the production of prostaglandin and leukotriene to modulate the immune response. Omega-3 fatty acids EPA and DHA inhibit inflammatory mediators such as prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) as well as cytokines such as IL-1β and TNF-α. Therefore, fish oil containing EPA/DHA is beneficial for inflammatory diseases (e.g. Crohn's disease). Its potential safety concerns are possible increased bleeding time (risk of hemorrhage), increased liver function enzymes, skin hypersensitivity, and gastrointestinal upset. Furthermore, omega-3 fatty acids can alter the synthesis of triglycerides and cholesterol production by the liver, affect the hypothalamus-pituitary-adrenal (HPA) axis, and may also modulate thyroid hormone production.

The Sponsor conducted no pharmacology studies. Based on repeat-dose toxicology studies, no safety concern for cardiovascular or neurological toxicities is evident. The respiratory toxicity in rodents studies was due to gavage-treatment and was not relevant to humans. Potential safety concerns have been identified for increased liver function enzymes.

PK/ADME: The Sponsor did not submit the general ADME studies. Findings of limited submitted studies suggested that Epanova at concentrations of 0.5% to 1%, *in vitro* permeation of Methotrexate across Caco-2 cell monolayer, showed no influence on the transport of Methotrexate *in vitro* model of the intestinal barrier. Epanova effects on different CYP450 isoenzymes were concentration dependent. In addition, significant drug-drug interaction is not expected up to 10 μM omefas. Moreover, EPA and DHA are inhibitors and substrates of several cytochrome P450 isoenzymes.

Toxicokinetics: The Sponsor conducted TK studies in the repeat-dose toxicity studies in mice, rats and dogs. Findings of these studies generally suggested that the levels of EPA and DHA increased over time and with dose levels.

Toxicology Studies

In general, repeat-dose toxicity studies showed the intended pharmacological effect of Epanova by decreased plasma levels of total cholesterol and triglycerides. In rodent, Epanova (omefas) up to 4g/kg/day showed generally no mortality; however, after three months, all studies showed mortality in a dose-response manner with clinical signs of abnormal sneezing, wheezing respiration, subdued behavior, piloerection, and excess salivation. In general, mortality in these studies was treatment-related because of gavage procedure with oily, acidic formulation of omefas, which caused abnormal sneezing and/or wheezing respiration and excessive salivation (dose-response) and the respiratory tract lesions. The liver was the target organ toxicity across species (rat, dog) based on increased serum liver enzyme activities.

Epanova is comprised of the free fatty acid forms of EPA and DHA and is acidic. The sponsor indicates that the acidity is (b) (4) . It is thought that aspiration of the formulation either as a single event or as multiple aspirations over time results in irritation and subsequent changes to the respiratory tract. These changes to the respiratory tract appear to be dose volume related and where therefore more pronounced in rodents, especially rats given the highest volume of 2.2 ml/kg/dose (2000 mg/kg/day).

Mice study: Dose-range study was conducted in the wild type rasH2 mice with omefas up to 4000mg/kg/day to select dose levels for the 6-month transgenic carcinogenicity study. The MTD exceeded 4000mg/kg/day omefas; therefore, this dose level was established for NOAEL (5 fold safety margin to MRHD of 4g/day based on the body surface area comparison).

Rat studies: The 4-week oral toxicity study was conducted with omefas up to 5000mg/kg/day. The NOAEL was established at 1000 mg/kg/day based on increased the plasma levels of ALT and ALP activities at dose levels above 1000mg/kg/day.

The 13-week oral (gavage) bridging toxicity TK study was conducted with two formulations of omefas (up to 2000mg/kg/day) and approved fish oil, Lovaza (Omacor, at 2160 mg/kg/day) to determine the dose-selection for the rat carcinogenicity study with omefas. Findings of this study showed the higher bioavailability for omefas (AUC for EPA and DHA was 1.7- and 2.5-fold higher, respectively) compared to omacor treated animals. This higher bioavailability was based on free fatty acid form of omefas, which does not require lipases prior to absorption. Also, in this study, differences existed in body weight gains and food consumptions between animals that were treated at similar dose levels with these two formulations (lower in omefas-treated animals). These differences were not considered for the dose-selection for the 2-year-carcinogencity study. In addition, combinations of these two compounds DHA and EPA, with free fatty acid (Epanova) or ethyl ester (Lovaza) formulations along with a significant difference in ratio of these compounds probably make different in pharmacological properties of each formulation. Therefore, the dose-selection for the 2-year carcinogenicity study with Lovaza was not valuable for Epanova in this study.

Target organ toxicity was at 2000mg/kg/day for liver, lung and kidney. In the liver, changes in liver enzymes activities for ALP, ALT, and AST were reported, which were correlated with higher liver weight at 2000 mg/kg/day omefas and microscopic findings of cholangiohepatitis with widespread biliary proliferation with hepatocellular necrosis in one 2000mg/kg/day treated male. In the kidney, dose-related trend in mild microscopic basophilic cortical tubules was reported in all 2000mg/kg/day treated males and one female in comparator. In the lung, dose-response alveolar macrophage accumulation was reported in all animals. Moreover, in the heart, in one 2000 mg/kg/day treated female, moderate inflammation of the epicardial surface of the heart and mild inflammation of the pleura were reported (probably was due to gavage injury). NOAEL was at 600mg/kg/day for omefas treated animals.

The 26-week oral toxicity study was conducted with omefas up to 2000 mg/kg/day. Findings of this study showed mortality in a dose-response manner (more in males). The cause of death

was treatment-related because of gavage procedure and microscopic findings in the respiratory tract lesions. Target organ treatment-related toxicity was liver at 2000 mg/kg/day (liver weight increased with increased ALP enzyme activity). NOAEL was at 600mg/kg/day omefas.

Dog studies: The 4-week subacute toxicity study in dogs was conducted with Epanova soft gel capsules (oral) up to 3000mg/kg/day. Target organ toxicity was identified for liver based on increased serum levels of ALP, liver weights, and microscopic finding of increased in the severity of plant cell structures in the liver. NOAEL was at 1000 mg/kg/day Epanova soft gel capsules.

In the 39-week oral toxicity study in dogs, Epanova soft gel capsules were given (oral) to dogs up to 1000 mg/kg/day. Dogs had incidences of liquid/loose feces in a dose response manner. The target organ toxicity was liver, based on changes in serum enzymes activities of ALP and AST and microscopic finding of focal necrosis (1/4). Microscopic findings were reported for 2/4 male dogs at 1000mg/kg/day as follows: in the heart: 1/4 dog with granuloma /macrophage aggregates, epicardial, focal; and in the aorta: 1/4 dog with mineralization, adventitial, focal. One of these 2 dogs also was noted with liver focal necrosis.

Genotoxicity Studies:

Epanova was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, the chromosomal aberration study, and in the *in vivo* rat micronucleus study.

Carcinogenicity Studies:

The 2-year rat study: Rats were given omefas orally (gavage) at 0 (corn oil), 100, 600, and 2000 mg/kg/day or 2.2, 0.11, 0.65, or 2.2 mL/kg/day, respectively. The dose-selection was not submitted to the Agency. The HD was selected based on MTD from the 13-week oral repeat-dose toxicity study and available carcinogenicity data from approved fish oil Lovaza. There was no mortality issue for these two studies. However, because of the low survival rate, there were deviations from the protocol regarding the early discontinuation of dosing and termination of all groups (with ECAC consultation). Therefore, animals were treated for at least 83 weeks for males and at least for 65 weeks for females. Treatment-related mortality was statistically significant for the trend in dose and in the comparison among groups (CDER biostatistics Males: $p \leq 0.0004$, Females: $p<0.0001$). The cause of death was non-neoplastic and was due to respiratory tract lesions based on clinical signs (excess salivation, and abnormal respiration) and gross / microscopic lesions findings.

Drug-related benign sex cord stromal tumors of the ovaries at 2000mg/kg/day were observed, which were statistically significant for both trend (P=0.0005) and pairwise comparison (P=0.0054). The benign ovarian sex cord tumor at 2000mg/kg/day (5 fold to the MHRD of 4g/day) exceeded concurrent control and historical controls and was drug-related dispute early discontinuation of dosing and termination of 2000mg/kg/day treated females.

Non-neoplastic findings were reported in the respiratory tract (larynx: squamous metaplasia; lungs: bronchus-associated lymphoid tissues in males; nasal cavity: squamous metaplasia; and

trachea), in the kidney (tubular dilatation); large and small intestine (lumen dilation and crypt hyperplasia); and liver (focal mononuclear cell inflammatory infiltrates).

Late in the review cycle, CMC identified the safety issue for the Sponsor's specification limit of (b) (4) as an impurity in Epanova capsules. (b) (4) is a rodent carcinogen and likely human carcinogen based on the International Agency for Research on Cancer (IARC) classifications. The sex chord stromal ovarian tumors reported in the Sponsor's 2-year rat study were also noted in the Sponsor's justification for the tumor profile of (b) (4) provided by (b) (4) (Table 3.3.1-2, Page 7 of the (b) (4) report as well as ovarian granulosa from the NTP 2004 carci study with (b) (4); sex chord stromal tumors are a subtype of ovarian granulosa tumors). The preclinical data would support a specification of (b) (4) ppm. In addition, the Agency requested that the Sponsor revise their specification as low as possible because of the potential concern.

The sponsor has indicated that (b) (4) this specification was lower than those based on ICHM7 guidelines for genotoxic impurities and that (b) (4).

The 26-week Tg.rasH2 mice study: Mice were treated with omefas at 0 (water), 500, 1000, 2000, and 4000 mg/kg/day or 4.4 (Water), 0.55, 1.1, 2.2 and 4.4 mL/kg/day, respectively (ECAC concurred). Mortality in this study increased statistically significantly in all dose groups for both genders. The high dose (4000mg/kg/day) animals were removed from the study on Day 73 with 50% surviving. The cause of death was considered to be non-plastic based on pathological findings in the respiratory tract. No drug-related neoplasms were found in mice that were considered treatment-related up to 2000mg/kg/day (5 fold to the MHRD of 4 g/day based on a body surface area comparison). Non-neoplastic findings were reported for hyperplasia in the non-glandular portion of the stomach and for inflammatory lesions in the nasal cavity, trachea, and lungs.

Reproductive Toxicology Studies:

Findings from these studies in rats suggested no treatment effects on reproductive performance, early embryonic development, maternal or fetal toxicity were in treated rats up to 2000mg/kg/day (5 fold to MHRD of 4 g/day; based on systemic exposure). In rabbits, NOAELs were established for the maternal at 500 mg/kg/day and for the embryo-fetal development at 100 mg/kg/day (about 2.4 and 0.5 fold, respectively to MHRD of 4g/day; based on a body surface area). At higher exposure, 750 mg/kg/day, there was mortality due to abortion, body weight loss and fetal skeletal variation in treated animals.

In the pre/post natal rat oral study, F0 animals showed mortality (9/24 at 2000mg/kg/day) due to difficulties during or shortly after parturition. In addition, these animals showed lower body weight gain/food consumption with macroscopic revealed abnormal stomach and/or intestinal contents and glandular mucosa abnormalities. Therefore, at this dose level, there were fewer live litters and fewer pups (surviving to day 4) for evaluation. At F1, there were no effects on growth or development or on their ability to initiate and maintain a pregnancy. However, there

was an increased incidence of pup (F2) mortality at 600 and 2000mg/kg/day. The NOAEL were established for the treated F0 and F1 generations at 600 and 100 mg/kg/day, respectively (1.5 and 0.25 folds to MRHD based on a body surface area, respectively). The Sponsor did not submit any TK data; therefore, it is not known if pregnancy alters after exposure.

12 Appendix/Attachments

Histopathological Tables for the 104 Week Carcinogenicity Study in Rats:

b(4)

Test Facility: [redacted]
Study No. 518911: 104 Week Carcinogenicity Study of Epanova by Oral Gavage in Rats
List of tumours by status and fatality

Group		MALE				FEMALE				
Dosage level (mg/kg/day)		0	100	600	2000	0	100	600	2000	Total
ADRENAL CORTEX: ADENOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	2	1	1	0	3	2	0	0	9
ADRENAL CORTEX: CARCINOMA [M]										
Fatal	n	0	0	0	0	1	0	0	0	1
Incidental	n	0	0	0	0	1	0	0	0	1
Total	n	0	0	0	0	2	0	0	0	2
ADRENAL MEDULLA: BENIGN PHAEOCHROMOCYTOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	7	9	4	5	1	1	1	1	29
ADRENAL MEDULLA: PHAEOCHROMOCYTOMA, COMPLEX [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	0	0	1	0	0	0	0	0	1
ADRENAL MEDULLA: MALIGNANT PHAEOCHROMOCYTOMA [M]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	1	2	0	0	0	0	0	0	3
BRAIN: ASTROCYTOMA LOW GRADE [M]										
Fatal	n	0	0	1	0	0	0	0	0	1
Incidental	n	1	1	0	0	0	0	0	1	3
Total	n	1	1	1	0	0	0	0	1	4
BRAIN: ASTROCYTOMA HIGH GRADE [M]										
Fatal	n	0	1	1	0	0	0	0	0	2
Incidental	n	1	0	1	1	0	0	0	0	3
Total	n	1	1	2	1	0	0	0	0	5
BRAIN: OLIGODENDROGLIOMA LOW GRADE [M]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	1	0	0	1	0	0	0	0	2
BRAIN: BENIGN GRANULAR CELL TUMOUR [B]										
Fatal	n	0	0	0	1	0	0	0	0	1
Incidental	n	1	1	0	0	0	0	0	1	3
Total	n	1	1	0	1	0	0	0	1	4
CERVIX: LEIOMYOMA [B]										
Fatal	n					0	0	0	0	0
Incidental	n					0	1	0	0	1

Pathologist: [redacted]
Organs examined routinely in all groups
Reported by [redacted] on 26-APR-13 11:08:49

b(4)

Table 1

Test Facility: b(4)

Study No. 518911: 104 Week Carcinogenicity Study of Epanova by Oral Gavage in Rats
List of tumours by status and fatality

Group		MALE				FEMALE				
Dosage level (mg/kg/day)		0	100	600	2000	0	100	600	2000	Total
CERVIX: BENIGN GRANULAR CELL TUMOUR [B]										
Fatal	m					0	0	0	0	0
Incidental	m					2	0	0	0	2
CERVIX:ENDOMETRIAL STROMAL POLYP [B]										
Fatal	m					0	0	0	0	0
Incidental	m					0	0	0	1	1
CERVIX: MALIGNANT SCHWANNOMA [M]										
Fatal	m					0	0	0	1	1
Incidental	m					0	0	0	0	0
EPIDIDYMIDES: MALIGNANT MESOTHELIOMA [M]										
Fatal	m	0	0	0	0					0
Incidental	m	1	0	0	0					1
HEART: BENIGN SCHWANNOMA [B]										
Fatal	m	0	0	0	0	0	0	0	0	0
Incidental	m	0	0	1	0	0	0	0	0	1
KIDNEYS: NEPHROBLASTOMA [M]										
Fatal	m	0	0	0	0	0	1	0	0	1
Incidental	m	0	0	0	0	0	0	0	0	0
KIDNEYS:TUBULAR CELL CARCINOMA [M]										
Fatal	m	0	0	0	0	0	0	0	0	0
Incidental	m	1	0	0	0	0	0	0	0	1
KIDNEYS: LIPOMA [B]										
Fatal	m	0	0	0	0	0	0	0	0	0
Incidental	m	0	1	1	0	0	0	0	0	2
KIDNEYS: MALIGNANT MESENCHYMAL TUMOUR [M]										
Fatal	m	1	0	0	0	0	0	0	0	1
Incidental	m	0	0	0	0	0	0	0	0	0
LIVER:HEPATOCELLULAR ADENOMA [B]										
Fatal	m	0	0	0	0	0	0	0	0	0
Incidental	m	1	2	0	0	0	0	0	0	4
LIVER:HEPATOCELLULAR CARCINOMA [M]										
Fatal	m	0	0	0	0	0	0	0	0	0
Incidental	m	1	0	0	0	0	0	0	0	1

Pathologist: b(4)
Organs examined routinely in all groups
Reported by [redacted] on 26-APR-13 11:11:00

b(4)

Table 4

Test Facility: —

Study No. 518911: 104 Week Carcinogenicity Study of Epanova by Oral Gavage in Rats
List of tumours by status and fatality

Group		MALE				FEMALE				
Dosage level (mg/kg/day)		0	100	600	2000	0	100	600	2000	Total
LIVER: HAEMANGIOSARCOMA [M]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	0	0	0	0	0	1	0	0	1
LIVER: CHOLANGIOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	0	0	0	0	1	0	0	0	1
LUNGS:BRONCHIOLO-ALVEOLAR ADENOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	2	0	1	1	0	0	0	0	4
LUNGS:BRONCHIOLO-ALVEOLAR CARCINOMA [M]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	0	0	0	0	0	0	1	0	1
LUNGS: LEIOMYOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	0	0	0	1	0	0	0	0	1
LYMPH NODE: MESENTERIC: LYMPHANGIOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	1	2	0	1	0	1	0	0	5
LYMPH NODE: MESENTERIC: HAEMANGIOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	0	1	0	1	0	0	0	0	2
MAMMARY GLAND: FIBROADENOMA [B]										
Fatal	n	0	0	0	0	11	8	4	1	24
Incidental	n	1	0	1	3	15	13	9	5	47
Total	n	1	0	1	3	26	21	13	6	71
MAMMARY GLAND: ADENOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	1	0	0	0	1	2	0	0	4
MAMMARY GLAND: FIBROADENOMA WITH ATYPIA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	0	0	0	0	8	4	6	3	21

Pathologist: —
Organs examined routinely in all groups
Reported by — on 26-APR-13 11:15:38

b(4)

b(4)

Table 4

Test Facility: [redacted]

Study No. 518911: 104 Week Carcinogenicity Study of Epanova by Oral Gavage in Rats

List of tumours by status and fatality

Group		MALE				FEMALE				
Dosage level (mg/kg/day)		0	100	600	2000	0	100	600	2000	Total
MAMMARY GLAND: ADENOCARCINOMA [M]										
Fatal	n	0	0	0	0	6	4	2	0	12
Incidental	n	0	0	0	0	13	12	14	8	47
Total	n	0	0	0	0	19	16	16	8	59
MAMMARY GLAND: ADENOCARCINOMA IN FIBROAD. [M]										
Fatal	n	0	0	0	0	1	6	1	0	8
Incidental	n	0	0	0	0	6	4	6	2	18
Total	n	0	0	0	0	7	10	7	2	26
MAMMARY GLAND: MALIGNANT MIXED MAMMARY TUMOUR [M]										
Fatal	n	0	0	0	0	0	1	1	0	2
Incidental	n	0	0	0	0	0	0	0	0	0
OVARIES: BENIGN SEX CORD STROMAL TUMOUR [B]										
Fatal	n					0	0	0	0	0
Incidental	n					5	4	6	11	26
OVARIES: MALIGN. GRANULOSA CELL TUMOUR [M]										
Fatal	n					0	0	0	0	0
Incidental	n					0	1	0	0	1
OVARIES: PAPILLARY CYSTADENOMA [B]										
Fatal	n					0	0	0	0	0
Incidental	n					2	0	0	0	2
OVARIES: TUBULOSTROMAL ADENOMA [B]										
Fatal	n					0	0	0	0	0
Incidental	n					1	0	0	0	1
PANCREAS:EXOCRINE ADENOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	1	0	0	1	0	0	0	0	2
PANCREAS:ISLET CELL ADENOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	5	4	2	3	2	0	2	0	18
PANCREAS:ISLET CELL CARCINOMA [M]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	1	0	0	0	0	0	1	0	2

Pathologist: [redacted]

Organs examined routinely in all groups

Reported by [redacted] 26-APR-13 11:18:41

b(4)

b(4)

Table 4

Test Facility: [redacted]

Study No. 518911: 104 Week Carcinogenicity Study of Epanova by Oral Gavage in Rats
List of tumours by status and fatality

Group		MALE				FEMALE				
Dosage level (mg/kg/day)		0	100	600	2000	0	100	600	2000	Total
PANCREAS:DUCT ADENOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	0	1	0	1	0	0	0	0	2
PARATHYROID GLANDS: ADENOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	2	0	0	0	2	0	0	2	6
PITUITARY GLAND:PARS DISTALIS ADENOMA [B]										
Fatal	n	13	19	12	8	14	18	16	21	121
Incidental	n	25	18	13	20	37	27	19	14	173
Total	n	38	37	25	28	51	45	35	35	294
PITUITARY GLAND:PARS DISTALIS CARCINOMA [M]										
Fatal	n	0	1	0	0	0	1	0	0	2
Incidental	n	0	0	0	0	0	0	1	0	1
Total	n	0	1	0	0	0	1	1	0	3
PITUITARY GLAND:PARS INTERMEDIA ADENOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	0	0	0	1	1	0	0	0	2
SALIVARY GLAND: SUBLINGUAL: ADENOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	1	0	0	0	0	0	0	0	1
SPLEEN: LIPOSARCOMA [M]										
Fatal	n	0	0	1	0	0	0	0	0	1
Incidental	n	0	0	0	0	0	0	0	0	0
STOMACH: GLANDULAR: ADENOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	0	0	0	0	1	0	0	0	1
STOMACH: GLANDULAR: LEIOMYOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	0	0	0	1	0	0	0	0	1
TESTES:INTERSTITIAL CELL ADENOMA [B]										
Fatal	n	0	0	0	0					0
Incidental	n	1	1	0	0					2

Pathologist: [redacted]
Organs examined routinely in all groups
Reported by [redacted] 26-APR-13 11:21:43

b(4)

b(4)

Table 4

Test Facility: ———

Study No. 518911: 104 Week Carcinogenicity Study of Epanova by Oral Gavage in Rats
List of tumours by status and fatality

Group		MALE				FEMALE				
Dosage level (mg/kg/day)		0	100	600	2000	0	100	600	2000	Total
THYMUS: BENIGN THYMOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	0	0	0	0	2	0	3	0	5
THYROID GLAND:C-CELL ADENOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	6	9	1	2	1	4	0	0	23
THYROID GLAND:C-CELL CARCINOMA [M]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	0	2	1	0	1	0	0	1	5
THYROID GLAND:FOLLICULAR CELL ADENOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	0	2	0	0	1	1	0	0	4
THYROID GLAND:FOLLICULAR CELL CARCINOMA [M]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	1	0	0	1	0	0	0	0	2
URINARY BLADDER: TRANSITIONAL CELL PAPILLOMA [B]										
Fatal	n	0	0	0	0	0	0	0	0	0
Incidental	n	0	0	1	0	0	0	0	0	1
UTERUS:ENDOMETRIAL STROMAL POLYP [B]										
Fatal	n					1	0	0	0	1
Incidental	n					5	11	3	4	23
Total	n					6	11	3	4	24
UTERUS: MALIGNANT SCHWANNOMA [M]										
Fatal	n					1	0	1	0	2
Incidental	n					1	0	0	0	1
Total	n					2	0	1	0	3
UTERUS: LEIOMYOMA [B]										
Fatal	n					0	0	0	0	0
Incidental	n					0	0	0	1	1
UTERUS: LEIOMYOSARCOMA [M]										
Fatal	n					0	0	0	0	0
Incidental	n					0	1	0	0	1

Pathologist: ———
Organs examined routinely in all groups
Reported by ——— on 26-APR-13 11:27:12

b(4)

Table 4

Test Facility: [redacted] b(4)

Study No. 518911: 104 Week Carcinogenicity Study of Epanova by Oral Gavage in Rats
List of tumours by status and fatality

Group		MALE				FEMALE				
Dosage level (mg/kg/day)		0	100	600	2000	0	100	600	2000	Total
UTERUS:ENDOMETRIAL SQUAMOUS CELL PAPILLOMA [B]										
Fatal	n					0	0	0	0	0
Incidental	n					0	0	1	0	1
UTERUS:ENDOMETRIAL ADENOCARCINOMA [M]										
Fatal	n					0	0	0	0	0
Incidental	n					1	0	0	0	1
VAGINA: MALIGNANT SCHWANNOMA [M]										
Fatal	n					0	0	0	0	0
Incidental	n					0	0	1	0	1
VAGINA: BENIGN GRANULAR CELL TUMOUR [B]										
Fatal	n					0	0	0	0	0
Incidental	n					2	7	1	2	12

Pathologist: [redacted] b(4)
Organs examined routinely in all groups
Reported by [redacted] on 26-APR-13 11:29:33

Historical Control Data

Group	:	1	2	3	4
Test Item	:	Control	----------	Epanova	----------
Dosage (mg/kg/day)	:	0	100	600	2000

	N	Mean	SD	Mean-2 SD	Mean+2 SD	Min/Max		C. Limit % 2.50	97.50
Female									
Basophils	55	0.01	0.01	-0.01	0.03	0.00	0.05	0.00	0.03
Eosinophils	55	0.14	0.08	-0.02	0.30	0.03	0.47	0.04	0.35
Haemoglobin	55	13.90	1.05	11.80	16.00	11.20	16.10	11.90	15.60
Haematocrit	55	0.41	0.03	0.35	0.48	0.34	0.48	0.35	0.48
Large Unclassified Cells	55	0.07	0.20	-0.32	0.47	0.01	1.47	0.01	0.31
Lymphocytes	55	3.75	1.19	1.37	6.13	1.44	8.00	1.84	5.89
Mean Cell Haemoglobin	55	19.22	1.18	16.85	21.58	15.90	24.10	16.70	21.40
Mean Cell Haemoglobin Con	55	33.79	1.10	31.58	36.00	31.40	36.80	31.70	36.20
Mean Cell Volume	55	56.86	2.96	50.93	62.79	49.00	67.60	52.40	61.80
Monocytes	55	0.34	0.25	-0.16	0.84	0.03	1.46	0.05	1.14
Neutrophils	55	2.52	2.26	-2.00	7.04	0.68	16.12	0.69	5.48
Platelet Count	55	803.07	225.09	352.90	1253.25	273.00	1346.00	300.00	1138.00
Red Blood Cell Count	55	7.26	0.64	5.97	8.54	4.96	8.25	6.02	8.24
Red Cell Distribution Width	14	13.39	1.40	10.59	16.18	11.60	16.60	11.60	16.60
Reticulocyte Count	14	166.00	45.95	74.10	257.90	114.00	252.00	113.60	252.10
Reticulocytes	28	2.26	0.67	0.93	3.59	1.40	3.80	1.40	3.80
White Blood Cell Count	55	6.84	3.38	0.07	13.61	2.67	26.41	2.72	11.77
Male									
Basophils	92	0.03	0.02	-0.02	0.08	0.00	0.12	0.00	0.08
Eosinophils	92	0.20	0.10	0.00	0.39	0.04	0.53	0.07	0.50
Haemoglobin	92	14.84	0.98	12.89	16.79	9.90	16.90	12.90	16.30
Haematocrit	92	0.45	0.03	0.39	0.51	0.32	0.52	0.39	0.50
Large Unclassified Cells	92	0.10	0.06	-0.03	0.23	0.02	0.49	0.03	0.23
Lymphocytes	92	6.56	2.01	2.54	10.58	3.45	15.57	3.67	11.61
Mean Cell Haemoglobin	92	17.79	0.85	16.08	19.50	16.00	20.00	16.30	19.50
Mean Cell Haemoglobin Con	92	32.98	0.90	31.19	34.78	31.20	35.10	31.30	35.00
Mean Cell Volume	92	53.93	2.35	49.23	58.63	49.60	59.60	50.10	59.10
Monocytes	92	0.46	0.27	-0.08	1.00	0.02	1.68	0.13	1.15
Neutrophils	92	2.86	2.02	-1.18	6.90	0.60	16.52	1.15	7.63
Platelet Count	92	954.77	264.67	425.42	1484.12	197.00	1667.00	361.00	1422.00
Red Blood Cell Count	92	8.36	0.66	7.04	9.68	5.33	9.62	6.82	9.46
Red Cell Distribution Width	28	13.50	0.78	11.94	15.06	12.00	14.90	12.00	14.90
Reticulocyte Count	28	134.68	29.10	76.49	192.87	78.00	200.00	78.20	200.10
Reticulocytes	52	2.00	0.70	0.60	3.40	0.90	4.40	0.90	3.50
White Blood Cell Count	92	10.20	3.20	3.79	16.61	5.53	22.58	5.97	20.83

Histopathological Tables for the 26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 Mice:

8 Context of Tumor Summary Tables
Table 8.1 Context of Tumor Summary: Males

				Number of Animals with Tumor (a)					
ORGAN	TUMOR	DAY	CONTEXT	Control	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day	Positive Control
EAR	HEMANGIOMA (B)	109	F/M	0	1	0	0	0	0
HARDERIAN GLANDS	ADENOMA (B)	1-EOS	I	0/0	0/5	0/3	0/14	0/30	0/0
		Term	I	2/30	2/25	0/27	0/16	0/0	0/0
	CARCINOMA (M)	1-EOS	I	0/0	0/5	0/3	0/14	0/30	0/0
		Term	I	0/30	0/25	0/27	1/16	0/0	0/0
	CARCINOMA/ADENOMA	1-EOS	I	0/0	0/5	0/3	0/14	0/30	0/0
		Term	I	2/30	2/25	0/27	1/16	0/0	0/0
KIDNEYS	HEMANGIOSARCOMA (M)	1-EOS	I	0/0	0/5	0/3	0/14	0/30	0/0
		Term	I	0/30	1/25	0/27	0/16	0/0	0/0
LIVER	HEPATOCELLULAR ADENOMA (B)	1-EOS	I	0/0	0/5	0/3	0/14	0/30	0/0
		Term	I	1/30	0/25	0/27	0/16	0/0	0/0
LUNGS WITH BRONCHI	ALVEOLAR-BRONCHIOLAR ADENOMA (B)	Inter	I	0/0	0/0	0/0	0/0	0/0	14/14
		1-EOS	I	0/0	0/5	0/3	0/14	0/30	1/2
		Term	I	1/30	2/25	1/27	1/16	0/0	0/0
		58	F/M	0	0	0	0	0	1
		66	F/M	0	0	0	0	0	1
		83	F/M	0	0	0	0	0	1
		101	F/M	0	0	0	0	0	1
	ALVEOLAR-BRONCHIOLAR CARCINOMA (M)	Inter	I	0/0	0/0	0/0	0/0	0/0	7/14
		1-EOS	I	0/0	0/4	0/3	0/14	0/30	1/6
		Term	I	0/30	0/25	0/27	0/16	0/0	0/0
		116	F/M	0	1	0	0	0	0
	ALVEOLAR-BRONCHIOLAR CARCINOMA/ADENOMA	Inter	I	0/0	0/0	0/0	0/0	0/0	14/14
		1-EOS	I	0/0	0/4	0/3	0/14	0/30	1/2

Context - Context of tumor for statistical analysis: I = Incidental; F/M = Fatal or Mortality Independent
(a) I: Number of animals with tumor/Number of Animals examined in the time interval
F/M: Number of animals with tumor at specified study day
Inter = Intermittent Sacrifice; Term = Terminal Sacrifice
EOS = end of study (up to terminal sacrifice) (B) - Benign (M) - Malignant

Table 8.1 Context of Tumor Summary: Males

				Number of Animals with Tumor (a)					
ORGAN	TUMOR	DAY	CONTEXT	Control	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day	Positive Control
LUNGS WITH BRONCHI	ALVEOLAR-BRONCHIOLAR CARCINOMA/ADENOMA	Term	I	1/30	2/25	1/27	1/16	0/0	0/0
		58	F/M	0	0	0	0	0	1
		66	F/M	0	0	0	0	0	1
		83	F/M	0	0	0	0	0	1
		101	F/M	0	0	0	0	0	1
		116	F/M	0	1	0	0	0	0
	HEMANGIOSARCOMA (M)	Inter	I	0/0	0/0	0/0	0/0	0/0	4/14
		1-EOS	I	0/0	0/4	0/3	0/14	0/30	0/6
		Term	I	0/30	1/25	0/27	0/16	0/0	0/0
		113	F/M	0	1	0	0	0	0
MULTIPLE ORGANS	HEMANGIOSARCOMA/HEMANGIOMA	Inter	I	0/0	0/0	0/0	0/0	0/0	14/14
		1-EOS	I	0/0	0/3	0/3	0/14	1/30	1/5
		Term	I	4/30	3/25	2/27	0/16	0/0	0/0
		101	F/M	0	0	0	0	0	1
		109	F/M	0	1	0	0	0	0
		113	F/M	0	1	0	0	0	0
SKIN (MAMMARY AREA)	LYMPHANGIOMA (B)	1-EOS	I	0/0	1/5	0/3	0/14	0/30	0/0
		Term	I	0/30	0/25	0/27	0/16	0/0	0/0
SKULL CAP	HEMANGIOSARCOMA (M)	Term	I	0/0	1/1	0/0	0/0	0/0	0/0
SPLEEN	HEMANGIOSARCOMA (M)	Inter	I	0/0	0/0	0/0	0/0	0/0	14/14
		1-EOS	I	0/0	0/5	0/3	0/14	1/30	1/5
		Term	I	4/30	0/25	1/27	0/16	0/0	0/0
		101	F/M	0	0	0	0	0	1
STOMACH	PAPILLOMA (B)	1-EOS	I	0/0	0/5	0/3	1/14	0/30	0/0
		Term	I	0/30	0/25	0/27	0/16	0/0	0/0

Context - Context of tumor for statistical analysis: I = Incidental; F/M = Fatal or Mortality Independent
(a) I: Number of animals with tumor/Number of Animals examined in the time interval
F/M: Number of animals with tumor at specified study day
Inter = Intermittent Sacrifice; Term = Terminal Sacrifice
EOS = end of study (up to terminal sacrifice) (B) - Benign (M) - Malignant

Table 8.1 Context of Tumor Summary: Males

				Number of Animals with Tumor (a)					
ORGAN	TUMOR	DAY	CONTEXT	Control	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day	Positive Control
TESTES	HEMANGIOMA (B)	1-EOS	I	0/0	0/5	0/3	0/14	0/30	0/0
		Term	I	0/30	0/25	1/27	0/16	0/0	0/0

Table 8.2 Context of Tumor Summary: Females

ORGAN	TUMOR	DAY	CONTEXT	Number of Animals with Tumor (a) Control	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day	Positive Control
BONE, STERNUM	ALVEOLAR-BRONCHIOLAR CARCINOMA (M)	1-EOS	I	0/1	0/6	0/4	0/10	0/15	0/0
		Term	I	0/29	0/24	0/25	0/20	0/15	0/0
		150	F/M	0	0	1	0	0	0
CAVITY, NASAL	SARCOMA (M)	1-EOS	I	0/1	0/6	0/5	0/10	0/15	0/0
		Term	I	0/29	1/24	0/25	0/20	0/15	0/0
HARDERIAN GLANDS	ADENOMA (B)	1-EOS	I	0/1	0/6	0/5	0/10	0/15	0/0
		Term	I	1/29	1/24	0/25	0/20	0/15	0/0
	CARCINOMA (M)	1-EOS	I	0/1	0/6	0/5	0/10	0/15	0/0
		Term	I	1/29	0/24	0/25	0/20	0/15	0/0
	CARCINOMA/ADENOMA	1-EOS	I	0/1	0/6	0/5	0/10	0/15	0/0
		Term	I	2/29	1/24	0/25	0/20	0/15	0/0
HEART	SARCOMA (M)	1-EOS	I	0/1	0/6	0/5	0/10	0/15	0/0
		Term	I	0/29	1/24	0/25	0/20	0/15	0/0
LUNGS WITH BRONCHI	ALVEOLAR-BRONCHIOLAR ADENOMA (B)	Inter	I	0/0	0/0	0/0	0/0	0/0	13/13
		1-EOS	I	0/1	1/6	0/5	0/10	1/15	0/0
		Term	I	0/29	0/24	0/25	3/20	2/15	0/0
		93	F/M	0	0	0	0	0	1
		103	F/M	0	0	0	0	0	1
		106	F/M	0	0	0	0	0	1
		112	F/M	0	0	0	0	0	1
		117	F/M	0	0	0	0	0	1
		118	F/M	0	0	0	0	0	1
		120	F/M	0	0	0	0	0	1
	ALVEOLAR-BRONCHIOLAR CARCINOMA (M)	Inter	I	0/0	0/0	0/0	0/0	0/0	11/13
		1-EOS	I	0/1	0/6	0/4	0/10	0/15	0/4
		Term	I	1/29	1/24	0/25	0/20	0/15	0/0

Context - Context of tumor for statistical analysis: I = Incidental; F/M = Fatal or Mortality Independent
(a) I: Number of animals with tumor/Number of Animals examined in the time interval
F/M: Number of animals with tumor at specified study day
Inter = Intermittent Sacrifice; Term = Terminal Sacrifice
EOS = end of study (up to terminal sacrifice) (B) - Benign (M) - Malignant

ORGAN	TUMOR	DAY	CONTEXT	Control	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day	Positive Control
LUNGS WITH BRONCHI	ALVEOLAR-BRONCHIOLAR CARCINOMA (M)	112	F/M	0	0	0	0	0	1
		117	F/M	0	0	0	0	0	1
		120	F/M	0	0	0	0	0	1
		150	F/M	0	0	1	0	0	0
	ALVEOLAR-BRONCHIOLAR CARCINOMA/ADENOMA	Inter	I	0/0	0/0	0/0	0/0	0/0	13/13
		1-EOS	I	0/1	1/6	0/4	0/10	1/15	0/0
		Term	I	1/29	1/24	0/25	3/20	2/15	0/0
		93	F/M	0	0	0	0	0	1
		103	F/M	0	0	0	0	0	1
		106	F/M	0	0	0	0	0	1
		112	F/M	0	0	0	0	0	1
		117	F/M	0	0	0	0	0	1
		118	F/M	0	0	0	0	0	1
		120	F/M	0	0	0	0	0	1
		150	F/M	0	0	1	0	0	0
	HEMANGIOSARCOMA (M)	Inter	I	0/0	0/0	0/0	0/0	0/0	4/13
		1-EOS	I	0/1	0/6	0/5	0/10	0/15	0/7
		Term	I	0/29	0/24	0/25	0/20	0/15	0/0
LYMPH NODE, MANDIBULAR	LYMPHANGIOMA (B)	1-EOS	I	0/1	0/6	0/5	1/10	0/15	0/0
		Term	I	0/29	0/24	0/25	0/20	0/15	0/0
MAMMARY GLAND	HEMANGIOSARCOMA (M)	1-EOS	I	0/1	0/6	0/5	0/9	0/15	0/0
		Term	I	0/29	0/24	0/25	0/20	0/15	0/0
		114	F/M	0	0	0	1	0	0
	LYMPHANGIOMA (B)	1-EOS	I	0/1	0/6	0/5	0/10	0/15	0/0
		Term	I	0/29	1/24	0/25	0/20	0/15	0/0
MULTICENTRIC	HEMANGIOSARCOMA (M)	Inter	I	0/0	0/0	0/0	0/0	0/0	0/13

Context - Context of tumor for statistical analysis: I = Incidental; F/M = Fatal or Mortality Independent
(a) I: Number of animals with tumor/Number of Animals examined in the time interval
F/M: Number of animals with tumor at specified study day
Inter = Intermittent Sacrifice; Term = Terminal Sacrifice
EOS = end of study (up to terminal sacrifice) (B) - Benign (M) - Malignant

Table 8.2 Context of Tumor Summary: Females

				Number of Animals with Tumor (a)					
ORGAN	TUMOR	DAY	CONTEXT	Control	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day	Positive Control
MULTICENTRIC	HEMANGIOSARCOMA (M)	1-EOS	I	0/0	0/6	0/5	0/10	0/15	0/7
		Term	I	0/29	0/24	0/25	0/20	0/15	0/0
		113	F/M	1	0	0	0	0	0
MULTIPLE ORGANS	HEMANGIOSARCOMA/HEMANGIOMA	Inter	I	0/0	0/0	0/0	0/0	0/0	12/13
		1-EOS	I	0/0	0/5	0/5	0/9	0/14	0/0
		Term	I	1/29	3/24	1/25	1/20	0/15	0/0
		93	F/M	0	0	0	0	0	1
		103	F/M	0	0	0	0	0	1
		106	F/M	0	0	0	0	0	1
		112	F/M	0	0	0	0	0	1
		113	F/M	1	0	0	0	0	0
		114	F/M	0	0	0	1	0	0
		117	F/M	0	0	0	0	0	1
		118	F/M	0	0	0	0	0	1
		120	F/M	0	0	0	0	0	1
		140	F/M	0	0	0	0	1	0
		154	F/M	0	1	0	0	0	0
SALIVARY GLANDS	HEMANGIOSARCOMA (M)	1-EOS	I	0/1	0/5	0/5	0/10	0/15	0/0
		Term	I	0/29	1/24	0/25	0/20	0/15	0/0
		154	F/M	0	1	0	0	0	0
SKIN	HEMANGIOSARCOMA (M)	1-EOS	I	0/1	0/0	0/0	0/0	0/0	0/0
		140	F/M	0	0	0	0	1	0
SPLEEN	HEMANGIOSARCOMA (M)	Inter	I	0/0	0/0	0/0	0/0	0/0	12/13
		1-EOS	I	0/1	0/6	0/5	0/10	0/15	0/0
		Term	I	1/29	1/24	0/25	1/20	0/15	0/0
		93	F/M	0	0	0	0	0	1
		103	F/M	0	0	0	0	0	1
		106	F/M	0	0	0	0	0	1
		112	F/M	0	0	0	0	0	1

Context - Context of tumor for statistical analysis: I = Incidental; F/M = Fatal or Mortality Independent
(a) I: Number of animals with tumor/Number of Animals examined in the time interval
F/M: Number of animals with tumor at specified study day
Inter = Intermittent Sacrifice; Term = Terminal Sacrifice
EOS = end of study (up to terminal sacrifice) (B) - Benign (M) - Malignant

Table 8.2 Context of Tumor Summary: Females

				Number of Animals with Tumor (a)					
ORGAN	TUMOR	DAY	CONTEXT	Control	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day	Positive Control
SPLEEN	HEMANGIOSARCOMA (M)	117	F/M	0	0	0	0	0	1
		118	F/M	0	0	0	0	0	1
		120	F/M	0	0	0	0	0	1
STOMACH	PAPILLOMA (B)	1-EOS	I	0/1	0/6	0/5	1/10	0/15	0/0
		Term	I	1/29	0/24	0/25	0/20	0/15	0/0
UTERUS	HEMANGIOSARCOMA (M)	1-EOS	I	0/1	0/6	0/5	0/10	0/15	0/0
		Term	I	0/29	1/24	1/25	0/20	0/15	0/0

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	MALES					
Removal Reason: Terminal Sacrifice	0 mg/kg/ day	1000 mg/kg /day	500 mg/kg /day	1000 mg/kg /day	2000 mg/kg /day	4000 mg/kg /day
Number of Animals on Study :	30	0	25	27	16	0
Number of Animals Completed:	(30)	(0)	(25)	(27)	(16)	(0)
Adrenal Glands;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	27	16	0
Aorta;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	27	16	0
Bone Marrow, Femur;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	27	16	0
Bone Marrow, Sternum;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	27	16	0
Bone, Femur;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	27	16	0
Bone, Sternum;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	27	16	0
necrosis; costo-chondral junction	(0)	(0)	(0)	(0)	(0)	(0)
minimal	0	0	0	0	0	0
mild	0	0	0	0	0	0
inflammation, pyogranulomatous; peripheral; adipocyte	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	0	0	0
Brain;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	29	0	24	27	16	0
necrosis; hemorrhagic	(0)	(0)	(1)	(0)	(0)	(0)
marked	0	0	1	0	0	0
proliferation; vascular; meninges	(1)	(0)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	0	0

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AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	MALES					
Removal Reason: Terminal Sacrifice	0 mg/kg/ day	1000 mg/kg /day	500 mg/kg /day	1000 mg/kg /day	2000 mg/kg /day	4000 mg/kg /day
Number of Animals on Study :	30	0	25	27	16	0
Number of Animals Completed:	(30)	(0)	(25)	(27)	(16)	(0)
Cavity, Nasal;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	21	0	14	6	4	0
inflammation; submucosa	(8)	(0)	(10)	(20)	(9)	(0)
minimal	8	0	8	11	8	0
mild	0	0	2	9	1	0
inflammation, exudative	(1)	(0)	(1)	(4)	(9)	(0)
minimal	1	0	0	2	3	0
mild	0	0	1	1	5	0
moderate	0	0	0	1	0	0
marked	0	0	0	0	1	0
hypertrophy/hyperplasia; epithelium	(1)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	0	0	0
moderate	1	0	0	0	0	0
inflammation, granulomatous	(0)	(0)	(0)	(0)	(0)	(0)
minimal	0	0	0	0	0	0
sarcoma; malignant; primary; incidental	0	0	0	0	0	0
Ear;						
Examined	(0)	(0)	(0)	(0)	(0)	(0)
Within Normal Limits	0	0	0	0	0	0
hyperplasia; epidermal	(0)	(0)	(0)	(0)	(0)	(0)
moderate	0	0	0	0	0	0
inflammation	(0)	(0)	(0)	(0)	(0)	(0)
moderate	0	0	0	0	0	0
Epididymides;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	26	15	0
inflammation	(0)	(0)	(0)	(0)	(1)	(0)
moderate	0	0	0	0	1	0
sperm granuloma	0	0	0	1	0	0
oligospermia	(0)	(0)	(0)	(0)	(1)	(0)
moderate	0	0	0	0	1	0
dilation	(0)	(0)	(0)	(0)	(1)	(0)
moderate	0	0	0	0	1	0
metaplasia; squamous	(0)	(0)	(0)	(0)	(1)	(0)

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	MALES					
Removal Reason: Terminal Sacrifice	0 mg/kg/ day	1000 mg/kg /day	500 mg/kg /day	1000 mg/kg /day	2000 mg/kg /day	4000 mg/kg /day
Number of Animals on Study :	30	0	25	27	16	0
Number of Animals Completed:	(30)	(0)	(25)	(27)	(16)	(0)
Epididymides; (continued)						
moderate	0	0	0	0	1	0
Esophagus;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	26	16	0
inflammation; muscularis	(0)	(0)	(0)	(1)	(0)	(0)
mild	0	0	0	1	0	0
Eyes;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	27	16	0
Gall Bladder;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	27	16	0
missing	0	0	0	0	0	0
inclusion; eosinophilic; epithelium	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	0	0	0
Harderian Glands;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	27	0	23	27	14	0
hyperplasia	(1)	(0)	(0)	(0)	(1)	(0)
moderate	0	0	0	0	1	0
marked	1	0	0	0	0	0
adenoma; benign; primary; incidental	2	0	2	0	0	0
carcinoma; malignant; primary; incidental	0	0	0	0	1	0
Heart;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	27	16	0
sarcoma; atrium; malignant; primary; incidental	0	0	0	0	0	0
Intestine, Cecum;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	27	16	0

Pathology - Intergroup Comparison of Histo Pathology Observations

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	MALES					
Removal Reason: Terminal Sacrifice	0 mg/kg/ day	1000 mg/kg /day	500 mg/kg /day	1000 mg/kg /day	2000 mg/kg /day	4000 mg/kg /day
Number of Animals on Study :	30	0	25	27	16	0
Number of Animals Completed:	(30)	(0)	(25)	(27)	(16)	(0)
Intestine, Colon;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	27	16	0
Intestine, Duodenum;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	21	16	9	0
infiltration; pigmented macrophages	(0)	(0)	(4)	(11)	(7)	(0)
minimal	0	0	4	11	7	0
Intestine, Ileum;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	24	27	16	0
inflammation; muscularis	(0)	(0)	(1)	(0)	(0)	(0)
mild	0	0	1	0	0	0
herniation; glandular	(0)	(0)	(1)	(0)	(0)	(0)
mild	0	0	1	0	0	0
Intestine, Jejunum;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	27	16	0
Intestine, Rectum;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	27	16	0
proliferation; vascular; serosa	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	0	0	0
Kidneys;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	27	0	24	25	16	0
infarction	(0)	(0)	(0)	(1)	(0)	(0)
minimal	0	0	0	1	0	0
inflammation; pelvis; artery	(1)	(0)	(0)	(0)	(0)	(0)
mild	1	0	0	0	0	0
necrosis; corticomedullary junction; tubule; bilateral	(0)	(0)	(0)	(1)	(0)	(0)
mild	0	0	0	1	0	0

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Pathology - Intergroup Comparison of Histo Pathology Observations

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	MALES					
Removal Reason: Terminal Sacrifice	0 mg/kg/day	1000 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day
Number of Animals on Study :	30	0	25	27	16	0
Number of Animals Completed:	(30)	(0)	(25)	(27)	(16)	(0)
Kidneys; (continued)						
regeneration; tubule	(1)	(0)	(0)	(0)	(0)	(0)
mild	1	0	0	0	0	0
infiltration; lymphoplasmacytic	(0)	(0)	(0)	(0)	(0)	(0)
marked	0	0	0	0	0	0
infiltration; lymphoplasmacytic; pelvis	(1)	(0)	(0)	(0)	(0)	(0)
mild	1	0	0	0	0	0
dilation; cortex; tubule; unilateral	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	0	0	0
glomerulonephrosis; right	(0)	(0)	(0)	(0)	(0)	(0)
marked	0	0	0	0	0	0
hemangiosarcoma; malignant; primary; incidental	0	0	1	0	0	0
Liver;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	17	0	22	24	15	0
inflammation; portal	(1)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	0	0	0
moderate	1	0	0	0	0	0
necrosis	(1)	(0)	(0)	(0)	(1)	(0)
minimal	1	0	0	0	1	0
moderate	0	0	0	0	0	0
depletion; glycogen	(0)	(0)	(0)	(1)	(0)	(0)
mild	0	0	0	1	0	0
infiltration, lipid	(10)	(0)	(2)	(1)	(0)	(0)
minimal	0	0	0	1	0	0
mild	10	0	2	0	0	0
tension lipidosis	(0)	(0)	(1)	(1)	(0)	(0)
minimal	0	0	1	1	0	0
extra-medullary hematopoiesis	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	0	0	0
telangiectasis	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	0	0	0
hepatocellular adenoma; benign; primary; incidental	1	0	0	0	0	0
Lungs With Bronchi;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	MALES					
Removal Reason: Terminal Sacrifice	0 mg/kg/day	1000 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day
Number of Animals on Study :	30	0	25	27	16	0
Number of Animals Completed:	(30)	(0)	(25)	(27)	(16)	(0)
Lungs With Bronchi; (continued)						
Within Normal Limits	20	0	17	14	7	0
thrombosis	(0)	(0)	(0)	(0)	(0)	(0)
minimal	0	0	0	0	0	0
mild	0	0	0	0	0	0
hyperplasia; alveolar epithelium	(1)	(0)	(1)	(1)	(1)	(0)
minimal	1	0	0	1	0	0
mild	0	0	0	0	0	0
moderate	0	0	0	0	0	0
marked	0	0	1	0	1	0
infiltration, histiocytic	(8)	(0)	(6)	(12)	(8)	(0)
minimal	5	0	1	5	2	0
mild	3	0	5	6	6	0
moderate	0	0	0	1	0	0
ossification	(0)	(0)	(0)	(0)	(0)	(0)
minimal	0	0	0	0	0	0
missing	0	0	0	1	0	0
alveolar-bronchiolar adenoma; single; benign; primary; incidental	1	0	2	1	1	0
alveolar-bronchiolar carcinoma; malignant; primary; incidental	0	0	0	0	0	0
hemangiosarcoma; malignant; primary; incidental	0	0	1	0	0	0
Lymph Node, Mesenteric;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	29	0	24	22	4	0
infiltration; pigmented macrophages	(0)	(0)	(1)	(5)	(12)	(0)
minimal	0	0	1	4	8	0
mild	0	0	0	1	4	0
necrosis; lymphoid	(1)	(0)	(0)	(0)	(1)	(0)
minimal	0	0	0	0	1	0
mild	1	0	0	0	0	0
missing	0	0	0	0	0	0
Lymph Node, Mandibular;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	29	0	23	23	13	0
missing	1	0	0	0	1	0
hyperplasia; lymphoid	(0)	(0)	(2)	(4)	(2)	(0)

Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	MALES					
Removal Reason: Terminal Sacrifice	0 mg/kg/ day	1000 mg/kg /day	500 mg/kg /day	1000 mg/kg /day	2000 mg/kg /day	4000 mg/kg /day
Number of Animals on Study :	30	0	25	27	16	0
Number of Animals Completed:	(30)	(0)	(25)	(27)	(16)	(0)
Lymph Node, Mandibular; (continued)						
minimal	0	0	0	1	1	0
mild	0	0	2	3	1	0
plasmacytosis	(0)	(0)	(0)	(1)	(1)	(0)
minimal	0	0	0	1	1	0
mild	0	0	0	0	0	0
hemangiosarcoma; malignant; secondary; incidental	0	0	0	0	0	0
Mammary Gland;						
Examined	(-)	(-)	(-)	(-)	(-)	(-)
Within Normal Limits	-	-	-	-	-	-
lymphangioma; benign; primary; incidental	-	-	-	-	-	-
Nerve, Sciatic;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	27	16	0
Ovaries;						
Examined	(-)	(-)	(-)	(-)	(-)	(-)
Within Normal Limits	-	-	-	-	-	-
Pancreas;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	24	27	16	0
depletion; zymogen	(0)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	0	0	0
inflammation	(0)	(0)	(1)	(0)	(0)	(0)
minimal	0	0	1	0	0	0
Parathyroid Glands;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	23	0	23	20	14	0
missing	6	0	2	7	2	0
pigmentation	(1)	(0)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	0	0

AD29PL7G8 - AD29PL.7G8M.BTL:Epanova: 26-week Repeated Dose Oral Carcinogenicity
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	MALES					
Removal Reason: Terminal Sacrifice	0 mg/kg/ day	1000 mg/kg /day	500 mg/kg /day	1000 mg/kg /day	2000 mg/kg /day	4000 mg/kg /day
Number of Animals on Study :	30	0	25	27	16	0
Number of Animals Completed:	(30)	(0)	(25)	(27)	(16)	(0)
Pituitary Gland;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	24	27	16	0
missing	0	0	1	0	0	0
Prostate Gland;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	27	16	0
Salivary Glands;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	29	0	25	26	16	0
inflammation, pyogranulomatous; peripheral; adipocyte	(1)	(0)	(0)	(1)	(0)	(0)
minimal	1	0	0	1	0	0
hemangiosarcoma; malignant; primary; incidental	0	0	0	0	0	0
Seminal Vesicles;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	27	16	0
Spinal Cord, Cervical;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	27	16	0
cyst; keratinized	0	0	0	0	0	0
Spinal Cord, Thoracic;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	27	16	0
Spinal Cord, Lumbar;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	30	0	25	27	16	0
Spleen;						
Examined	(30)	(0)	(25)	(27)	(16)	(0)
Within Normal Limits	24	0	25	23	15	0
pigmentation, hemosiderin	(2)	(0)	(0)	(1)	(0)	(0)

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	MALES					
Removal Reasons: All of those SELECTED	0 mg/kg/day	1000 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day
Number of Animals on Study :	30	20	30	30	30	30
Number of Animals Completed:	(30)	(20)	(30)	(30)	(30)	(30)
Spleen; (continued)						
depletion; lymphoid	(0)	(0)	(1)	(1)	(0)	(0)
mild	0	0	1	1	0	0
pigmentation, hemosiderin	(2)	(0)	(0)	(1)	(1)	(0)
minimal	0	0	0	0	1	0
mild	2	0	0	1	0	0
necrosis; lymphoid	(0)	(0)	(0)	(3)	(8)	(7)
minimal	0	0	0	1	0	0
mild	0	0	0	2	8	6
moderate	0	0	0	0	0	1
inflammation, acute	(0)	(0)	(0)	(0)	(0)	(1)
mild	0	0	0	0	0	1
extra-medullary hematopoiesis	(0)	(1)	(1)	(2)	(0)	(0)
mild	0	1	1	2	0	0
hemangiosarcoma; malignant; primary; incidental	4	15	0	1	0	1
hemangiosarcoma; malignant; primary; fatal	0	1	0	0	0	0
Stomach;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	26	0	23	23	20	19
erosion; non-glandular	(0)	(0)	(0)	(0)	(0)	(1)
minimal	0	0	0	0	0	1
hyperplasia; non-glandular	(0)	(0)	(2)	(4)	(6)	(11)
minimal	0	0	1	2	5	5
mild	0	0	0	1	1	3
moderate	0	0	1	0	0	3
marked	0	0	0	1	0	0
ulceration; non-glandular	(0)	(0)	(0)	(1)	(0)	(0)
marked	0	0	0	1	0	0
vacuolation; glandular; epithelium	(0)	(0)	(0)	(1)	(0)	(0)
minimal	0	0	0	1	0	0
infiltration, inflammatory cells; glandular	(4)	(0)	(5)	(4)	(4)	(1)
minimal	4	0	3	4	4	1
mild	0	0	2	0	0	0
pustule	(0)	(0)	(0)	(0)	(1)	(0)
mild	0	0	0	0	1	0
autolysis	0	0	0	0	1	0

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	MALES					
Removal Reasons: All of those SELECTED	0 mg/kg/day	1000 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day
Number of Animals on Study :	30	20	30	30	30	30
Number of Animals Completed:	(30)	(20)	(30)	(30)	(30)	(30)
Stomach; (continued)						
papilloma; benign; primary; incidental	0	0	0	0	1	0
Testes;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	29	0	30	29	29	30
atrophy; right	(1)	(0)	(0)	(0)	(0)	(0)
mild	1	0	0	0	0	0
degeneration; subcapsular	(0)	(0)	(0)	(0)	(1)	(0)
mild	0	0	0	0	1	0
hemangioma; benign; primary; incidental	0	0	0	1	0	0
Thymus;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	26	28	22	22
hyperplasia; epithelial	(0)	(0)	(1)	(0)	(0)	(0)
mild	0	0	1	0	0	0
hyperplasia; lymphoid	(0)	(0)	(1)	(0)	(0)	(0)
moderate	0	0	1	0	0	0
necrosis	(0)	(0)	(0)	(0)	(3)	(4)
minimal	0	0	0	0	2	1
mild	0	0	0	0	1	3
involution	(0)	(0)	(2)	(2)	(5)	(7)
minimal	0	0	0	0	0	3
mild	0	0	0	0	4	4
moderate	0	0	2	2	1	0
Thyroid Glands;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	27	0	25	28	28	28
cyst	3	0	5	2	2	2
Trachea;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	27	29	23	30
inflammation	(0)	(0)	(3)	(1)	(7)	(0)
minimal	0	0	1	0	1	0

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	MALES					
Removal Reasons: All of those SELECTED	0 mg/kg/day	1000 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day
Number of Animals on Study :	30	20	30	30	30	30
Number of Animals Completed:	(30)	(20)	(30)	(30)	(30)	(30)
Trachea; (continued)						
mild	0	0	1	0	4	0
marked	0	0	1	1	2	0
Urinary Bladder;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	29	30	29	30
mineralization; serosa; artery	(0)	(0)	(1)	(0)	(1)	(0)
minimal	0	0	1	0	1	0
Skeletal Muscle (Thigh);						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	3	0	3	1	5	0
myopathy	27	0	27	29	25	30
infiltration; mast cell	(0)	(0)	(1)	(0)	(0)	(0)
minimal	0	0	1	0	0	0
inflammation; artery	(0)	(0)	(0)	(0)	(1)	(0)
mild	0	0	0	0	1	0
Ncf;						
Examined	(1)	(1)	(1)	(1)	(9)	(5)
Within Normal Limits	0	0	0	0	0	0
no microscopic correlation	1	1	1	1	9	5
Skin (Mammary Area);						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	29	29	30	29
inflammation	(0)	(0)	(0)	(1)	(0)	(0)
minimal	0	0	0	1	0	0
lymphangioma; benign; primary; incidental	0	0	1	0	0	0
Artery, Mesenteric;						
Examined	(5)	(0)	(8)	(6)	(11)	(2)
Within Normal Limits	0	0	0	0	0	0
thrombosis	(5)	(0)	(8)	(6)	(11)	(1)
minimal	0	0	0	0	1	0
mild	0	0	1	2	2	1

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	MALES					
Removal Reasons: All of those SELECTED	0 mg/kg/day	1000 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day
Number of Animals on Study :	30	20	30	30	30	30
Number of Animals Completed:	(30)	(20)	(30)	(30)	(30)	(30)
Artery, Mesenteric; (continued)						
moderate	5	0	7	4	8	0
proliferation	(0)	(0)	(0)	(0)	(0)	(1)
moderate	0	0	0	0	0	1
Skull Cap;						
Examined	(0)	(0)	(1)	(0)	(0)	(0)
Within Normal Limits	0	0	0	0	0	0
hemangiosarcoma; malignant; primary; incidental	0	0	1	0	0	0

Pathology - Intergroup Comparison of Histo Pathology Observations

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	FEMALES					
Removal Reasons: All of those SELECTED	0 mg/kg/day	1000 mg/kg /day	500 mg/kg /day	1000 mg/kg /day	2000 mg/kg /day	4000 mg/k /day
Number of Animals on Study :	30	20	30	30	30	30
Number of Animals Completed:	(30)	(20)	(30)	(30)	(30)	(30)
Multi-centric Tumours;						
hemangiosarcoma; malignant; fatal	1	-	-	-	-	-
Adrenal Glands;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	30	30	30	30
Aorta;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	30	29	30	30
periarteritis nodosa	(0)	(0)	(0)	(1)	(0)	(0)
mild	0	0	0	1	0	0
Bone Marrow, Femur;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	30	30	30	30
Bone Marrow, Sternum;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	30	30	30	30
Bone, Femur;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	30	30	30	30
Bone, Sternum;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	30	28	28	30
necrosis; costo-chondral junction	(0)	(0)	(0)	(1)	(1)	(0)
minimal	0	0	0	0	1	0
mild	0	0	0	1	0	0
inflammation, pyogranulomatous; peripheral; adipocyte	(0)	(0)	(0)	(0)	(1)	(0)
mild	0	0	0	0	1	0
alveolar-bronchiolar carcinoma; malignant; secondary; fatal	0	0	0	1	0	0
Brain;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)

Pathology - Intergroup Comparison of Histo Pathology Observations

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	FEMALES					
Removal Reasons: All of those SELECTED	0 mg/kg/day	1000 mg/kg /day	500 mg/kg /day	1000 mg/kg /day	2000 mg/kg /day	4000 mg/kg /day
Number of Animals on Study :	30	20	30	30	30	30
Number of Animals Completed:	(30)	(20)	(30)	(30)	(30)	(30)
Brain; (continued)						
Within Normal Limits	29	0	29	30	30	30
proliferation; vascular; meninges	(1)	(0)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	0	0
congestion	(0)	(0)	(1)	(0)	(0)	(0)
mild	0	0	1	0	0	0
Cavity, Nasal;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	5	0	11	2	3	1
inflammation; submucosa	(25)	(0)	(17)	(25)	(23)	(28)
minimal	22	0	11	21	18	25
mild	3	0	6	4	5	3
inflammation, exudative	(0)	(0)	(2)	(11)	(20)	(29)
minimal	0	0	1	2	4	5
mild	0	0	0	5	10	15
moderate	0	0	1	4	6	8
marked	0	0	0	0	0	1
hypertrophy/hyperplasia; epithelium	(0)	(0)	(0)	(0)	(1)	(1)
mild	0	0	0	0	1	0
moderate	0	0	0	0	0	1
inflammation, granulomatous	(0)	(0)	(0)	(0)	(1)	(0)
minimal	0	0	0	0	1	0
sarcoma; malignant; primary; incidental	0	0	1	0	0	0
Ear;						
Examined	(0)	(0)	(0)	(0)	(1)	(1)
Within Normal Limits	0	0	0	0	0	0
hyperplasia; epidermal	(0)	(0)	(0)	(0)	(1)	(1)
moderate	0	0	0	0	1	1
inflammation	(0)	(0)	(0)	(0)	(1)	(1)
moderate	0	0	0	0	1	1
Esophagus;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	30	30	30	29
inflammation; muscularis	(0)	(0)	(0)	(0)	(0)	(1)

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	FEMALES					
Removal Reasons: All of those SELECTED	0 mg/kg/day	1000 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/k/day
Number of Animals on Study :	30	20	30	30	30	30
Number of Animals Completed:	(30)	(20)	(30)	(30)	(30)	(30)
Esophagus; (continued)						
mild	0	0	0	0	0	1
Eyes;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	30	30	30	30
Gall Bladder;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	27	26	29	26
autolysis	0	0	2	3	1	4
missing	0	0	0	1	0	0
inclusion; eosinophilic; epithelium	(0)	(0)	(1)	(0)	(0)	(0)
mild	0	0	1	0	0	0
Harderian Glands;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	28	0	29	30	30	30
adenoma; benign; primary; incidental	1	0	1	0	0	0
carcinoma; malignant; primary; incidental	1	0	0	0	0	0
Heart;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	29	29	30	30
periarteritis nodosa	(0)	(0)	(0)	(1)	(0)	(0)
mild	0	0	0	1	0	0
sarcoma; atrium; malignant; primary; incidental	0	0	1	0	0	0
Intestine, Cecum;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	30	30	29	30
inflammation	(0)	(0)	(0)	(0)	(1)	(0)
moderate	0	0	0	0	1	0
Intestine, Colon;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	30	30	30	27

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Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	FEMALES					
Removal Reasons: All of those SELECTED	0 mg/kg/day	1000 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/k/day
Number of Animals on Study :	30	20	30	30	30	30
Number of Animals Completed:	(30)	(20)	(30)	(30)	(30)	(30)
Intestine, Colon; (continued)						
autolysis	0	0	0	0	0	3
Intestine, Duodenum;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	15	18	18	13
infiltration; pigmented macrophages	(0)	(0)	(14)	(10)	(12)	(13)
minimal	0	0	14	10	12	13
autolysis	0	0	1	2	0	4
Intestine, Ileum;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	29	27	29	24
autolysis	0	0	1	3	1	6
Intestine, Jejunum;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	29	27	30	25
autolysis	0	0	1	3	0	5
Intestine, Rectum;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	29	0	30	30	30	30
proliferation; vascular; serosa	(1)	(0)	(0)	(0)	(0)	(0)
mild	1	0	0	0	0	0
Kidneys;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	29	30	29	28
infiltration; lymphoplasmacytic	(0)	(0)	(0)	(0)	(0)	(1)
marked	0	0	0	0	0	1
dilation; cortex; tubule; bilateral	(0)	(0)	(0)	(0)	(1)	(1)
mild	0	0	0	0	1	1
dilation; cortex; tubule; unilateral	(0)	(0)	(1)	(0)	(0)	(0)
mild	0	0	1	0	0	0
glomerulonephrosis; right	(0)	(0)	(0)	(0)	(0)	(1)
marked	0	0	0	0	0	1

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	FEMALES					
Removal Reasons: All of those SELECTED	0 mg/kg/day	1000 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day
Number of Animals on Study :	30	20	30	30	30	30
Number of Animals Completed:	(30)	(20)	(30)	(30)	(30)	(30)
Liver;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	27	0	22	25	20	16
inflammation; portal	(0)	(0)	(1)	(0)	(0)	(0)
mild	0	0	1	0	0	0
necrosis	(1)	(0)	(1)	(0)	(2)	(3)
minimal	1	0	0	0	0	2
mild	0	0	0	0	2	1
moderate	0	0	1	0	0	0
depletion; glycogen	(0)	(0)	(5)	(5)	(10)	(13)
mild	0	0	5	5	10	13
infiltration, lipid	(0)	(0)	(0)	(0)	(1)	(1)
mild	0	0	0	0	1	1
tension lipidosis	(1)	(0)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	0	0
extra-medullary hematopoiesis	(1)	(0)	(2)	(0)	(1)	(0)
minimal	1	0	1	0	0	0
mild	0	0	1	0	1	0
telangiectasis	(0)	(0)	(1)	(0)	(0)	(0)
mild	0	0	1	0	0	0
Lungs With Bronchi;						
Examined	(30)	(20)	(30)	(30)	(30)	(30)
Within Normal Limits	14	0	17	15	12	16
thrombosis	(0)	(0)	(1)	(2)	(0)	(0)
minimal	0	0	1	1	0	0
mild	0	0	0	1	0	0
hyperplasia; alveolar epithelium	(1)	(0)	(0)	(1)	(1)	(1)
minimal	1	0	0	0	0	0
mild	0	0	0	1	1	0
moderate	0	0	0	0	0	1
infiltration, histiocytic	(16)	(0)	(7)	(12)	(13)	(11)
minimal	13	0	4	9	6	6
mild	3	0	3	3	6	5
moderate	0	0	0	0	1	0
inflammation, acute; bronchus	(0)	(0)	(2)	(1)	(4)	(2)
moderate	0	0	1	1	2	2

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	FEMALES					
Removal Reasons: All of those SELECTED	0 mg/kg/day	1000 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day
Number of Animals on Study :	30	20	30	30	30	30
Number of Animals Completed:	(30)	(20)	(30)	(30)	(30)	(30)
Lungs With Bronchi; (continued)						
marked	0	0	1	0	2	0
bronchiectasis	(0)	(0)	(1)	(0)	(0)	(0)
mild	0	0	1	0	0	0
inflammation, granulomatous	(0)	(0)	(1)	(0)	(0)	(0)
minimal	0	0	1	0	0	0
inflammation; bronchiole	(0)	(0)	(1)	(0)	(1)	(1)
minimal	0	0	0	0	0	1
mild	0	0	1	0	1	0
inflammation; interstitium	(0)	(0)	(0)	(0)	(0)	(1)
minimal	0	0	0	0	0	1
ossification	(0)	(0)	(0)	(1)	(0)	(0)
minimal	0	0	0	1	0	0
atelectasis	(0)	(0)	(0)	(0)	(0)	(1)
marked	0	0	0	0	0	1
missing	0	0	1	0	0	0
alveolar-bronchiolar adenoma; single; benign; primary; incidental	0	0	1	0	3	3
alveolar-bronchiolar adenoma; multiple; benign; primary; incidental	0	13	0	0	0	0
alveolar-bronchiolar adenoma; multiple; benign; primary; fatal	0	7	0	0	0	0
alveolar-bronchiolar carcinoma; malignant; primary; incidental	1	11	1	0	0	0
alveolar-bronchiolar carcinoma; malignant; primary; fatal	0	3	0	1	0	0
hemangiosarcoma; malignant; primary; incidental	0	4	0	0	0	0
Lymph Node, Mesenteric;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	24	20	8	5
infiltration; pigmented macrophages	(0)	(0)	(5)	(9)	(18)	(20)
minimal	0	0	5	5	11	5
mild	0	0	0	4	7	15
necrosis; lymphoid	(0)	(0)	(1)	(1)	(9)	(8)
minimal	0	0	0	0	2	2
mild	0	0	1	1	7	6
autolysis	0	0	0	0	0	1
missing	0	0	0	0	0	2
Lymph Node, Mandibular;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	FEMALES					
Removal Reasons: All of those SELECTED	0 mg/kg/day	1000 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day
Number of Animals on Study :	30	20	30	30	30	30
Number of Animals Completed:	(30)	(20)	(30)	(30)	(30)	(30)
Lymph Node, Mandibular; (continued)						
Within Normal Limits	22	0	24	26	23	22
missing	0	0	2	1	1	3
hyperplasia; lymphoid	(8)	(0)	(3)	(2)	(3)	(2)
minimal	4	0	2	2	2	1
mild	4	0	1	0	1	1
plasmacytosis	(0)	(0)	(1)	(0)	(2)	(2)
minimal	0	0	1	0	2	0
mild	0	0	0	0	0	2
necrosis; lymphoid	(0)	(0)	(0)	(1)	(2)	(3)
minimal	0	0	0	1	2	3
congestion	(0)	(0)	(0)	(0)	(1)	(0)
mild	0	0	0	0	1	0
hemangiosarcoma; malignant; secondary; incidental	0	0	1	0	0	0
lymphangioma; benign; primary; incidental	0	0	0	0	1	0
Mammary Gland;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	29	30	29	30
hemangiosarcoma; malignant; primary; fatal	0	0	0	0	1	0
lymphangioma; benign; primary; incidental	0	0	1	0	0	0
Nerve, Sciatic;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	30	30	30	30
Ovaries;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	30	30	30	30
Pancreas;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	29	0	27	27	29	29
depletion; zymogen	(1)	(0)	(3)	(2)	(0)	(1)
mild	0	0	3	2	0	1
moderate	1	0	0	0	0	0
periarteritis nodosa	(0)	(0)	(0)	(1)	(0)	(0)

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	FEMALES					
Removal Reasons: All of those SELECTED	0 mg/kg/day	1000 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/k/day
Number of Animals on Study :	30	20	30	30	30	30
Number of Animals Completed:	(30)	(20)	(30)	(30)	(30)	(30)
Pancreas; (continued)						
mild	0	0	0	1	0	0
periarteritis	(0)	(0)	(0)	(0)	(1)	(0)
mild	0	0	0	0	1	0
Parathyroid Glands;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	28	0	28	25	30	28
missing	2	0	2	5	0	2
Pituitary Gland;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	28	30	30	30
missing	0	0	2	0	0	0
Salivary Glands;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	27	0	28	30	30	29
inflammation, pyogranulomatous; peripheral; adipocyte	(2)	(0)	(0)	(0)	(0)	(1)
minimal	2	0	0	0	0	1
hemangiosarcoma; malignant; primary; incidental	0	0	1	0	0	0
hemangiosarcoma; malignant; primary; fatal	0	0	1	0	0	0
Skin;						
Examined	(1)	(0)	(0)	(0)	(0)	(1)
Within Normal Limits	0	0	0	0	0	0
hemangiosarcoma; malignant; primary; fatal	0	0	0	0	0	1
Spinal Cord, Cervical;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	29	0	30	30	29	30
cyst; keratinized	1	0	0	0	1	0
Spinal Cord, Thoracic;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	30	30	30	30

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	FEMALES					
Removal Reasons: All of those SELECTED	0 mg/kg/day	1000 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day
Number of Animals on Study :	30	20	30	30	30	30
Number of Animals Completed:	(30)	(20)	(30)	(30)	(30)	(30)
Spinal Cord, Lumbar;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	30	30	30	30
Spleen;						
Examined	(30)	(20)	(30)	(30)	(30)	(30)
Within Normal Limits	27	1	22	27	24	18
pigmentation, hemosiderin	(1)	(0)	(3)	(0)	(1)	(0)
minimal	1	0	2	0	0	0
mild	0	0	1	0	1	0
necrosis; lymphoid	(0)	(0)	(2)	(3)	(3)	(11)
minimal	0	0	1	0	0	0
mild	0	0	1	3	3	11
extra-medullary hematopoiesis	(1)	(3)	(4)	(0)	(2)	(1)
mild	0	0	1	0	1	1
moderate	0	2	1	0	0	0
marked	1	1	2	0	1	0
hemangiosarcoma; malignant; primary; incidental	1	12	1	0	1	0
hemangiosarcoma; malignant; primary; fatal	0	7	0	0	0	0
Stomach;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	24	0	29	29	22	23
erosion; glandular	(0)	(0)	(0)	(0)	(1)	(0)
minimal	0	0	0	0	1	0
hyperplasia; non-glandular	(0)	(0)	(1)	(0)	(5)	(3)
minimal	0	0	0	0	3	2
mild	0	0	1	0	2	0
moderate	0	0	0	0	0	1
vacuolation; glandular; epithelium	(0)	(0)	(0)	(0)	(0)	(2)
minimal	0	0	0	0	0	1
mild	0	0	0	0	0	1
infiltration, inflammatory cells; glandular	(5)	(0)	(0)	(0)	(0)	(1)
minimal	3	0	0	0	0	1
mild	2	0	0	0	0	0
pustule	(0)	(0)	(1)	(0)	(1)	(0)
mild	0	0	1	0	1	0

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	FEMALES					
Removal Reasons: All of those SELECTED	0 mg/kg/day	1000 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day
Number of Animals on Study :	30	20	30	30	30	30
Number of Animals Completed:	(30)	(20)	(30)	(30)	(30)	(30)
Stomach; (continued)						
autolysis	0	0	0	1	0	1
papilloma; benign; primary; incidental	1	0	0	0	1	0
Thymus;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	26	0	26	24	15	13
hyperplasia; epithelial	(0)	(0)	(0)	(1)	(1)	(1)
minimal	0	0	0	1	1	0
marked	0	0	0	0	0	1
necrosis	(0)	(0)	(0)	(2)	(4)	(2)
minimal	0	0	0	1	4	2
mild	0	0	0	1	0	0
involution	(3)	(0)	(4)	(3)	(11)	(13)
minimal	3	0	1	2	4	6
mild	0	0	1	1	7	6
moderate	0	0	1	0	0	1
marked	0	0	1	0	0	0
missing	0	0	0	1	1	1
inflammation, granulomatous	(1)	(0)	(0)	(0)	(0)	(0)
mild	1	0	0	0	0	0
Thyroid Glands;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	27	0	28	27	24	27
cyst	3	0	2	2	6	2
hyperplasia; follicle	(1)	(0)	(0)	(0)	(0)	(0)
mild	1	0	0	0	0	0
inflammation	(1)	(0)	(0)	(0)	(0)	(0)
mild	1	0	0	0	0	0
missing	0	0	0	0	0	1
periarteritis nodosa	(0)	(0)	(0)	(1)	(0)	(0)
mild	0	0	0	1	0	0
Trachea;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	28	28	24	22

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	FEMALES					
Removal Reasons: All of those SELECTED	0 mg/kg/day	1000 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day
Number of Animals on Study :	30	20	30	30	30	30
Number of Animals Completed:	(30)	(20)	(30)	(30)	(30)	(30)
Trachea; (continued)						
inflammation	(0)	(0)	(2)	(2)	(6)	(8)
mild	0	0	0	0	1	4
moderate	0	0	1	1	1	1
marked	0	0	1	1	4	3
Urinary Bladder;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	29	0	30	29	30	29
mineralization; serosa; artery	(1)	(0)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	0	0
periarteritis nodosa	(0)	(0)	(0)	(1)	(0)	(0)
mild	0	0	0	1	0	0
autolysis	0	0	0	0	0	1
Uterus;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	25	0	28	28	28	27
dilation	(1)	(0)	(0)	(0)	(0)	(0)
marked	1	0	0	0	0	0
proliferation; vascular	(3)	(0)	(2)	(0)	(0)	(1)
minimal	1	0	0	0	0	1
mild	1	0	1	0	0	0
moderate	0	0	1	0	0	0
marked	1	0	0	0	0	0
atrophy	(1)	(0)	(0)	(1)	(2)	(2)
mild	1	0	0	1	2	2
hemangiosarcoma; malignant; primary; incidental	0	0	1	1	0	0
Vagina;						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	30	0	30	30	30	30
Skeletal Muscle (Thigh);						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	1	0	1	2	2	3
myopathy	29	0	29	28	28	27

AD29PL7G8 - AD29PL.7G8R.BTL:Epanova: 26-Week Repeated Dose Oral Carcinogenicty
Study In Tg.rasH2 Mice (AD29PL7G8, Tg.rasH2 main study, TA AD29PL)

Observations: Neo-Plastic and Non Neo-Plastic	FEMALES					
Removal Reasons: All of those SELECTED	0 mg/kg/day	1000 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/
Number of Animals on Study :	30	20	30	30	30	30
Number of Animals Completed:	(30)	(20)	(30)	(30)	(30)	(30)
Ncf;						
Examined	(1)	(0)	(4)	(3)	(4)	(5)
Within Normal Limits	0	0	0	0	0	0
no microscopic correlation	1	0	4	3	4	5
Skin (Mammary Area);						
Examined	(30)	(0)	(30)	(30)	(30)	(30)
Within Normal Limits	28	0	30	30	30	30
inflammation	(2)	(0)	(0)	(0)	(0)	(0)
minimal	2	0	0	0	0	0
Artery, Mesenteric;						
Examined	(0)	(0)	(1)	(0)	(1)	(1)
Within Normal Limits	0	0	0	0	0	0
thrombosis	(0)	(0)	(1)	(0)	(1)	(1)
mild	0	0	0	0	1	0
moderate	0	0	1	0	0	1
Skull Cap;						
Examined	(0)	(0)	(1)	(0)	(0)	(0)
Within Normal Limits	0	0	0	0	0	0
hemangiosarcoma; malignant; secondary; incidental	0	0	1	0	0	0

(b) (4)

Historical Control Database of rasH2 Mouse 6 Month Studies

Vehicle (Negative) Control TgrasH2 Mice	Male		
Study Numbers	Total	%	Range
Number of Animals Examined	600	100.0	
Lungs			
Lungs, adenoma; single	57	9.5	0-6
Lungs, adenoma; multiple	8	1.3	0-1
Lungs, carcinoma	4	0.7	0-2
Combined incidence of lung tumors			0-7
Spleen			
Spleen, hemangiosarcoma	19	3.2	0-4
Multiple organs Hemangiosarcoma other than spleen			
Testes	4	0.7	0-1
Liver	1	0.2	0-1
Lungs	1	0.2	0-1
Seminal vesicles	1	0.2	0-1
Nasal cavity	1	0.2	0-1
Subcutis	1	0.2	0-1
Bone Marrow, Sternum	1	0.2	0-1
Epididymides	1	0.2	0-1
Multiple organs Hemangioma			
Liver	1	0.2	0-1
Lymph node	1	0.2	0-1
Penis	1	0.2	0-1
Combined incidence of hemangiosarcoma and hemangioma in all organs			0-4
Other Tumors			
Spleen, lymphoma	1	0.2	0-1
Skin, papilloma	2	0.3	0-1
Harderian glands, adenoma	8	1.3	0-2
Stomach, nonglandular, papilloma	2	0.3	0-1
Stomach, nonglandular, squamous cell carcinoma	2	0.3	0-1
Skin, sarcoma	1	0.2	0-1
Prostate, transitional cell carcinoma	1	0.2	0-1
Multiple organ, mesothelioma	2	0.3	0-1
Jaw. Sarcoma	1	0.2	0-1
Liver, adenoma	1	0.2	0-1
Thyroid gland, adenoma	1	0.2	0-1
Multi-centric, sarcoma	1	0.2	0-1
Madible, squamous cell carcinoma	1	0.2	0-1
Nasal Cavity, adenoma	3	0.5	0-2

(b) (4)

Historical Control Database of rasH2 Mouse 6 Month Studies

Vehicle (Negative) Control TgrasH2 Mice	Female		
Study Numbers	Total	%	Range
Number of Animals Examined	600	100.0	
Lungs			
Lungs, adenoma; single	38	6.3	0-6
Lungs, adenoma; multiple	5	0.8	0-1
Lungs, carcinoma	4	0.7	0-1
Combined incidence of lung tumors			0-6
Spleen			
Spleen, hemangiosarcoma	22	3.7	0-4
Multiple organs Hemangiosarcoma other than spleen			
Mammary glands	1	0.2	0-1
Skin (multiple sites)	3	0.5	0-1
Uterus	9	1.5	0-2
Lungs	1	0.2	0-1
Kidney	1	0.2	0-1
Bone	1	0.2	0-1
Ovary	2	0.3	0-1
Subcutis	1	0.2	0-1
Multi-centric	1	0.2	0-1
Vagina	1	0.2	0-1
Combined incidence of hemangiosarcoma in all organs			0-5
Other Tumors			
Spleen, lymphoma	4	0.7	0-2
Spleen, leukemia	2	0.3	0-1
Liver, leukemia	1	0.2	0-1
Harderian glands, adenoma	17	2.8	0-4
Harderian glands, carcinoma	3	0.5	0-2
Stomach, nonglandular, papilloma	3	0.5	0-1
Stomach, nonglandular, squamos cell carcinoma	1	0.2	0-1
Lymphoma, multiple organ	3	0.5	0-1
Skin; squamos cell carinoma	1	0.2	0-1
Nasal cavity, adenocarcinoma	5	0.8	0-1
Ovaries; teratoma	1	0.2	0-1
Ovaries; leiomyosarcoma	1	0.2	0-1
Multiple organ, mesothelioma	2	0.3	0-1
Thymus, thymoma	2	0.3	0-1
Salivary glands, mesothelioma	1	0.2	0-1
Multi-centric, lymphangioma	1	0.2	0-1
Multi-centic, mesothelioma	1	0.2	0-1
Stomach; adenocarcinoma	1	0.2	0-1

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/s/

PARVANEH ESPANDIARI
03/28/2014

KAREN L DAVIS BRUNO
03/28/2014
AP

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 205060 **Applicant:** Omthera Pharmaceuticals, Inc. **Stamp Date:** 7/03/2013

Drug Name: Epanova (omefas) Capsules **NDA Type:** 505(b)(1)

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		The eCTD submission has 5 modules – regional, common technical document summary, quality, nonclinical study reports, and clinical study reports.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		Nonclinical studies were conducted based on the Agency's recommendation during the PNDA meeting. The Sponsor conducted carcinogenicity, mutagenicity, teratogenicity, effects on fertility, and repeat dose toxicity studies. No formal safety pharmacology and ADME studies have been conducted with Epanova because of well-established information in the published literatures.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		All nonclinical studies were conducted with the same formulation and the route of the administration that are planned to be marketed.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		The proposed labeling has data express human dose multiples in mg/m2.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		According to the Sponsor, "(b) (4) is to be considered the starting material, which is also consistent with the guidance of ICH Q7 for an active pharmaceutical ingredient derived from an animal source."
11	Has the applicant addressed any abuse potential issues in the submission?		X	
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			All relevant studies have been submitted.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

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

Parvaneh Espandiari, Ph.D

Reviewing Pharmacologist Date

Karen Davis Bruno, Ph.D

Team Leader/Supervisor Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PARVANEH ESPANDIARI
08/08/2013

KAREN L DAVIS BRUNO
08/08/2013