CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208956Orig1s000

NON-CLINICAL 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:	208956
Supporting document/s:	SDN 1
Applicant's letter date:	August 29, 2016
CDER stamp date:	August 29, 2016
Product:	Triptorelin pamoate for (b) (4) suspension
Indication:	Central precocious puberty
Applicant:	Arbor Pharmaceuticals
Review Division:	DMEP
Reviewer:	Federica Basso
Supervisor/Team Leader:	Ron Wange
Division Director:	Jean-Marc Guettier
Project Manager:	Jennifer Johnson

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 208986 are owned by Arbor Pharmaceuticals or are data for which Arbor Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of NDA 208986 that Arbor Pharmaceuticals does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 208986.

TABLE OF CONTENTS

Table of Tables

Table of Figures

1 Executive Summary

1.1 Introduction

Triptorelin is a synthetic analog of the endogenous gonadotropin-releasing hormone (GnRH). Triptorelin 6-month formulation is a sustained release formulation of triptorelin pamoate designed to achieve and maintain LH suppression to prepubertal levels in children with central (gonadotropin-dependent) precocious puberty (CPP). The same formulation is approved for the palliative treatment of men with advanced prostate cancer under NDA22437.

1.2 Brief Discussion of Nonclinical Findings

Pharmacology and toxicology data have been submitted and reviewed under NDA 20715, 21288, and 22437, triptorelin 1-, 3-, and 6-month formulation for the prostate cancer indication. Arbor Pharmaceuticals has a written right-of-reference to these earlier submissions. No new nonclinical studies were submitted for the CPP indication.

General toxicity studies were conducted in rats, dogs, and monkeys for up to 6-month duration, with a recovery period of 2-month in monkeys and 4-month in male rats. In all species tested, toxicity was consistent with the drug pharmacology: decrease in serum LH and testosterone levels and suppression of testicular and ovarian function were observed starting at the clinical dose. All changes were reversible at dose cessation, except for the testicular changes in male rats (tubular atrophy, mineralization, and maturation arrest), which were partially reversible.

Increased incidence and earlier onset of pituitary adenoma and carcinoma were observed in a carcinogenicity study in rats starting at the clinical dose. Pituitary tumors appear to be species specific and are related to hyper-stimulation of the pituitary in the absence of negative feedback control by the gonadotrope hormones. No tumors were observed in mice at doses up to 8 fold the clinical dose, based on body surface area.

Following a wash out period and restoration of estrous cycle, no adverse effect on fertility was observed in females treated with triptorelin for two months. Embryofetal development studies showed maternal toxicity (decrease in maternal weight) and embryotoxicity (pre-implantation loss, increased resorptions, and reduced number of viable fetuses) in rats at 8-fold the clinical dose. None of these effects were apparent in mice at the same multiples to the clinical dose. Triptorelin was not teratogenic in mice or rats.

1.3 Recommendations

1.3.1 Approvability

Pharmacology/Toxicology recommends approval of triptorelin 6-month formulation for CPP.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The language proposed in the label is similar to the current label for the cancer indication. The safety margins have been corrected using a body weight of 20 kg and a Km value of 25.

8.1 Pregnancy

Risk Summary
TRIPTODUR is contraindicated in women who are pregnant [see Contraindications (4)] since expected hormonal changes that occur with TRIPTODUR treatment increase the risk for pregnancy loss. (b) (4) available data with triptorelin use in pregnant women are insufficient to determine a drug-associated risk of adverse developmental outcomes. Based on mechanism of action in humans and findings of increased pregnancy loss in animal studies TRIPTODUR may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% -20%, respectively.

Data

Animal Data

In pregnant rats administered triptorelin at doses of 2, 10, and 100 mcg/kg/day during the period of organogenesis, maternal toxicity (decrease in (b) (4) body weight) and embryo-fetal toxicity(pre-implantation loss, increased resorption, and reduced number of viable fetuses) was observed at 100 ug/kg, approximately 4 times the clinical dose based on body surface area. No embryonic and fetal developmental toxicities were observed in mice at doses up to 4 times the clinical dose. Teratogenic effects were not observed in viable fetuses in rats or mice.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis was evaluated in an 18-month study in mice and a 24-month study in rats. In rats, triptorelin doses of 120, 600, and 3000 mcg/kg given every 28 days (approximately 0.2, 0.8, and 4 times the human monthly dose based on body surface area) resulted in increased mortality with a drug treatment period of 13 to 19 months. The incidences of benign and malignant pituitary tumors and histosarcomas were increased in a dose-related manner. There were no treatment-related tumors in mice at exposure up to 4 fold higher than the clinical dose based on body surface area.

Mitogenicity studies performed with triptorelin using bacterial and mammalian systems (in vitro Ames test and chromosomal aberration test in CHO cells and an in vivo mouse micronucleus test) provided no evidence of mutagenic potential.

After 60 days of subcutaneous treatment followed by a minimum of four estrus cycles prior to mating, triptorelin at doses of 2, 20, and 200 mcg/kg (approximately 0.07, 0.7, and 7 times the estimated human daily dose based on body surface area) or two monthly injections as slow release microspheres (~20 mcg/kg/day) had no effect on the fertility or general reproductive function of female rats.

No studies were conducted to assess the effect of triptorelin on male fertility.

2 Drug Information

2.1 Drug

CAS Registry Number
57773-63-4

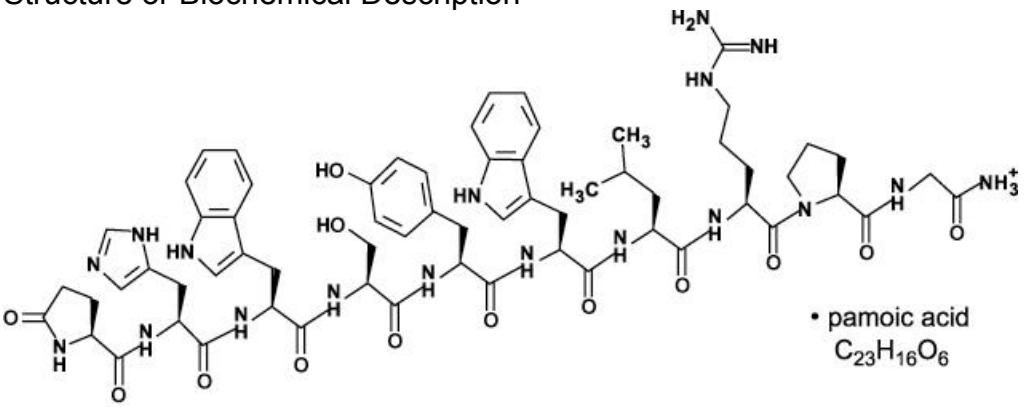
Generic Name
Triptorelin Pamoate

Code Name
D-Trp6-LHRH, Decapeptyl, CL118532

Chemical Name
5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-Lleucyl- L-arginyl-L-prolylglycine amide (pamoate salt)

Molecular Formula/Molecular Weight
$C_{64}H_{82}N_{18}O_{13} \cdot C_{23}H_{16}O_6$/1699.9

Structure or Biochemical Description



Pharmacologic Class
Gonadotropin releasing hormone (GnRH) agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 22058 (Histrelin, 1-year SC implant), NDA 20263 (Lupron Depot PED, 3-mo IM), NDA19886 (Synarel, nasal solution)

2.3 Drug Formulation

Triptorelin pamoate microgranules 22.5 mg is a sterile, lyophilized, biodegradable microgranule formulation supplied as a single-dose vial. For administration, 2 mL of Sterile Water for Injection is added to the vial containing the lyophilized microgranule formulation and mixed. The entire content of the vial is administered as a single dose.

Table 1. Quantitative composition for Triptorelin pamoate microgranules 22.5 mg

Ingredient	Reference to Quality Standard	Function	Quantity Per Dose	Quantity Per Vial[1]
triptorelin (peptide base) [triptorelin pamoate]	in-house DMF (b) (4)	active substance	22.5 mg 31 mg	(b) (4)
poly-*d,l*-lactide co-glycolide (b) (4)	in-house DMF (b) (4)	(b) (4)	(b) (4)	
(b) (4)				
mannitol	USP		74 mg	
carboxymethylcellulose sodium	NF		26 mg	
polysorbate 80	NF		1.7 mg	
water for injection	USP			(b) (4)
(b) (4)	NF			
	NF			
Total			(b) (4)	(b) (4)

(b) (4)

2.4 Comments on Novel Excipients

N/A

2.5 Comments on Impurities/Degradants of Concern

The triptorelin pamoate 6-month formulation is comprised of triptorelin peptide (b) (4) and poly(dl-lactide co-glycolide) (b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

TRIPTODUR 22.5 mg is administered as a single intramuscular injection once every 24 weeks in children with central precocious puberty.

2.7 Regulatory Background

Triptorelin pamoate 1-, 3-, and 6-month formulations are approved in the United States for the palliative treatment of prostate cancer (NDAs 20715, 21288, and 22437, respectively). Triptorelin pamoate for the treatment of central (gonadotropin-dependent) precocious puberty (CPP) has been approved in Europe since 1986 (1- and 3-month formulations).

The IND for triptorelin Pamoate 22.5 mg for the treatment of CPP was opened in May 2011. No new nonclinical studies were submitted, as a standard battery of nonclinical testing was performed with triptorelin pamoate under NDA 20715, triptorelin pamoate 1-month formulation, including evaluation of chronic toxicity in rats, dogs and monkeys, fertility and embryofetal development in mice and rats, and carcinogenicity studies in mice and rats. (b) (4) No additional nonclinical or juvenile animal studies were deemed necessary given the extensive clinical experience in the pediatric population with triptorelin 1- and 3-month formulations and other GnRH agonists.

3 Studies Submitted

3.1 Studies Reviewed

No new nonclinical studies were submitted for approval of triptorelin for the CPP indication. Nonclinical studies were conducted and reviewed under NDA 20715, triptorelin 1-month formulation for palliative treatment of prostate cancer.

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

NDA 20715, triptorelin pamoate 1-mo formulation for the palliative treatment of advanced prostate cancer.

4 Pharmacology

4.1 Primary Pharmacology

Triptorelin is a synthetic decapeptide agonist analog of the naturally occurring gonadotropin releasing hormone (GnRH), also called luteinizing hormone-releasing hormone (LHRH). GnRH is a decapeptide that is synthesized in the cell bodies of hypothalamic neurons and secreted in a pulsatile fashion directly into the hypothalamic-hypophyseal-portal circulation. On arrival at the anterior pituitary gland, GnRH selectively stimulates the gonadotroph cells to synthesize and release the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In turn, LH and FSH stimulate the gonadal production of sex steroid hormones and gametogenesis. Hypothalamic release of LHRH is controlled by bio-feedback mechanisms based on the amount of LH and FSH in the circulation. Administration of GnRH initially stimulates the release of LH and FSH, resulting in a temporary increase of gonadal steroidogenesis. However, continuous administration down-regulates pituitary GnRH receptors and results in suppression of pulsatile LH and FSH release, gonadal steroidogenesis, and gametogenesis.

Relatively to the native hormone, the substitution of the amino acid D-tryptophan at position 6 by L-glycine increases resistance to metabolic degradation and thus increases biological potency. In vitro studies have shown that triptorelin is 100-fold more active than native GnRH in stimulating LH release from monolayers of dispersed rat pituitary cells in culture, and 20-fold more active than native GnRH in displacing ^{125}I-GnRH from pituitary receptor sites (Pedroza et al 1977 and 1980). In immature male rats, triptorelin showed a 13-fold higher LH-releasing activity and 21-fold higher FSH-releasing activity than native GnRH (Coy et al 1976). Following a single intramuscular injection of triptorelin 6-month formulation in male SD rats, testosterone increased within the first 6 hours, and rapidly decreased and remained at castration levels thereafter (see PK/ADME section).

4.3 Safety Pharmacology

No treatment-related adverse effects were observed on the central nervous, cardiovascular, digestive, and renal systems of the rat at doses up to 1 mg/kg by SC or IV route (6mg/m^2, 36 fold the clinical dose) or in the cardiovascular system of the dog at doses up to 0.3 mg/kg by IV route (6 mg/m^2, 36 fold the clinical dose).

A muscle relaxant effect was noted in CD1 mice at 2-fold the clinical dose. However, no neuromuscular effects were noted in the long term chronic toxicity studies, suggesting a transient acute effect only.

CNS

In the Julou and Courvoisier muscle relaxation test in CD1 mice, triptorelin caused loss of motor capacity at doses of 0.1 and 1 mg/kg SC, with efficacy approximately one -half that of 1 mg/kg diazepam, and a maximal duration of 2 hours. While the muscle relaxant effect could be evocative of anxiolytic activity, no effects were seen in the other tests for anxiolytics (decrease in motor activity, antagonism of strychnine, potentialization of hypnotic effects of the barbiturates).

Table 2. Loss of motor capacity, % of falls vs. Ctrl (5% CI)

Drug	Dose mg/kg	Percentage falls			
		30 mn	60 mn	120 mn	180 mn
Diazepam	1	85 (62-97)	75 (51-91)	60 (81-56)	55 (32-77)
DTrp6-LHRH	0.01	0	0	0	0
	0.10	15 (3-38)	35 (15-59)	30 (12-54)	20 (6-44)
	1.00	20 (6-44)	40 (19-64)	20 (6-44)	10 (1-32)

Gastric secretion

Methods

Shay rat

Male SD rats were placed on a water-only diet for 24h. Pyloric ligature was carried out after laparotomy under light ether anesthesia. Triptorelin (0.1 and 1 mg/kg) and positive control (atropine sulfate, 1 mg/kg) were administered 30 minutes after ligature. Four hours after ligature, animals were sacrificed and the gastric contents taken. The following parameters were studied: volume secreted, pH, free acidity (dimethylaminoazobenzol indicator, pH 3.5), total acidity (phenolphthalein indicator, pH 8.5), and buffering power (differential acidity).

Gosh and Schild rat

Iffa Credo male Wistar rats were fasted for 48h in a cage with a perforated floor to avoid coprophagia. They were then anesthetized with urethane by intra-muscular injection; a catheter was introduced into the esophagus, and attached 5 mm above the cardia; a second catheter was introduced into the duodenum and fixed in place below the pylorus. After lavage of the stomach with 0.9% NaCl at 37.6°C, flowrate was set to a constant 0.7 ml/minute. After a 30 minute period of stabilization, the perfusate was collected every 10 minutes and acidity titrated with 0.01 N NaOH (phenolphthalein end-point). The first three specimens were used for calculation of mean basal acidity. Triptorelin (0.1 and 1 mg/kg), positive control (pentagastrin, 0.005 mg/kg) and physiological saline for the controls were then injected in a volume of 0.5 ml/100 g s.c.

Results

Triptorelin greatly increased basal gastric acid secretion in the Shay rat model at 1 mg/kg. However, no effect was observed with the Gosh and Schild method.

Table 3. Basal gastric secretion in the Shay rat model

Tests / Drug / Dose	Volume (ml)	Free acidity meq/4 h x 10^{-3}	Total acidity meq/4 h x 10^{-3}	Buffering power meq/4 h x 10^{-3}
Controls 5 ml/kg SC	4.25 ± 0.70 (2.595-5.905)	444.1 ± 94.97 (219.6-668.7)	524.5 ± 102.8 (281.5-767.5)	80.4 ± 10.18 (56.31.104.4)
Atropine sulfate 1 mg/kg SC	2.06 ± 0.37 (1.157-2.957)	145.6 ± 25.99 (81.95-209.2)	229.6 ± 38.5 (135.3-323.8)	84.0 ± 19.17 (37.07-130.9)
D-TRP6-LHRH 0.1 mg/kg	4.89 ± 1.12 (2.241-7.534)	537.3 ± 164.89 (133.7 - 940.8)	637.1 ± 167.2 (227.8-1046.5)	95.60 ± 10.9 (68.81-122.3)
D-TRP6-LHRH 1 mg/kg	7.55 ± 0.56 ** (6.235-8.865)	950.9 ± 93.6 ** (729.5- 1172)	1043 ± 86.6 ** (838.6-1248)	92.5 ± 19.7 (45.91-139.1)

Table 4. Basal secertion in the anestethized rat (Gosh and Schild method)

Drug	Dose mg/kg	Minimal acidity, mean value	Maximal acidity, mean value	Mean duration of maximal activity	p 100
Controls	0.5 ml/100 g SC	0.25 (0.199-0.308)	0.305 (0.145-0.465)	25.6 mn	+ 22 NS
Pentagastrin	0.005	0.22 (0.193-0.252)	0.619 (0.3779-0.8595)	42.5 mn	+ 181 ***
DTrp6-LHRH	0.1	0.20 (0.181-0.293)	0.269 (0.2120-0.3255)	42.5 mn	+ 35 NS
DTrp6-LHRH	1	0.20 (0.182-0.220)	0.275 (0.2292-0.3208)	46.3 mn	+ 38 NS

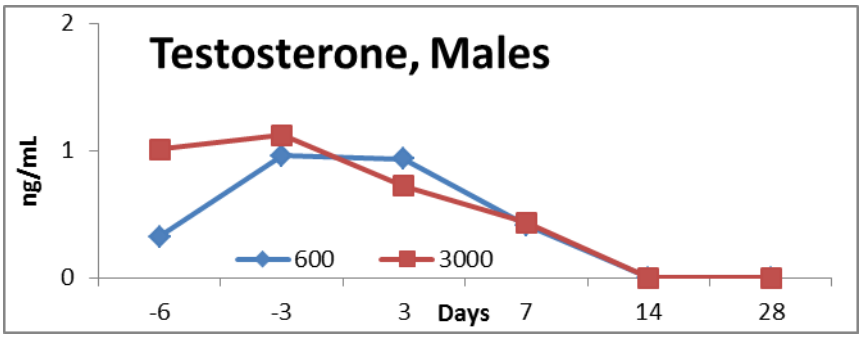
5 Pharmacokinetics/ADME/Toxicokinetics

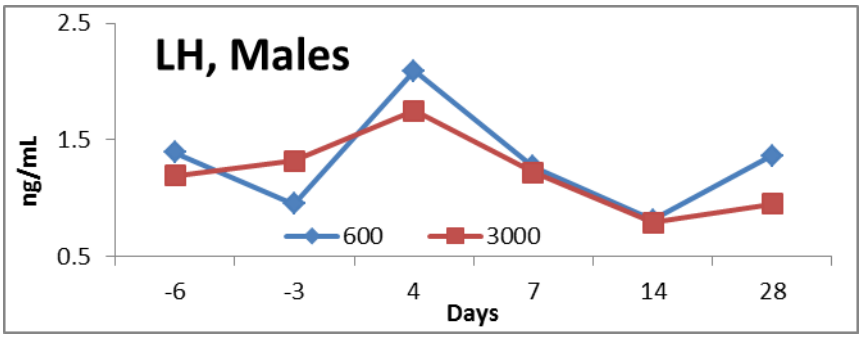
5.1 PK/ADME

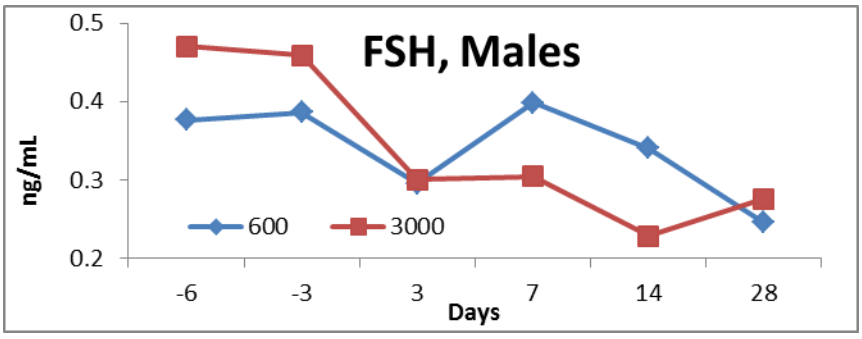
Pharmacokinetic studies with triptorelin pamoate were performed in rats and dogs. Following intramuscular injection of triptorelin pamoate microgranules (1-month formulation) in rats and dogs, there was a transient elevation of testosterone and LH (for 1-5 days), followed by a rapid decline and then continued suppression for 30-40 days. Following intramuscular injection of the triptorelin pamoate 6-month formulation in rats, testosterone rapidly decreased to very low levels and remained approximately at a plateau (~2.2 nmol/L) until Day 168 (24 weeks). A peak in serum triptorelin levels was measured within one day after administration, followed by a decrease up to Day 28 (4 weeks). Then, an increase of triptorelin levels, leading to a plateau of 800 to 1900 pg/mL, was observed until Day 140 (20 weeks). Triptorelin decreased to 300-350 pg/mL

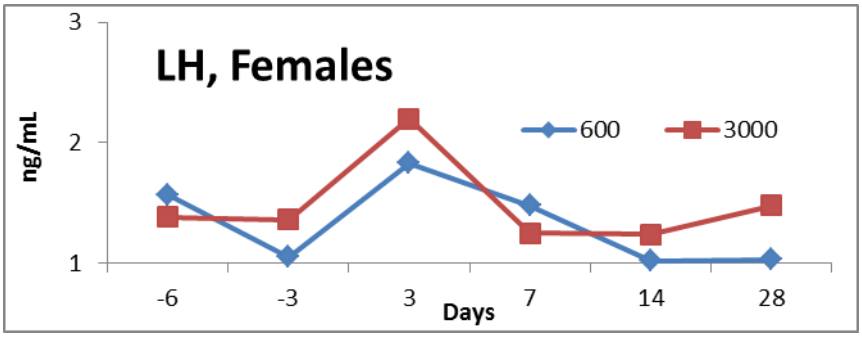
at Day 168 (24 weeks). The triptorelin release was consistently correlated with a low mean serum testosterone value.

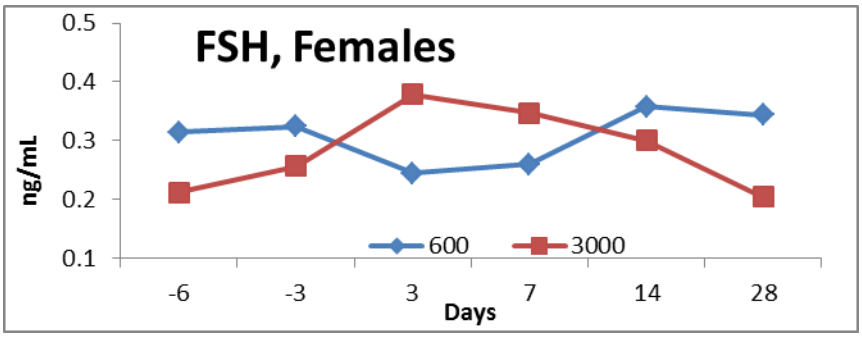
Table 5. Pharmacokinetics of triptorelin, testosterone, LH and FSH after a single IM administration of triptorelin pamoate 1-mo formulation in rats (Study # 88-3383)









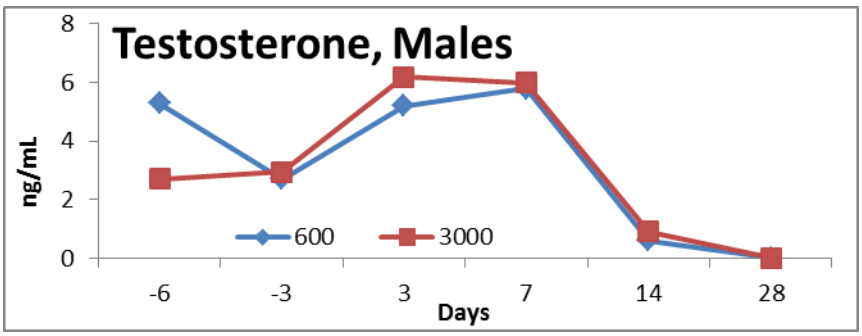


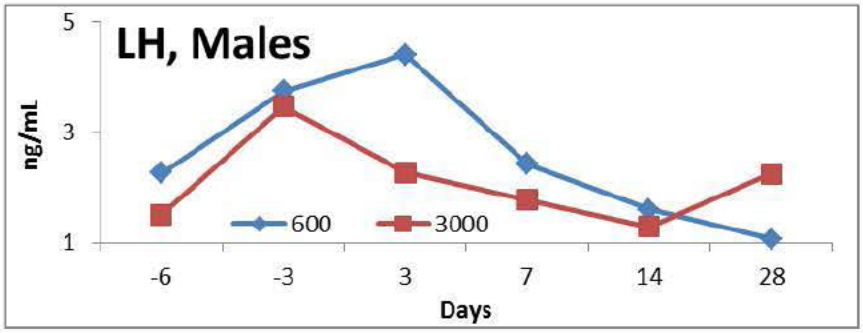
DECAPEPTYL RADIOIMMUNOASSAY

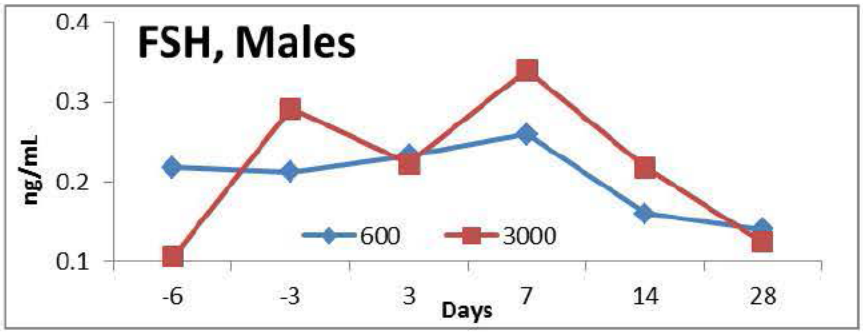
	Male		Female	
	600 mcg/kg	3000 mcg/kg	600 mcg/kg	3000 mcg/kg
Day:	pg/ml	pg/ml	pg/ml	pg/ml
1 (Pre-dose)	N.D.	N.D.	N.D.	N.D.
2 (5 Hr)	1932	36132	3225	22108
4	863	2234	906	2993
8	480	1609	374	3389
11	573	2579	320	4659
16	601	3281	461	5204
21	317	3422	317	3274
24	279	2973	150	3010
28	189	2119	111	1769
30	N.D.	1753	31	796

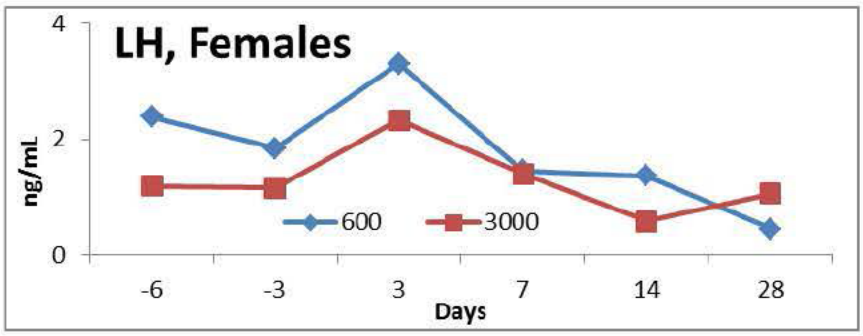
N.D. = Non detectable

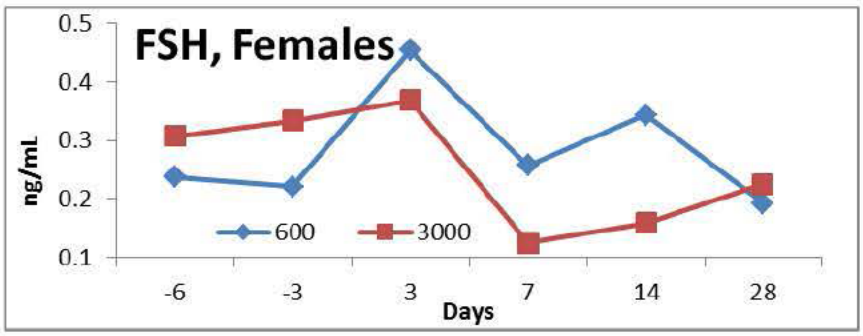
Table 6. Pharmacokinetics of triptorelin, testosterone, LH and FSH after a single IM administration of triptorelin pamoate 1-mo formulation in dogs (Study # 88-3885)




LH, Males
ng/mL
5
3
1
600
3000
-6
-3
3
7
14
28
Days


FSH, Males
ng/mL
0.4
0.3
0.2
0.1
600
3000
-6
-3
3
7
14
28
Days


LH, Females
ng/mL
4
2
0
600
3000
-6
-3
3
7
14
28
Days


FSH, Females
ng/mL
0.5
0.4
0.3
0.2
0.1
600
3000
-6
-3
3
7
14
28
Days

Project No. 88-3385 Dog
600 mcg/kg

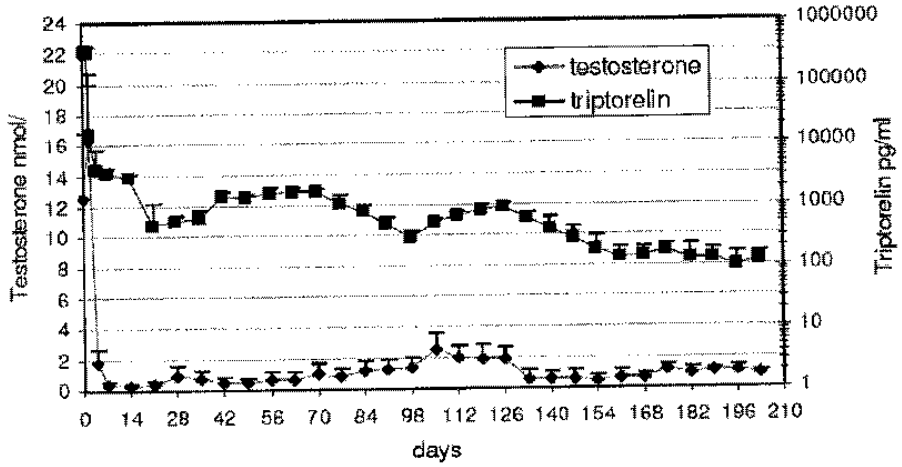
Day	Sample	pg/ml (mean ± S.D.	Day	Sample	pg/ml
0 (Pre-dose)	1 M	N.D.	16	21 M	1498[a]
	2 F	N.D.		22 F	3620 ± 164
0 (5 Hr)	5 M	20700 ± 2390	21	25 M	777 ± 64
	6 F	31610 ± 2775		26 F	1035 ± 46
4	9 M	611 ± 48	24	29 M	536 ± 137
	10 F	1107[a]		30 F	766 ± 89
8	13 M	974 ± 53	28	33 M	156 ± 31
	14 F	831 ± 178		34 F	943 ± 45
11	17 M	2215 ± 55	30	37 M	376 ± 75
	18 F	3039 ± 339		38 F	344 ± 37

[a] Sample volume did not allow replicates.

Project No. 88-3385 Dog
3000 mcg/kg

Day	Sample	pg/ml (mean ± S.D.	Day	Sample	pg/ml
0 (Pre-dose)	3 M	N.D.	16	23 M	5950 ± 239
	4 F	N.D.		24 F	16300 ± 1352
0 (5 Hr)	7 M	137933 ± 7435	21	27 M	11805 ± 1190
	8 F	105000 ± 7302		28 F	15663 ± 652
4	11 M	2022 ± 462	24	31 M	9408 ± 548
	12 F	1363 ± 202		32 F	11060 ± 1240
8	15 M	1162 ± 116	28	35 M	6810 ± 380
	16 F	802 ± 55		36 F	7166 ± 568
11	19 M	2392 ± 38	30	39 M	1250 ± 140
	20 F	2607 ± 217		40 F	2201 ± 142

Figure 1. Triptorelin and testoren levels in rats following a single IM injection of triptorelin 6-mo formulation



6 General Toxicology

Toxicity studies were conducted with triptorelin in rats, dogs, and monkey up to a 6-month duration (Table 7). Both the acetate and pamoate formulations were used, which showed a similar toxicity profile. Overall, triptorelin was well tolerated and findings were consistent with the expected physiological action of the drug. Decrease in serum levels of testosterone and LH, decrease in reproductive organ weights, atrophy of the testes and spermatogenic arrest, and atrophy of the ovary characterized by absence of developed follicles and corpora lutea were noted in all species starting at the clinical dose based on body surface area. Hyperplasia and adenoma of the adenohypophysis was noted in rats after 6-months of dosing, and lead to early mortality in a rat carcinogenicity study. Due to mortality, the 2-year study was terminated earlier, and pituitary adenomas were found in almost all treated rats. No tumors were noted in mice treated for 18 months at doses up to 4 fold the clinical dose based on body surface area.

Table 7. Toxicity studies conducted with triptorelin

Study type and duration (Study Number)	Route of Admin.	Species	Compound(s) administered	Location in NDA #20-715	
				Vol.	page
Single-dose toxicity	IP	Rat and mouse	Triptorelin acetate	1.20	003-017
Single-dose toxicity	SC	Rat and mouse	Triptorelin acetate	1.20	018-032
Subchronic repeat-dose toxicity 6 weeks (Study KM-83-718)	IM	Rat	Triptorelin acetate microspheres	1.20	033-203
Subchronic repeat-dose toxicity 3 months (Study 84103)	IM	Rat	Triptorelin acetate and triptorelin acetate microspheres	1.20	204-603
Chronic repeat-dose toxicity 6 months + 4 months recovery period (Study 84166)	IM	Rat	Triptorelin acetate and triptorelin acetate microspheres	1.27 1.28	001-329 001-361
Chronic repeat-dose toxicity 6 months (Study 88-3366)	IM	Rat	Triptorelin pamoate microgranules	1.21 1.22	001-384 001A-313
Chronic repeat-dose toxicity 6 months + 2 months recovery period (Study T514)	SC	Rat	Triptorelin acetate	1.23 1.24 1.25 1.26	001-556 001-473 001-530 001-455
Chronic repeat-dose toxicity 6 months (Study 88-3367)	IM	Dog	Triptorelin pamoate microgranules	1.32	005-468
Chronic repeat-dose toxicity 6 months (Study 84165)	IM	Dog	Triptorelin acetate and triptorelin acetate microspheres	1.29	001-183
Chronic repeat-dose 6 months (Study T633)	IM	Dog	Triptorelin acetate microspheres	1.29 1.30 1.31	183A-434 001-404 001-381
Chronic repeat-dose 6 months	SC	Monkey	Triptorelin acetate microspheres	1.33 1.34	001-426 001-373
in vitro Mutagenicity Study (Study 85007)	NIA	*Salmonella typhimurium*	Triptorelin acetate	1.47	001-023
in vitro Mutagenicity Study (Study 316)	NIA	*Salmonella typhimurium*	Triptorelin acetate	1.47	024-490
in vitro Mutagenicity Study (Study 2MLREJPS.005)	NIA	Mouse Lymphoma L5178Y Cells	Triptorelin acetate	1.47	055-086
In vitro Mutagenicity Study (Study E-9738-0-437)	NIA	Chinese Hamster Ovary Cells	Triptorelin acetate	1.47	030-054
In vivo Mutagenicity Study (Study 9738-0-455)	IP	Mouse	Triptorelin acetate	1.47	087-104

Study type and duration (Study Number)	Route of Admin.	Species	Compound(s) administered	Location in NDA #20-715	
				Vol.	page
Carcinogenicity study 18 months (Study 88-3370)	IM	Mouse	Triptorelin pamoate microgranules	1.35 1.36 1.37 1.38 1.39 1.40	001-608 001-339 001-361 001-483 001-436 001-445
Carcinogenicity study 24 months (Study 88-3371)	IM	Rat	Triptorelin pamoate microgranules	1.41 1.42 1.43 1.44 1.45 1.46	001-205 001-410 001-340 001-457 001-486 001-482
Fertility study (Study704-534/4)	SC IM	Rat	Triptorelin acetate and triptorelin acetate microspheres	1.48	001-324
Teratology study (Study 88-3368)	SC	Mouse	Triptorelin pamoate	1.47	105-490
Teratology study (Study 88-3369)	SC	Rat	Triptorelin pamoate	1.49	001-348
Reproductive and developmental toxicity (Study 691-534/3)	SC	Rabbit	Triptorelin acetate	1.49	349-394
Local tolerance (Study 014 TO 4E)	IM	Rat	Triptorelin acetate microspheres	Provided in this submission	
Local Tolerance	IM	Rat	Triptorelin acetate microspheres and triptorelin pamoate microgranules	Csernus et al 1990	

6.1 Single-Dose Toxicity

In acute toxicity studies, triptorelin was well tolerated in either mice or rats up to 10 mg/kg, which is above 179 fold the daily therapeutic dose in children (22.5mg/6mo, 167.5 ug/m^2 in a 20kg child, using a Km of 25). Mortality occurred at 100 and 200 mg/kg in rats and mice respectively, at above 3500 fold MRHD in either species.

6.2 Repeat-Dose Toxicity

Clinical observations, ophthalmoscopy, body weight, food consumption, hematology, clinical chemistry, urinalyses, macroscopic and microscopic changes were assessed in all toxicity studies.

A chronic 6 month toxicity study in the rat with Decapeptyl via intramuscular injection.

Study no.:	88-3366
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 2, 1989
GLP compliance:	No
QA statement:	Yes
Drug, lot #, and % purity:	Decapeptyl, DPG 0689, DPG 0889

Key Study Findings

Decrease in testosterone levels, atrophy of the reproductive organs, maturation arrest of testicular seminiferous tubules, oligospermia, and absence of developed follicles and corpora lutea in the ovary.

Methods

Doses:	60, 600, 3000 ug/kg/28day
Frequency of dosing:	Once a month, ~ every 28 days
Route of administration:	IM injection
Dose volume:	2 mL/Kg
Formulation/Vehicle:	Not specified
Species/Strain:	SD rats
Number/Sex/Group:	15 males and 20 females per group
Age:	12 weeks
Weight:	M: 371-440g. F: 240-285g
Satellite groups:	NA
Unique study design:	No
Deviation from study protocol:	NA

Table 8. Six-month rat study design

Group	Test Substance	Dose Level[a] mcg/kg	Dose Volume (ml/kg)	Number of Animals: Total M	Total F	Clinical Laboratory Studies Month 3 & 6 M	Clinical Laboratory Studies Month 3 & 6 F	Testosterone Levels M	Necropsy and Histopathology M	Necropsy and Histopathology F
I	Control	0	2	15	20	10	10	15	15	20
II	Decapeptyl	60	2	15	20	10	10	15	15	20
III	Decapeptyl	600	2	15	20	10	10	15	15	20
IV	Decapeptyl	3000	2	15	20	10	10	15	15	20

[a] The dose of Decapeptyl Microgranules was administered intramuscularly once per month for six months; theoretical daily doses are 2, 20 and 100 mcg/kg. Doses were based on previous studies conducted with this test material.

Observations and Results

Mortality

None

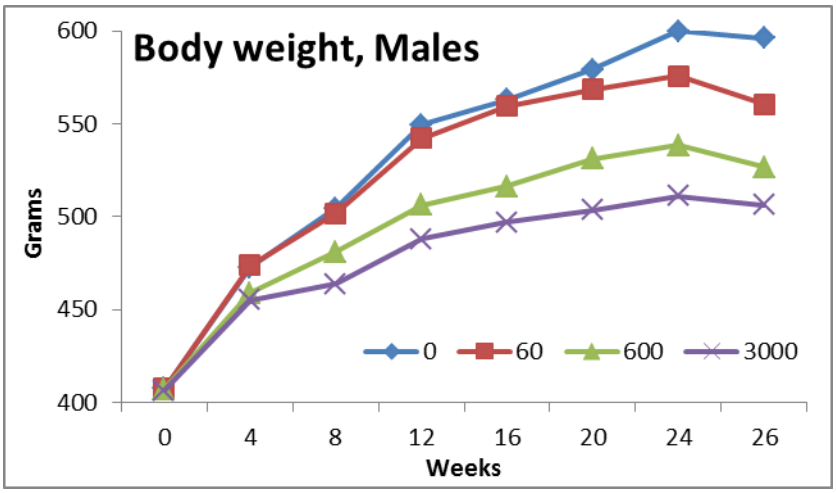
Clinical Signs

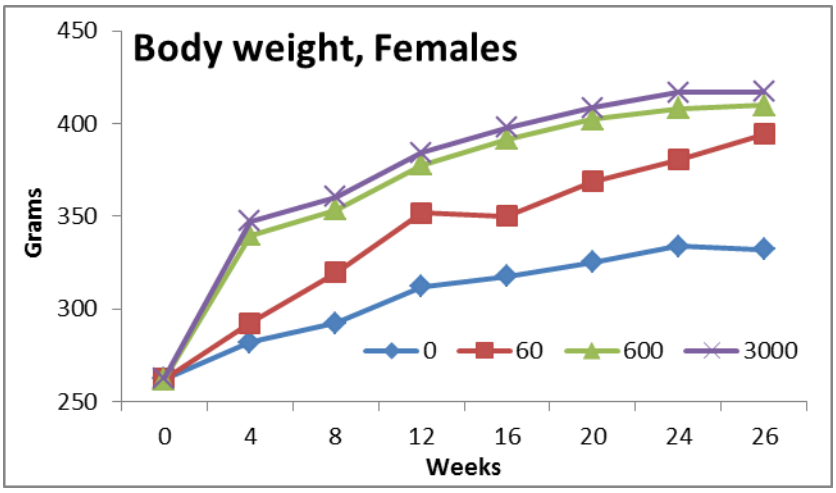
Unremarkable

Body Weights

Body weight was decreased in males (10-15%) and increased in females (6-23%), due to suppression of testosterone and estrogen in treated males and females, respectively.

Figure 2. Rat body weight





Feed Consumption

Slight decrease in food consumption was noted at >600 ug/kg during the first three months of dosing in males and throughout dosing in females.

Ophthalmoscopy

No treatment related changes were observed.

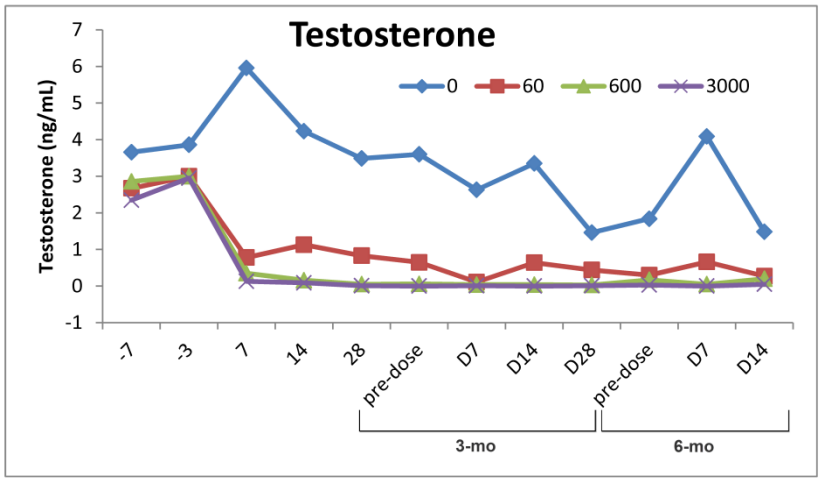
ECG

NA

Testosterone

Significant decrease in testosterone compared to control and baseline levels was noted in all treated male groups during the first week of dosing, and remained lower throughout the study.

Figure 3. Testosterone levels in rats



Hematology/Clinical Chemistry/ Urinalysis

No treatment related changes were observed at month 3 or 6 of dosing.

Gross Pathology

The reproductive organs of most treated rats appeared small when compared to the control rats.

Table 9. Summary of macroscopic findings in the rat

	Groups			
	I	II	III	IV
# of male rats examined:	15	15	15	15
Small				
Testes	1	11	13	15
Epididymides	0	4	11	12
Prostate	0	4	5	8
Seminal Vesicles	0	13	15	15
# of female rats examined:	20	20	20	20
Ovaries	1	17	20	19
Uterus	0	14	19	19

Organ Weights

Dose related decrease in mean absolute and relative testes, epididymes, prostate, ovaries, and pituitary weight.

Table 10. Organ weight changes in rats

Organ weight changes, % of controls								
	Males					Females		
	BW	Epi	Testes	Pituitary		BW	Ovary	Pituitary
60	-5	**-43**	**-39**	**-17**		**18**	**-78**	**-21**
600	**-12**	**-49**	**-59**	**-23**		**25**	**-88**	**-45**
3000	**-15**	**-72**	**-81**	**-24**		**26**	**-88**	**-46**

Bold values indicate statistical significant changes

Histopathology

Adequate Battery Yes

Peer Review No

Histological Findings

Testes

Dose related increased incidence of atrophy and maturation arrest of testicular seminiferous tubules, accompanied by epididymal oligospermia, in all treated male groups, and seminal vesicles and prostatic atrophy at ≥600 ug/kg.

Ovary

Ovarian atrophy characterized by absence of developed follicles and corpora lutea, in all treated female groups. No treatment-related changes were noted in the pituitary.

Table 11. Rat histopathological findings

ORGAN AND FINDING DESCRIPTION	NUMBER:	--- NUMBER OF ANIMALS ---							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	15	15	15	15	20	20	20	20
TESTES (TE)	NUMBER EXAMINED:	15	15	15	15	0	0	0	0
--B/SEMI[N]FEROUS TUBULES:ATROPHY/MATURATION ARREST		0	3	11	14	0	0	0	0
--U/DEGENERATION OF GERMINAL EPITHELIUM		1	0	0	0	0	0	0	0
--B/DEGENERATION OF GERMINAL EPITHELIUM		5	3	1	1	0	0	0	0
EPIDIDYMIDES (EP)	NUMBER EXAMINED:	15	15	15	15	0	0	0	0
--U/OLIGOSPERMIA		1	0	0	0	0	0	0	0
--B/OLIGOSPERMIA		2	8	12	15	0	0	0	0
--U/SPERM GRANULOMA		0	1	0	0	0	0	0	0
--B/SUBACUTE/CHRONIC INFLAMMATION		0	0	1	0	0	0	0	0
PROSTATE (PR)	NUMBER EXAMINED:	15	15	15	14	0	0	0	0
--ATROPHY		0	0	8	12	0	0	0	0
--SUBACUTE/CHRONIC INFLAMMATION		1	2	4	0	0	0	0	0
SEMINAL VESICLES (SV)	NUMBER EXAMINED:	15	15	15	15	0	0	0	0
--ATROPHY		0	0	8	14	0	0	0	0
OVARIES (OV)	NUMBER EXAMINED:	0	0	0	0	20	20	20	17
--U/ATROPHY		0	0	0	0	0	1	1	4
--B/ATROPHY		0	0	0	0	0	11	19	12
UTERUS (UT)	NUMBER EXAMINED:	0	0	0	0	20	19	19	20
--ATROPHY		0	0	0	0	0	12	19	17
--HYDROMETRA		0	0	0	0	1	2	0	0
PITUITARY GLAND (PG)	NUMBER EXAMINED:	15	0	0	15	20	0	0	19
--CONGESTION		0	0	0	0	1	0	0	0

Toxicokinetics

NA

Dosing Solution Analysis

NA

A chronic toxicity study of CL 118,532 after intramuscular administration to male rats with a recovery phase

Study no.:	84166
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 29, 1984
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CL118,532, batch # PC 0607, 81%

Key Study Findings

- Decrease in serum testosterone, LH and FSH, reproductive organ atrophy, oligospermia and spermatogenic maturation arrest. Testicular findings persisted into recovery.
- Hyperplasia of the adenohypophysis and adenomas, not reversible.

Methods

Doses:	Triptorelin microcapsule: 10, 20, 200 ug/kg Triptorelin solution: 20 ug/kg/day
Frequency of dosing:	Every 28 days
Route of administration:	IM injection
Dose volume:	Microcapsule: 0.25mL/100g Solution: 2.5 mL/kg
Formulation/Vehicle:	Microcapsules: aqueous tween 20/CMC 2% Solution: 0.9% NaCl
Species/Strain:	SD rats
Number/Sex/Group:	15 males/ group
Age:	17 weeks old
Weight:	324-577g
Satellite groups:	Recovery: 20 males/group
Unique study design:	No
Deviation from study protocol:	NA

Table 12. Six month male rat study design

Group	Treatment	Theoretical Daily Dose (mcg/kg)	Overall Mean Projected Daily Dose[a] (mcg/kg)	Number of Males
1	Microcapsule vehicle[b]	0	0.0	35
4	CL 118,532 (Microcapsule)	2	1.3	35
		5	1.7	
		10	6.3	
5	CL 118,532 (Microcapsule)	20	14.4	35
6	CL 118,532 (Microcapsule)	100	73.8	35
2	Saline vehicle	0	0.0	35
3	CL 118,532 (Solution)	20	16.6	35

[a] Based on concentration analyses and the anticipated release of drug in the case of the microcapsules.

Observations and Results

Mortality

There was no treatment-related mortality.

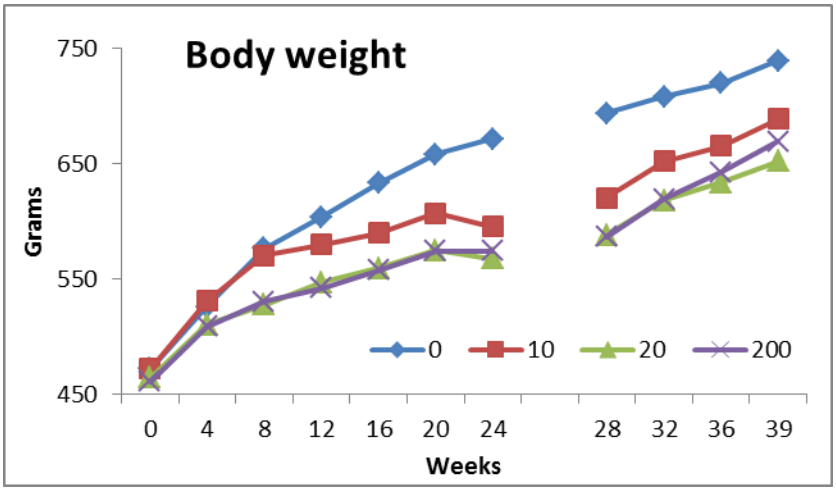
Clinical Signs

Unremarkable

Body Weights/Food Consumption

Body weight and food consumption was decreased in rats receiving triptorelin microcapsules. No changes were noted in the group receiving triptorelin solution.

Figure 4. Body weight in the male rat



% change vs. Ctrl		
ug/kg	Wk 24	Wk 39
10	-11	-7
20	-15	-12
200	-15	-9

Ophthalmoscopy

No treatment-related changes were observed.

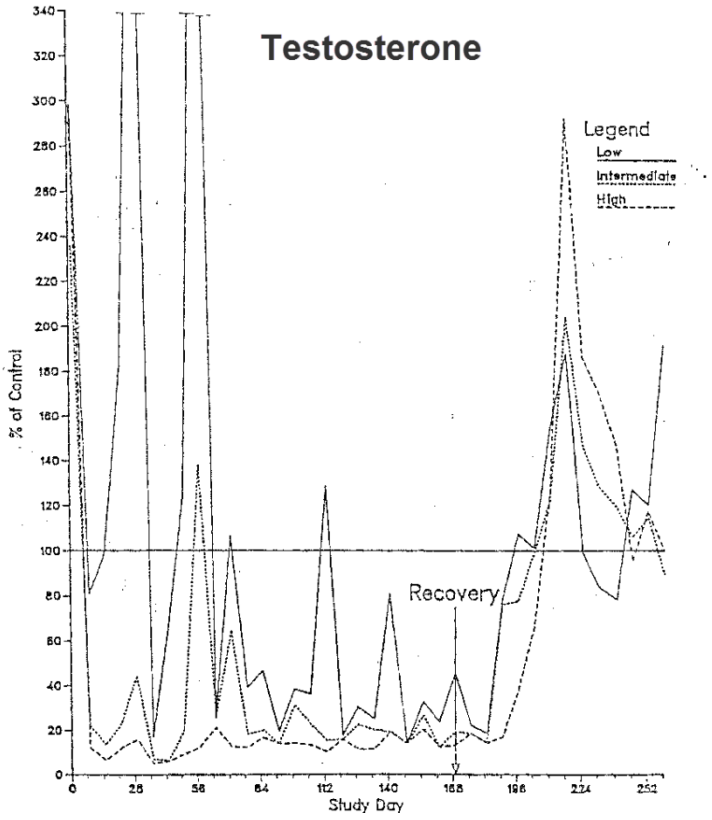
ECG

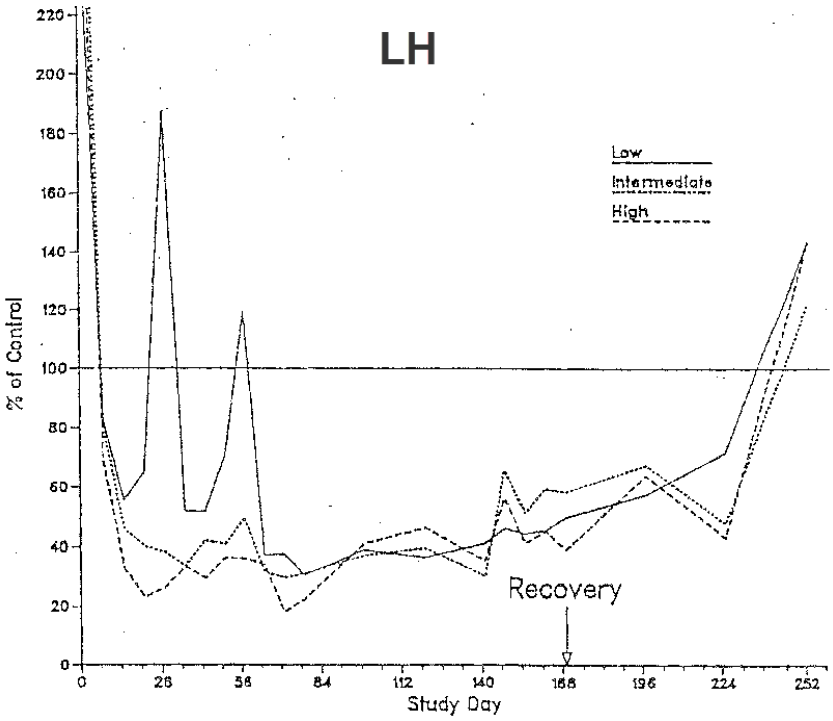
NA

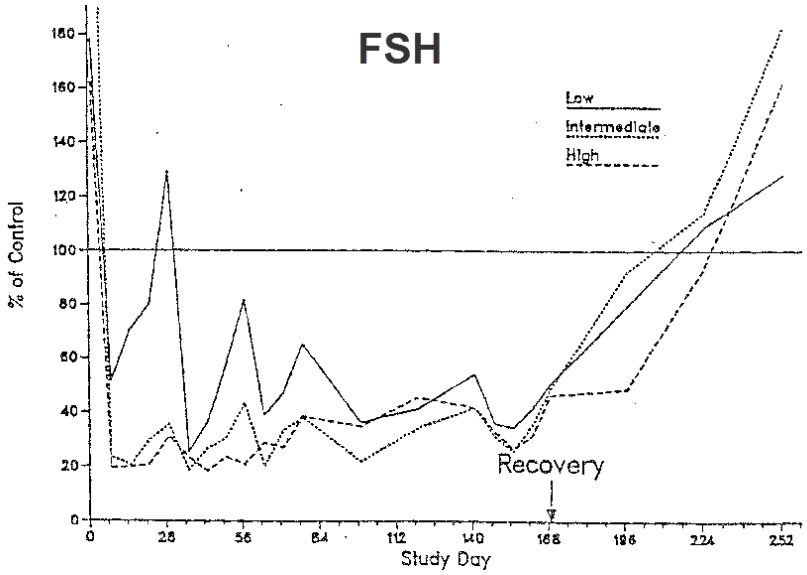
Hormones

Serum testosterone, LH and FSH were decreased with both triptorelin microcapsules (tables below) and solution (not shown). By the end of the recovery period, hormone levels were comparable or higher to that of controls.

Figure 5. Hormones levels in the male rat







Hematology/Clinical Chemistry/Urinalysis

No treatment related changes were observed during dosing or at the end of the 4-month recovery.

Gross Pathology

Reduction in size of testes, epididymis, prostate, and seminal vesicles was noted in all treated groups. The incidence was similar in both microcapsule and solution treated animals except for the flaccidity of testes which was increased in the high dose group of microcapsules. No treatment related gross findings were seen after the recovery phase.

Table 13. Macroscopic findings in the male rat

Incidence Summary of Drug Related Gross Postmortem Findings

Group Number in Group	1 15	2 15	3 15	4 15	5 15	6 15
Testes Flaccid	0	3	3	1	0	7
Testes small	0	5	13	14	13	15
Small prostate and seminal vesicles	1	2	12	12	14	11
Epididymis small	0	2	11	13	12	13

2	Saline vehicle	0	1	Microcapsule vehicle	0
3	CL 118,532 (Solution)	20 mcg/kg	4	CL 118,532 (Microcapsule)	10 mcg/kg
			5	CL 118,532 (Microcapsule)	20 mcg/kg
			6	CL 118,532 (Microcapsule)	100 mcg/kg

Organ Weights

Dose related decrease in testes and prostate weight was noted in all treatment groups, more notably in the microcapsule groups. All weights normalized by the end of recovery.

Table 14. Organ weight changes in the male rat

Organ weight changes % of controls						
Formulation	Dose ug/kg	Dosing			Recovery	
		Testes	Prostate		Testes	Prostate
Microcapsules	10	**-39**	**-57**		-6	-9
	20	**-47**	**-64**		**-8**	-9
	200	**-62**	**-69**		**-8**	**-16**
Solution	20	-23	-41		-10	-11

Bold values indicate statistical significant changes

Histopathology

Adequate Battery: Yes

Peer Review: No

Histological Findings
Reproductive organs
Tubular atrophy, mineralization, necrosis, and maturation arrest in the testes were noted in all treated groups. All findings persisted into recovery, except for the tubular necrosis. Interstitial cells hypertrophy was observed with triptorelin solution during dosing and recovery, and with the microcapsules during recovery. Oligospermia and prostate atrophy were noted in all treatment groups and were reversible.

Pituitary
Hyperplasia of the adenohypophysis and adenomas were noted in the triptorelin microcapsules treated groups during dosing and recovery, without dose relationship. In the triptorelin solution group, pituitary hyperplasia and adenomas were noted at the end of recovery.

Injection site
Injection site reactions were noted in all treatment groups (mononuclear cell accumulation with triptorelin solution, foreign body giant cell with triptorelin microcapsules) and were reversible.

Table 15. Microscopic findings in the male rat

Incidence Summary of Selected Microscopic Findings
(Initial Sacrifice)

Group	1	2	3	4	5	6
Number in Group	15	15	15	15	15	15
Testes						
Tubular Atrophy	0	8	14	5	4	8
Mineralization Tubules	0	2	13	4	4	5
Maturation Arrest	0	4	15	10	11	15
Tubular Necrosis	0	1	5	1	2	3
Decreased Spermatogenesis with Giant Cells	0	0	3	0	0	0
Hypertrophy Interstitial Cells	0	7	15	0	0	0
Epididymis						
Oligospermia	0	0	11	4	1	5
Desquamation	0	1	15	5	5	12
Aspermia	0	0	0	0	2	3
Atrophy	0	0	0	1	3	4
Prostate Gland						
Desquamation	6	7	6	4	3	4
Atrophy	0	0	1	1	4	7
Seminal Vesicles						
Atrophy	0	0	1	1	4	9
Injection Site						
Interstitial Accumulation Mononuclear Cells	1	5	3	0	0	0
Foreign Body Giant Cells	0	0	0	1	3	8
Pituitary Gland						
Hyperplasia Adenohypophysis	0	0	0	5	8	6
Adenoma	0	0	0	2	1	2

Table 16. Microscopic findings in the male rat, recovery period

Incidence Summary of Selected Microscopic Findings
(Recovery Sacrifice)

Group	1	2	3	4	5	6
Number in Group	20	20	20	20	20	20
Testes						
Maturation arrest	0	1	5	2	2	2
Tubular Atrophy	3	4	17	1	4	5
Mineralization Tubules	0	3	13	2	8	6
Edema Interstitial	13	11	12	10	10	10
Hypertrophy Interstitial Cells	5	3	10	5	4	3
Epididymis						
Oligospermia	3	2	0	0	0	0
Desquamation	2	2	2	0	0	0
Aspermia	0	0	0	0	0	0
Atrophy	0	0	0	0	0	0
Prostate Gland						
Desquamation	11	12	12	8	12	0
Mineralization	11	8	9	4	2	0
Acute Inflammation	8	9	5	6	2	3
Atrophy	0	0	0	0	0	0
Seminal Vesicles						
Atrophy	0	0	0	0	0	0
Pituitary Gland						
Hyperplasia Adenohypophysis	0	0	4	10	5	7
Adenoma	0	0	1	3	3	6

Toxicokinetics

NA

Dosing Solution Analysis

Triptorelin concentration was lower than the nominal concentration in all treatment groups (see study design table).

A 6-month toxicity study in the dog with decapeptyl microgranules (Pamoate 1-mo formulation) via intramuscular injection

Study no.:	88-3367
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 1988
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Decapeptyl, DPG 0689, DPG 0889

Key Study Findings

Decrease in serum testosterone in males, atrophy of male and female reproductive organs, maturation arrest/atrophy of the germinal epithelium, oligospermia, and decreased incidence of vesicular ovarian follicles and corpora lutea.

Methods

Doses:	60, 600, 3000 ug/kg IM
Frequency of dosing:	Once every 28 days
Route of administration:	IM injection
Dose volume:	1 mL/kg
Formulation/Vehicle:	Not stated
Species/Strain:	Beagle Dogs
Number/Sex/Group:	3 males/group; 5 females/group
Age:	14 months
Weight:	M: 9.6-14.4 Kg. F: 7.5-9.9 Kg
Satellite groups:	NA
Unique study design:	No
Deviation from study protocol:	NA

Table 17. Six month dog study design

Group mcg/kg	Test Substance	Dose Level[a]	Number of Animals: Total M	Total F	Clinical Laboratory Studies[b]: Pretest M	Pretest F	Month 3 & 6[c] M	Month 3 & 6[c] F	Testosterone Levels[d]: Pretest	Day 28	Month 3 & 6	Necropsy: Month 6 M	Necropsy: Month 6 F	Histopathology M	Histopathology F
I	Control[e]	0	3	5	3	5	3	4	3	3	3	3	4	3	4
II	Decapeptyl	60	3	5	3	5	3	5	3	-	-	3	5	3	5
III	Decapeptyl	600	3	5	3	5	3	5	3	-	-	3	5	3	5
IV	Decapeptyl	3000	3	5	3	5	3	5	3	3	3	3	5	3	5

[a] The dose of Decapeptyl Microgranules was administered intramuscularly once per month for six months; theoretical daily doses are 2, 20 and 100 mcg/kg. Doses were based on previous studies conducted with this test material.
[b] Clinical Laboratory Studies include hematology, clinical chemistry, urinalysis and ophthalmoscopic examinations.
[c] Animal 1502 was sacrificed moribund on Day 1 of the study.
[d] Testosterone levels were determined in all male dogs twice pretest and on the control and high-dose male dogs at Day 28 and the end of Month 3 and Month 6.
[e] Control animals received the vehicle (Vehicle Decapeptyl Suspension) at the same dose volume (1 ml/kg/dose) as administered to the treated animals.

Observations and Results

Mortality

None treatment-related.

Clinical Signs

None treatment-related.

Body Weights/Feed Consumption

No treatment-related changes were observed.

Ophthalmoscopy

No treatment-related changes were observed.

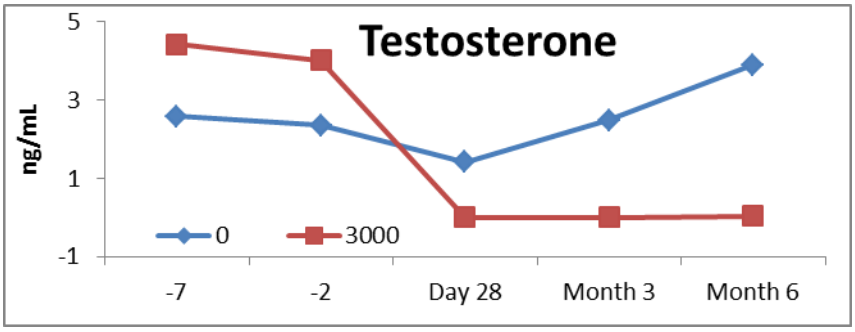
ECG

NA

Testosterone

Testosterone levels were decreased in high dose males throughout dosing as compared to baseline and control values. Serum testosterone was note measured in low and mid dose male groups.

Figure 6. Testosterone levels in the dog



Hematology/Clinical Chemistry/Urinalysis

No treatment-related changes were observed.

Gross Pathology

Small testes and prostate were noted in all treated male groups.

Organ Weights

Decrease in mean absolute and relative reproductive organs was noted in all treated male and female groups compared to control animals.

Table 18. Organ weight changes in the dog

Organ weight changes, % of controls								
	Males					Females		
	BW	Epi	Testes	Prostate		BW	Ovary	Uterus
60	15	**-61**	**-71**	**-76**		-2	**-54**	-71
600	-1	**-56**	**-71**	-61		5	**-52**	-73
3000	13	**-56**	**-66**	-67		4	**-54**	-74

Bold values indicate statistical significant changes

Histopathology

Adequate Battery: Yes

Peer Review: No

Histological Findings

Severe maturation arrest/atrophy of the germinal epithelium, oligospermia and tubular atrophy in the epididymes, and moderate to marked atrophy of the prostate was observed in all treated males.

Dose related decrease in the incidence of vesicular ovarian follicles and corpora lutea was noted. The endometrium of treated females was considered to be in anestrus. Mammary ductal acinar hyperplasia was observed in control females only.

Table 19. Microscopic findings in the dog

ORGAN/TISSUE EXAMINED		--- NUMBER OF ANIMALS ---							
	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	3	3	3	3	5	5	5	5
TESTES (TE)	NUMBER EXAMINED:	3	3	3	3	0	0	0	0
--8/ GERMINAL EPITHELIUM:	4>	0	3	3	3	0	0	0	0
MATURATION ARREST/ATROPHY	TL>	0	3	3	3	0	0	0	0
EPIDIDYMIDES (EP)	NUMBER EXAMINED:	3	3	3	3	0	0	0	0
--U/ OLIGOSPERMIA	4>	0	1	0	0	0	0	0	0
	TL>	0	1	0	0	0	0	0	0
--8/ OLIGOSPERMIA	4>	0	2	3	3	0	0	0	0
	TL>	0	2	3	3	0	0	0	0
--U/ TUBULAR ATROPHY	4>	0	1	0	0	0	0	0	0
	TL>	0	1	0	0	0	0	0	0
--8/ TUBULAR ATROPHY	4>	0	2	3	3	0	0	0	0
	TL>	0	2	3	3	0	0	0	0
PROSTATE (PR)	NUMBER EXAMINED:	3	3	3	3	0	0	0	0
--ATROPHY	3>	0	3	1	0	0	0	0	0
	4>	0	0	2	3	0	0	0	0
	TL>	0	3	3	3	0	0	0	0

ORGAN/TISSUE EXAMINED		--- NUMBER OF ANIMALS ---							
	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	3	3	3	3	5	5	5	5
OVARIES (OV)	NUMBER EXAMINED:	0	0	0	0	5	5	5	5
--U/ VESICULAR FOLLICLES	1>	0	0	0	0	0	0	1	0
	TL>	0	0	0	0	0	0	1	0
--8/ VESICULAR FOLLICLES	1>	0	0	0	0	0	1	1	0
	2>	0	0	0	0	3	2	0	0
	3>	0	0	0	0	2	0	0	0
	TL>	0	0	0	0	5	3	1	0
--U/ PROMINENT CORPORA LUTEA	2>	0	0	0	0	1	0	0	0
	TL>	0	0	0	0	1	0	0	0
--8/ PROMINENT CORPORA LUTEA	2>	0	0	0	0	0	1	0	0
	3>	0	0	0	0	3	0	0	0
	TL>	0	0	0	0	3	1	0	0
UTERUS (UT)	NUMBER EXAMINED:	0	0	0	0	5	5	5	5
--ENDOMETRIUM: ANESTRUS	P>	0	0	0	0	2	4	5	5
	TL>	0	0	0	0	2	4	5	5
--ENDOMETRIUM: METESTRUS	P>	0	0	0	0	3	1	0	0
	TL>	0	0	0	0	3	1	0	0
MAMMARY GLAND (MG)	NUMBER EXAMINED:	0	0	0	0	5	5	5	5
--DUCTAL/ACINAR HYPERPLASIA	3>	0	0	0	0	1	0	0	0
	4>	0	0	0	0	2	0	0	0
	TL>	0	0	0	0	3	0	0	0

1 - minimal 3 - moderate 5 - severe
2 - slight 4 - marked T_L - total number of lesion

Special Evaluation

NA

Toxicokinetics

NA

Dosing Solution Analysis

NA

A 6-month chronic subcutaneous toxicity of triptorelin in Cebus Apella monkeys, followed by a 2-month recovery period.

Study no.:	Not stated
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Not stated
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	D-Trp6-LH-RH, batch # R5316 and R5332

Key Study Findings

Decrease in LH, testosterone, estradiol and progesterone correlated with spermatogenesis and follicular maturation arrest. All findings were reversible.

Methods

Doses:	2, 20, 200 ug/kg
Frequency of dosing:	Once daily
Route of administration:	SC injection
Dose volume:	Not stated
Formulation/Vehicle:	NaCl 0.9%
Species/Strain:	Cebus apella monkeys
Number/Sex/Group:	3/sex/group
Age:	Not stated
Weight:	M: 2.29-2.5 kg. F:1.73-1.89 Kg
Satellite groups:	Recovery: 2/sex/group
Unique study design:	No
Deviation from study protocol:	NA

Cebus apella monkeys were chosen since the female of this species has regular menstrual cycles of 20.8 $\pm$ 1.2 days.

Observations and Results

Mortality

None

Clinical Signs

Unremarkable

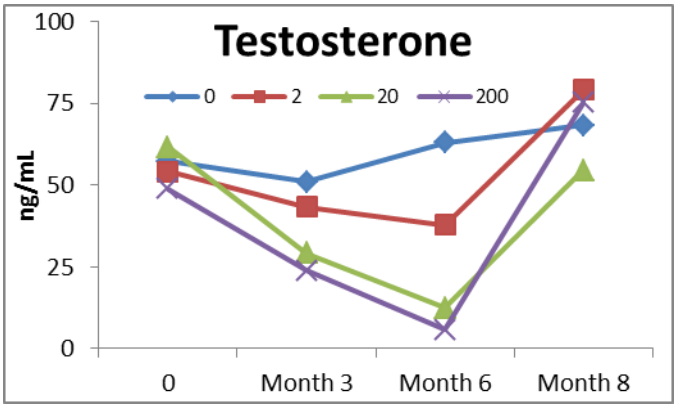
Body Weights

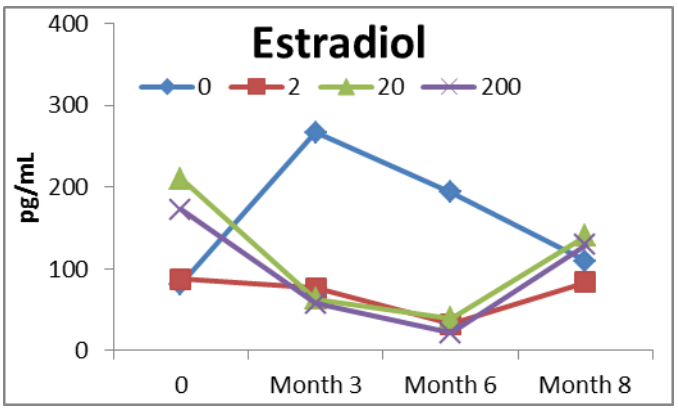
No treatment-related changes were observed.

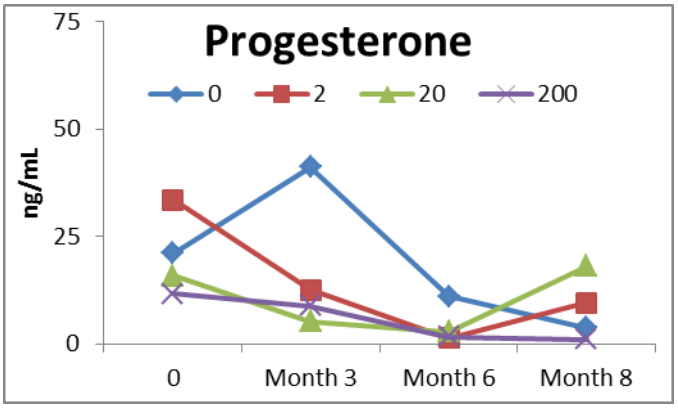
Hormones

Decrease in testosterone in males, and estradiol and progesterone in females was noted at all doses compared to baseline and control values. LH was below the limit of detection in most treated animals and in few controls. All changes were reversible.

Figure 7. Hormone levels in the monkey







Hematology/Clinical Chemistry

No treatment-related changes were observed.

Urinalysis

NA

Gross Pathology

Organ Weights

Decrease in ovary, testes and prostate weight at all doses, reversible.

Table 20. Organ weight changes in the monkey

Organ weight, % change vs. Ctrl			
	Testes	Prostate	Ovary
2	-21	-68	-15
20	-70	-27	-47
200	-59	-19	-39

Histopathology

Adequate Battery: Yes

Peer Review: No

Histological Findings

Arrest of spermatogenesis in one low dose male, and marked hyperplasia of interstitial tissue in another male were noted. At recovery, spermatogenesis returned to normal, whereas the interstitial tissue remained hyperplastic.

In females there was one case of disappearance of primordial follicles at the low dose; distinct arrest of follicular maturation and sclerous atrophy were noted in one animal each at the high-dose. After recovery, the number of primordial follicles was reduced at the mid- and high-dose. However, the presence of corpora lutea indicated that even though follicular stimulation was not very evident it did occur.

7 Genetic Toxicology

The mutagenicity of triptorelin was assessed in vitro and in vivo. Triptorelin showed no mutagenic or clastogenic activity against Salmonella strains, Chinese Hamster Ovary (CHO) cells, and mouse lymphoma cells, under either metabolic activation or non-activation conditions. In the mouse micronucleus assay, no significant increase in micronucleus frequency was observed in treated groups compared to negative control.

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

Mutagenicity test of D-Trp6-LH-RH on His-Salmonella Typhimurium using the B.N. Ames technique

Study no.:	85007
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 12, 1985
GLP compliance:	No. Study conducted in accordance with OECD and AFNOR recommendations
QA statement:	No
Drug, lot #, and % purity:	DTRP-LHRH, batch # R5925

Key Study Findings

Triptorelin was not mutagenic in the absence of metabolic activation.

Methods

Strains: TA100, TA98, TA1535, TA1537, TA1538
Concentrations in definitive study: 50, 150, 500, 1500, 5000ug/plate
Basis of concentration selection: Limit dose
Negative control: DMSO
Positive control:

STRAINS	WITHOUT METABOLIC ACTIVATION	DOSE mcg/dish
TA 1535	BETA-PROPRIOLACTONE	50
TA 1537	HYCANTHONE METHANE-SULPHONATE	50
TA 1538	2 NITROFLUORENE	2
TA 98	2 NITROFLUORENE	2
TA 100	SODIUM AZIDE	20

Formulation/Vehicle: DMSO
Incubation & sampling time: 48h at 37C

Study Validity

Selection of bacterial tester strains and dose selection based on limit dose were adequate; negative controls were within the historical range, and positive controls produced expected responses.

Results

Triptorelin did not significantly increase the number of revertant colonies at any dose.

Table 21. Ames test: Mean revertant counts

Solvent used: Distilled H_2O		NUMBER OF MUTANTS PER PLATE					
STRAINS	DOSES mcg/plate	Plate n° 1	2	3	MEAN	STANDARD DEVIATION	RATIO (1)
TA 1535	0	13	20	20	18	4	
	50	14	9	11	11	2,5	0,6
	150	15	16	18	16	1,5	0,9
	500	20	11	14	15	4,6	0,8
	1500	19	13	14	16	2,6	0,9
	5000	22	28	13	21	7,5	1,2
TA 1537	0	6	4	12	8	4	
	50	4	4	4	4	0	0,5
	150	5	5	5	5	0	0,6
	500	3	3	4	3	2,9	0,4
	1500	7	3	7	6	2,3	0,8
	5000	4	8	6	6	2	0,8
TA 1538	0	13	12	7	11	4	
	50	10	9	11	10	1	0,9
	150	11	11	10	11	0,6	1
	500	21	22	16	20	3,2	1,8
	1500	16	17	13	16	2,6	1,5
	5000	13	10	23	15	6,8	1,4
TA 98	0	12	14	15	13	1	
	50	13	15	22	17	4,7	1,3
	150	10	12	13	12	1,5	0,9
	500	22	22	14	19	4,6	1,5
	1500	27	17	27	24	4,6	1,8
	5000	17	20	14	17	3	1,3
TA 100	0	108	100	77	95	16,1	
	50	94	95	83	91	6,7	1
	150	79	88	96	88	8,5	0,9
	500	117	98	95	103	11,9	1,1
	1500	96	114	114	108	10,4	1,1
	5000	104	79	90	91	12,5	1

(1) Ratio = number of mutants in the presence of the compound/number of mutants in the presence of solvent

Detection of mutagens in the Salmonella/Microsome assay Ames test on D-Trp6-LH-RH

Study no.:	316
Study report location:	eCTD
Conducting laboratory and location:	Not reported
Date of study initiation:	February, 1985
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	DTRP-LHRH, batch # BM2124A

Key Study Findings

Triptorelin at 100 and 1000ug/plate was not mutagenic with and without metabolic activation.

Methods

Strains:	TA100, TA98, TA1535, TA1537, TA1538
Concentrations in definitive study:	100, 1000ug/plate
Basis of concentration selection:	Limit dose
Negative control:	Not stated
Positive control:	W/O S9: NA-Azide, 9 aminoacridine, 4-Nitro-O Phenyldiamine W/ S9: 2-aminoanthracene
Formulation/Vehicle:	Not stated
Incubation & sampling time:	48h at 37C

Study Validity

NA

Results

Triptorelin did not significantly increase the frequency of revertant colonies when tested with or without metabolic activation.

Table 22. Ames test: Mean revertant counts

Test Compound µg/plate	Metabolic Activation	Mean Number of Revertant Colonies per Plate TA 100	TA 98	TA 1535	TA 1537	TA [illegible]
D-Trp^6-LHRH						
1000	--	15	12	7	2	7
100	--	13	7	8	4	4
Na-Azide						
8 µg	--	541	--	737	--	--
9-Aminoacridine						
100 µg	--	--	--	--	287	--
4-Nitro-O-Phenyldiamine						
8 µg	--	--	512	--	--	614
Solvent	--	16	8	9	4	[illegible]
D-Trp^6-LHRH						
1000	+	22	4	8	2	6
100	+	22	6	4	2	[illegible]
2-Aminoanthracene						
1.5 µg	+	795	496	--	--	--
3.0	+	--	--	16	7	12
Solvent	+	22	10	8	2	[illegible]

7.2 *In Vitro* Assays in Mammalian Cells

Clastogenic evaluation of D-TRP6-LH-RH in an in vitro cytogenetic assay measuring chromosome aberration frequencies in Chinese Hamster Ovary (CHO) cells.

Study no.:	E9738-0-437
Study report location:	
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 12, 1987
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	D-Trp6-LHRH, batch # 0P1987

Key Study Findings

Triptorelin was not clastogenic in the presence or absence of metabolic activation.

Methods

Cell line:	Chinese hamster ovary (CHO) cells
Concentrations in definitive study:	2, 3, 4, 5 mg/mL
Basis of concentration selection:	Preliminary dose range finding study
Negative control:	10% PBS or McCoy's 5a medium
Positive control:	Mitomycin C (500 ng/mL), Cyclophospamide (25 ug/mL)
Formulation/Vehicle:	McCoy's 5a medium
Incubation & sampling time:	Without S9: 7h With S9: 2h + 8h

Study validity

One hundred cells from each duplicate culture for at least four dose levels of the test article were analyzed for chromosomal aberrations. Negative and positive controls showed expected results.

Results

In the range-finding assay with exogenous metabolic activation there was no serious toxicity. At the highest dose of 5.0 mg/ml a diminished number of mitotic cells was noted.

In the definitive assay, no statistically significant increase in cells with aberrations was observed with or without metabolic activation.

Table 23. Summary of chromosomal aberrations in CHO cells

Without Activation

TREATMENT	CELLS SCORED	NUMBER AND TYPE OF ABERRATION															NO. OF ABERRATIONS PER CELL	% CELLS WITH ABERRATIONS	% CELLS WITH >1 ABERRATIONS
		CHROMATID						CHROMOSOME											
		TB	TD	F	TR	QR	CR	SB	AF	D	R	MT	PU	E	GT	Other			
CONTROLS UNTREATED:	100																0.00	0.0	0.0
SOLVENT: PBS 2%	100										1						0.01	1.6	0.0
POSITIVE: Mitomycin-C 500.0 ng/ml	25	3			4	1		1			1						0.40	28.0	12.0
2.0 mg/ml A	100																0.00	0.0	0.0
2.0 mg/ml B	100																0.00	0.0	0.0
3.0 mg/ml A	100							1					1				>0.02	2.0	1.0
3.0 mg/ml B	100							1									0.01	1.0	0.0
4.0 mg/ml A	100																0.00	0.0	0.0
4.0 mg/ml B	100	1															0.01	1.0	0.0
5.0 mg/ml A	100	1															0.01	1.0	0.0
5.0 mg/ml B	100																0.00	0.0	0.0

Results pooled from replicate cultures

Without Activation

TREATMENT	CELLS SCORED	NUMBER AND TYPE OF ABERRATION															NO. OF ABERRATIONS PER CELL	% CELLS WITH ABERRATIONS	% CELLS WITH >1 ABERRATIONS
		CHROMATID						CHROMOSOME											
		TB	TD	F	TR	QR	CR	SB	AF	D	R	MT	PU	E	GT	Other			
CONTROLS UNTREATED AND SOLVENT:	200										1						0.005	0.5	0.0
POSITIVE: Mitomycin-C 500.0 ng/ml	25	3			4	1		1			1						0.400	28.0*	12.0
2.0 mg/ml	200																0.000	0.0	0.0
3.0 mg/ml	200							2					1				>0.015	1.5	0.5
4.0 mg/ml	200	1															0.005	0.5	0.0
5.0 mg/ml	200	1															0.005	0.5	0.0

*Significantly greater than solvent and untreated control, p<0.05.

TB: Chromatid break
TR: Triradial
QR: Quadriradial
SB: Chromosome break
R : Ring
PU: One or more fragmented chromosomes

S-9 Activation

TREATMENT	CELLS SCORED	NUMBER AND TYPE OF ABERRATION															NO. OF ABERRATIONS PER CELL	% CELLS WITH ABERRATIONS	% CELLS WITH >1 ABERRATIONS
		CHROMATID						CHROMOSOME											
		TB	TD	TF	TR	QR	CR	SB	AF	D	R	MT	PU	E	GT	Other			
CONTROLS UNTREATED:	100							1									0.01	1.0	0.0
SOLVENT: PBS 2%	100																0.00	0.0	0.0
POSITIVE: Cyclophosphamide 25.0 µg/ml	25	3			5	4	1	8		1						ID 1	0.92	48.0	32.0
2.0 mg/ml A	100																0.00	0.0	0.0
2.0 mg/ml B	100																0.00	0.0	0.0
3.0 mg/ml A	100							2									0.02	2.0	0.0
3.0 mg/ml B	100																0.00	0.0	0.0
4.0 mg/ml A	100																0.00	0.0	0.0
4.0 mg/ml B	100																0.00	0.0	0.0
5.0 mg/ml A	100																0.00	0.0	0.0
5.0 mg/ml B	100			1													0.01	1.0	0.0

Results pooled from replicate cultures

S-9 Activation

TREATMENT	CELLS SCORED	NUMBER AND TYPE OF ABERRATION															NO. OF ABERRATIONS PER CELL	% CELLS WITH ABERRATIONS	% CELLS WITH >1 ABERRATIONS
		CHROMATID						CHROMOSOME											
		TB	TD	TF	TR	QR	CR	SB	AF	D	R	MT	PU	E	GT	Other			
CONTROLS UNTREATED AND SOLVENT:	200							1									0.005	0.5	0.0
POSITIVE: Cyclophosphamide 25.0 µg/ml	25	3			5	4	1	8		1						ID 1	0.920	48.0*	32.0
2.0 mg/ml	200																0.000	0.0	0.0
3.0 mg/ml	200							2									0.010	1.0	0.0
4.0 mg/ml	200																0.000	0.0	0.0
5.0 mg/ml	200			1													0.005	0.5	0.0

*Significantly greater than solvent and untreated control, p<0.05.

TB: Chromatid break
TF: Chromatid fragment
TR: Triradial
QR: Quadriradial
CR: Complex rearrangement
SB: Chromosome break
ID: Interstitial deletion
D : Dicentric

Study to determine the ability of BIM 21003 to induce mutations to 6-Thioguanine resistance in test article: Mouse lymphoma L5178Y cells using a fluctuation assay

Study no.:	2MLREJPS005
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 23, 1988
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	BIM 21003, batch # 32-37A

Key Study Findings

Triptorelin was not mutagenic under the condition of this assay.

Methods

Cell line:	Mouse Lymphoma L5178Y
Concentrations in definitive study:	1000, 1500, 2000, 2500 ug/mL
Basis of concentration selection:	Precipitation in the dose-range assay (1-5000 ug/mL)
Negative control:	FM10 medium
Positive control:	4-nitroquinoline-1-oxide; benzo9a)pyrene
Formulation/Vehicle:	FM10 medium for test article; DMSO for positive controls
Incubation & sampling time:	Cell exposure to drug for 2 hours with and without S9; cells counted and expression incubation commenced for 7 days; viable colonies counted after 1-2 weeks

Study Validity

The assay was valid: the mutation frequencies in the negative control cultures fell within the normal range and at least one concentration of each of the positive control induced a clear increase in mutation frequency.

Results

In experiment 1, no increase in mutation frequency was noted with or without S9. The small increase noted in the absence of S-9 was not dose-related, could be due to lower number of viable colonies, and was not replicated in the second experiment.

In experiment 2, no statistically significant increase in mutation frequency was noted in the absence of S9. In the presence of S-9, a small statistically significant increase in mutation frequency was seen at the highest test concentration, but the data set did not show a dose-response by regression analysis (correlation coefficient r = 0.7 not significant).

Table 24. Percent relative survival and mutation frequency in the absence of S9 (Experiment 1)

Experiment 1

Treatment (ug/ml)		Relative survival %	Mutation frequency*	95% confidence limits lower	upper	Result + or -
0	A+B	100	12.8	10.2	16.1	
1.58	A+B	68	NP			
5	A+B	80	NP			
15.8	A+B	77	NP			
50	A+B	79	NP			
158	A+B	77	16.8	13.0	21.6	-
500	A+B	97	13.9	10.8	17.9	-
1580	A+B	72	28.1	22.3	35.4	+
5000	A+B	62	24.3	19.1	30.9	+
Positive control (NQO)						
0.1	A	34	44.1	34.0	57.1	+
0.15	A	45	27.0	20.9	34.9	+

* = 6TG-resistant mutants/10^6 viable cells at least 7 days after treatment.
NP = not plated for viability/6TG-resistance.

Table 25. Percent relative survival and mutation frequency in the presence of S9 (Experiment 1)

Experiment 1

Treatment (ug/ml)		Relative survival %	Mutation frequency*	95% confidence limits lower	upper	Result + or -
0	A+B	100	17.7	14.1	22.2	
1.58	A+B	100	NP			
5	A+B	89	NP			
15.8	A+B	162	NP			
50	A+B	111	NP			
158	A+B	106	13.4	10.5	17.0	-
500	A+B	106	18.8	15.1	23.4	-
1580	A+B	126	22.0	17.3	28.0	-
5000	A+B	85	18.3	14.5	23.1	-
Positive control (BP)						
2.0	A	143	20.7	15.3	28.0	-
3.0	A	83	41.4	31.6	54.3	+

* = 6TG-resistant mutants/10^6 viable cells at least 7 days after treatment.
NP = not plated for viability/6TG-resistance.

Table 26. Percent relative survival and mutation frequency in the absence of S9 (Experiment 2)

Experiment 2

Treatment (ug/ml)		Relative survival %	Mutation frequency*	95% confidence limits lower	upper	Result + or -
0	A+B	100	6.7	5.1	8.8	
1000	A+B	106	4.5	3.1	6.5	-
1500	A+B	85	6.2	4.6	8.3	-
2000	A+B	123	2.4	1.6	3.7	-
2500	A+B	136	4.8	3.4	6.8	-
Positive control (NQO)						
0.1	A	67	20.4	15.2	27.4	+
0.15	A	49	36.4	28.3	46.8	+

* = 6TG-resistant mutants/10^6 viable cells at least 7 days after treatment.

Table 27. Percent relative survival and mutation frequency in the presence of S9 (Experiment 2)

Experiment 2

Treatment (ug/ml)		Relative survival %	Mutation frequency*	95% confidence limits lower	upper	Result + or -
0	A+B	100	3.3	2.4	4.5	
1000	A+B	88	3.4	2.4	4.9	-
1500	A+B	92	5.4	4.0	7.3	-
2000	A+B	82	3.6	2.5	5.2	-
2500	A+B	78	6.4	4.8	8.5	+
Positive control (BP)						
2.0	A	62	12.2	8.7	17.1	+
3.0	A	64	19.4	14.2	26.4	+

* = 6TG-resistant mutants/10^6 viable cells at least 7 days after treatment.

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

Clastogenic evaluation of D- Trp6-LH-RH in the in vivo mouse micronucleus assay

Study no:	E9738-0-455
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 28, 1987
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	D-Trp6-LHRH, batch # 0P1987

Key Study Findings

Triptorelin did not induce a significant increase in micronuclei in bone marrow polychromatic erythrocytes under the conditions of this assay.

Methods

Doses in definitive study:	16, 53, 160 mg/kg
Frequency of dosing:	Single dose
Route of administration:	IP
Dose volume:	0.29-0.35mL
Formulation/Vehicle:	0.9% NaCl
Species/Strain:	CD1 mice
Number/Sex/Group:	5/sex/group/sampling time
Satellite groups:	NA
Basis of dose selection:	LD_{50} and MTD
Negative control:	0.9% NaCl
Positive control:	Cyclophosphamide (100 mg/kg)

Results

- MTD was reached at 160 mg/kg: 50% of the animals at this dose died within 1h following administration of the test article.
- No significant increase in micronuclei frequency was observed at any dose levels.

Table 28. Summary of mouse micronucleus bone marrow assessment

TREATMENT	DOSE	ROUTE OF ADMINIS-TRATION	NUMBER OF PCEs SCORED PER ANIMAL[a]	PERCENT MICRONUCLEATED CELLS: MEAN ± S.E.[b] MALES	FEMALES	TOTAL	PCE/RBC RATIO[c] MALES	FEMALES
Negative Control 0.9% NaCl	NA	I.P.	1000	0.18±0.086	0.08±0.037	0.13±0.047	0.8	0.8
Positive Control Cyclophosphamide	100 mg/Kg	I.P.	1000[d]	3.50±0.295*	3.24±0.103*	3.37±0.154*	0.6	0.5
Test article:								
24 hr kill	16 mg/kg	I.P.	1000[e]	0.26±0.040	0.06±0.024	0.16±0.040	0.7	0.9
	53 mg/kg	I.P.	1000	0.30±0.084	0.14±0.024	0.22±0.049	0.7	0.9
	160 mg/kg	I.P.	1000	0.17±0.033	0.20±0.058	0.18±0.031	0.9	1.0
48 hr kill	160 mg/kg	I.P.	1000	0.17±0.033	0.23±0.067	0.20±0.037	0.8	0.9
72 hr kill	160 mg/ml	I.P.	1000	†	0.10±0.058	0.10±0.058	-	0.9

[a] Only Polychromatic Erythrocytes (PCEs) scored.
[b] Data analyzed by one-tailed t-test. Each animal constituted a data point.
* Significant increase at $p \leq 0.05$.
** Significant increase at $p \leq 0.01$.
[c] Ratio of PCEs to mature erythrocytes (RBCs).
[d] In two animals only 500 PCEs were scored.
[e] In one animal only 500 PCEs were scored.
† All animals died before scheduled sacrifice.

8 Carcinogenicity

Carcinogenicity studies were performed in mice and rats. No tumors were observed in mice administered triptorelin for 18 months up to 6000 ug/kg/28d, 4X the clinical dose. In rats, adenomas of the pars distalis of the pituitary gland leading to premature deaths

due to brain compression were observed in all treatment groups starting at the clinical dose, with dose related onset. Pituitary tumors in rats are a known consequence of castration and are commonly seen with GnRH agonists, as gonadal suppression lead to hypertrophy and hyperplasia of the pars distalis, which progress to tumor formation. The relevance of rat pituitary adenoma to humans has not been established.

A 18-month oncogenicity study in mice with decapeptyl microgranules via intramuscular injection

Study no.:	88-3370
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 25, 1989
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Decapeptyl microgranules, several lots used
CAC concurrence:	Yes

Key Study Findings

- Triptorelin was not carcinogenic in mice.
- Atrophy of the reproductive organs and spermatogenic arrest were consistent with the pharmacology of triptorelin.

Adequacy of Carcinogenicity Study

Mouse carcinogenicity data were submitted to ECAC and were reviewed and approved in May 1994.

Appropriateness of Test Models

The mouse is a commonly used test model for carcinogenesis. The route and frequency of dosing was consistent with the intended clinical use of triptorelin.

Evaluation of Tumor Findings

There were no treatment-related tumors in any dose group.

Methods

Doses:	120, 850, 6000ug/kg
Frequency of dosing:	Once a month for 18 months
Dose volume:	4 mL/Kg
Route of administration:	Intramuscular injection
Formulation/Vehicle:	Not reported
Basis of dose selection:	Previous toxicity studies (not submitted)
Species/Strain:	CD1 mice
Number/Sex/Group:	50/sex/group
Age:	8 weeks old
Animal housing:	Animals were individually housed in elevated stainless steel wire mesh cages
Paradigm for dietary restriction:	NA
Dual control employed:	No
Interim sacrifice:	No
Satellite groups:	No
Deviation from study protocol:	NA

Table 29. Mouse carcinogenicity study design

Group	Test Substance	Dose Level[a] mcg/kg	Number of Animals: Total M	Total F	Clinical Laboratory Studies: Mon 12 M	Mon 12 F	Term M	Term F	Terminal Sacrifice M	Terminal Sacrifice F	Histopathology M	Histopathology F
I	Control	0	50	50	44	47	19	25	19	25	50	50
II	Decapeptyl	120	50	50	46	46	25	23	25	23	25	27
III	Decapeptyl	850	50	50	44	47	21	26	21	26	29	24
IV	Decapeptyl	6000	50	50	42	48	20	29	20	29	50	50

[a]Doses were selected by the sponsor based on previous toxicity studies conducted with this test substance. Each animal received an intramuscular injection once per month (every 28 days) for eighteen months.

Observations and Results

Mortality

There was no treatment related mortality.

Table 30. Summary of mortality in the mouse

Group mcg/kg	I 0	II 120	III 850	IV 6000
Males:	29/50 (58%)	25/50 (50%)	28/50 (56%)	29/50 (58%)
Females:	24/50 (48%)	27/50 (54%)	23/50 (46%)	21/50 (42%)

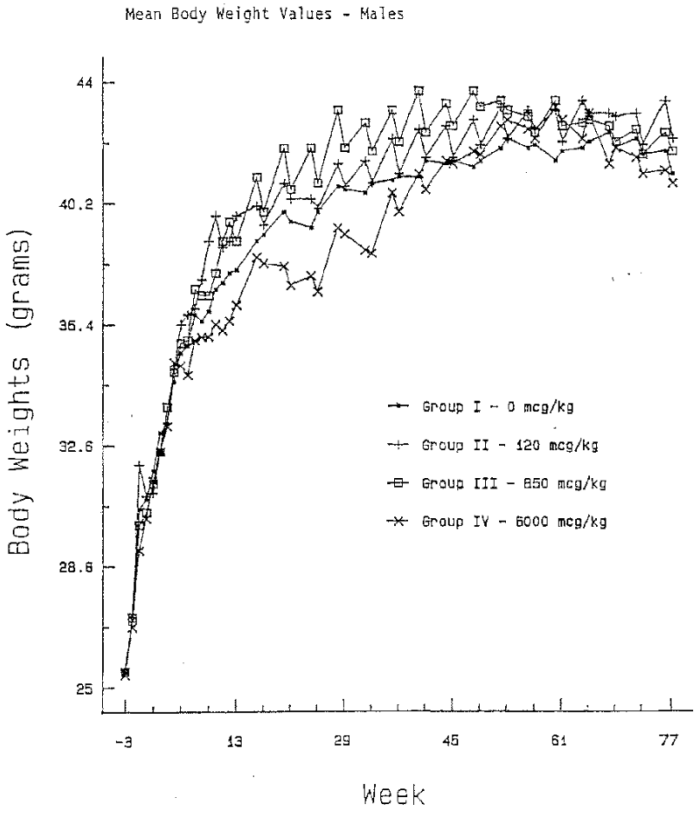
Clinical Signs

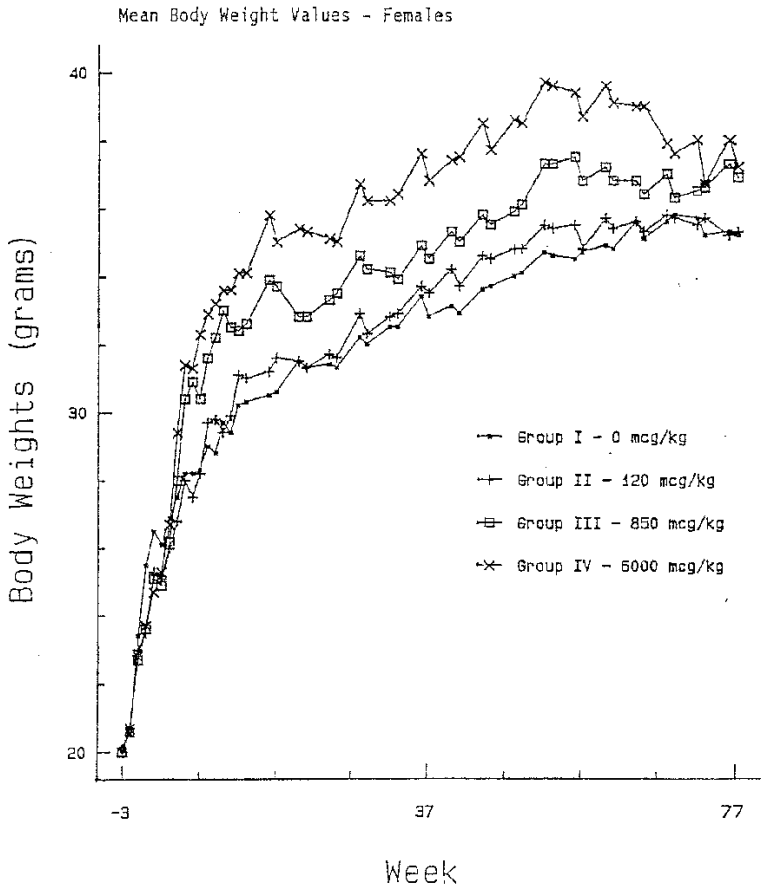
Unremarkable

Body Weights

A dose-related increase in body weight and body weight gain as compared to controls was observed in females at ≥850ug/kg, possibly due to the loss of estrogens during treatment. No changes were noted in males.

Figure 8. Body weight in the 2-yr mouse study

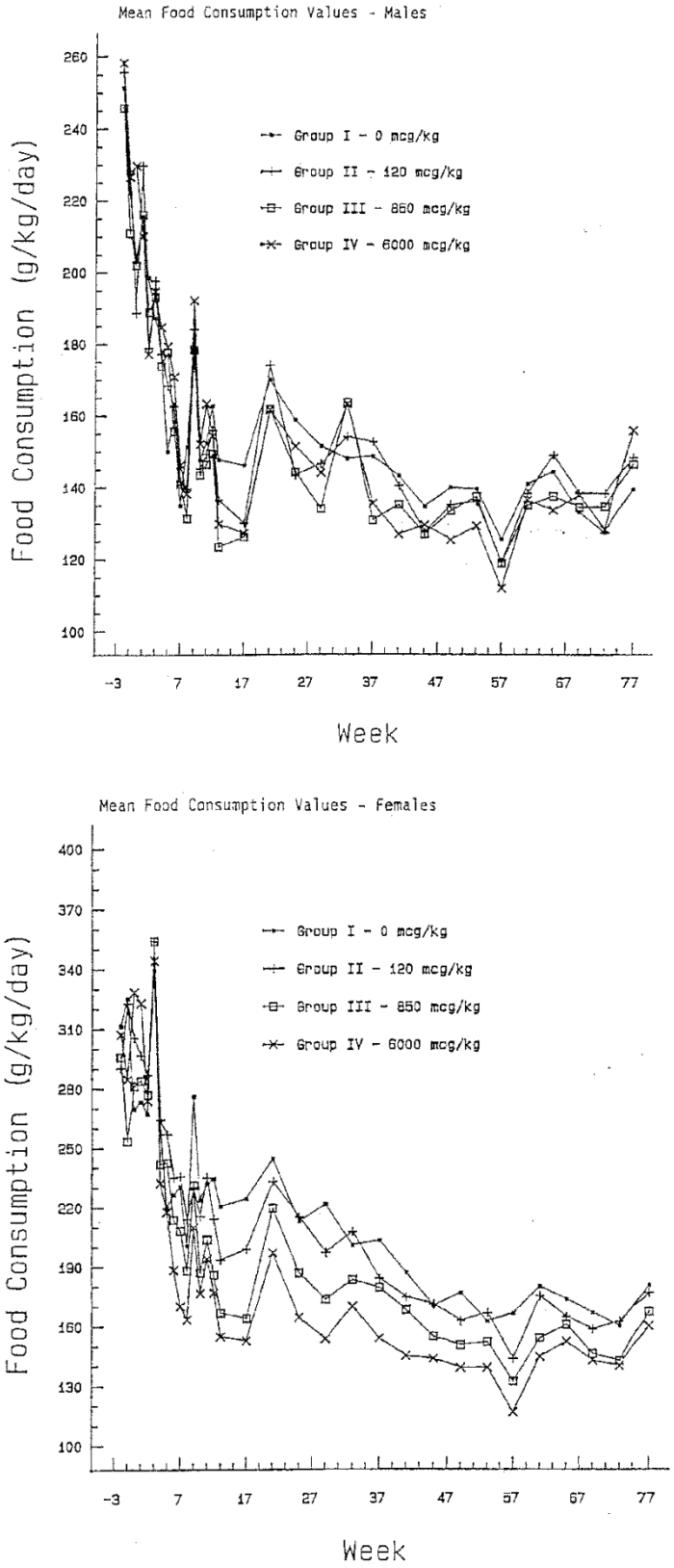




Feed Consumption

Lower food consumption was noted in females at ≥850ug/kg. No changes were noted in males.

Figure 9. Food consumption in the 2-yr mouse study



Hematology

No treatment related changes were observed.

Gross Pathology

Small reproductive organs in males at high dose and in females at ≥850 ug/kg.

Histopathology

Histopathological evaluations were performed for all animals in the control and high-dose groups. In addition, full histopathological evaluations were performed on all animals in the low- and mid-dose groups which were found dead or sacrificed in moribund condition during the course of the study.

Peer Review: Not done

Neoplastic
There were no tumor increases in any triptorelin treatment group that were considered treatment-related or biologically significant.

Table 31. Summary of neoplasms in the mouse

	--- NUMBER-OF-ANIMALS ---							
SEX:	-------MALE-------				------FEMALE------			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
NEOPLASM CLASSIFICATION SUMMARY NUMBER:	50	50	50	50	50	50	50	50
TOTAL PRIMARY NEOPLASMS	16	25	8	17	25	8	10	10
ANIMALS WITH ONE OR MORE	16	22	7	11	20	7	10	10
PERCENT WITH ONE OR MORE	32%	44%	14%	22%	40%	14%	20%	20%
TOTAL BENIGN NEOPLASMS	12	14	5	16	12	5	8	7
ANIMALS WITH ONE OR MORE	12	13	5	10	10	4	8	7
PERCENT WITH ONE OR MORE	24%	26%	10%	20%	20%	8%	16%	14%
TOTAL MALIGNANT NEOPLASMS	4	11	3	1	13	3	2	3
ANIMALS WITH ONE OR MORE	4	10	3	1	11	3	2	3
PERCENT WITH ONE OR MORE	8%	20%	6%	2%	22%	6%	4%	6%

Non Neoplastic
Non neoplastic findings were limited to the reproductive organs and were related to the expected pharmacologic activity.

Males
Maturation arrest of the germinal epithelium and degeneration/atrophy of the interstitial cells in the testes, oligospermia, atrophy and a decrease in the amount of secretory product in the prostate were observed mostly in the high dose group.

Females
Dose related increase in the incidence of atrophy in the ovaries and uterus was noted in all treated groups.

Table 32. Non neoplastic findings in mice

ORGAN AND FINDING DESCRIPTION	NUMBER:	--- NUMBER-OF-ANIMALS --- SEX: -------MALE------- GROUP: -1-	-2-	-3-	-4-
TESTES	NUMBER EXAMINED:	49	30	30	50
--U/ GERMINAL EPITHELIUM: MATURATION ARREST		0	1	0	4
--B/ GERMINAL EPITHELIUM: MATURATION ARREST		0	1	2	44
--B/ MINERALIZATION		6	2	2	20
--U/ MINERALIZATION		5	1	4	12
--U/ INTERSTITIAL CELLS: DEGENERATION/ATROPHY (VARIABLE AMOUNTS OF INTRACYTOPLASMIC BROWN PIGMENT)		0	0	0	3
--B/ INTERSTITIAL CELLS: DEGENERATION/ATROPHY (VARIABLE AMOUNTS OF INTRACYTOPLASMIC BROWN PIGMENT)		0	0	1	44
--U/ AMYLOID DEPOSITS		1	2	0	0
--B/ AMYLOID DEPOSITS		16	1	0	0
--B-U/ INTERSTITIAL CELL TUMOR		0	1	0	0
--S-B/ METASTATIC/INVASIVE NEOPLASM		0	1	0	0
EPIDIDYMIDES	NUMBER EXAMINED:	49	30	30	50
--U/ OLIGOSPERMIA		2	3	0	9
--B/ OLIGOSPERMIA		15	2	4	33
PROSTATE	NUMBER EXAMINED:	48	25	31	42
--LYMPHOID CELL AGGREGATE(S)		1	0	1	4
--ALVEOLI: CORPORA AMYLACIA/MINERALIZED GRANULES		37	11	13	0
--DECREASED SECRETORY PRODUCT/ATROPHY		6	1	7	41
SEMINAL VESICLES	NUMBER EXAMINED:	50	30	36	44
--B/ DECREASED SECRETORY PRODUCT/ATROPHY		4	1	12	42

ORGAN AND FINDING DESCRIPTION	NUMBER:	--- NUMBER-OF-ANIMALS --- SEX: ------FEMALE------ GROUP: -1-	-2-	-3-	-4-
OVARIES	NUMBER EXAMINED:	47	35	27	47
--U/ ATROPHY		0	1	5	8
--B/ ATROPHY		0	6	8	32
UTERUS	NUMBER EXAMINED:	49	34	35	48
--ATROPHY (ENDOMETRIAL GLANDS WERE VARIABLY DILATED)		0	10	28	46
--ENDOMETRIUM: HYPERPLASIA (CYSTIC/POLYPOID)		49	23	3	1
--ENDOMETRIUM: GLANDS-SQUAMOUS/SQUAMOID METAPLASIA		14	2	0	0
--CERVIX: SQUAMOUS CELL HYPERPLASIA		28	10	1	0

Toxicokinetics

NA

A 24-month oncogenicity study in the rat with decapeptyl microgranules via intramuscular injection

Study no.:	88-3371
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 15, 1988
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Decapeptyl microgranules, several lots used
CAC concurrence:	Yes

Key Study Findings

Dose related onset of pituitary adenomas and carcinomas at all doses.

Adequacy of Carcinogenicity Study

Excessive mortality was observed in the rat carcinogenicity study. However, given the considerable experience with this class of drugs, limited data from the rat carcinogenicity study and complete data from the mouse carcinogenicity study were considered sufficient to support the safety profile of triptorelin.

Appropriateness of Test Models

The rat is a commonly used test model for carcinogenesis. The route and frequency of dosing was consistent with the intended clinical use of triptorelin.

Evaluation of Tumor Findings

Adenomas and carcinomas of the pars distalis of the pituitary gland were seen in almost all treated animals starting at the clinical dose, with dose related onset.

Methods

Doses:	126, 600, 3000ug/kg
Frequency of dosing:	Once a month for 24 months
Dose volume:	2 mL/Kg
Route of administration:	Intramuscular injection
Formulation/Vehicle:	Not reported
Basis of dose selection:	Previous toxicity studies
Species/Strain:	SD rats
Number/Sex/Group:	50/sex/group
Age:	6 weeks old
Animal housing:	Animals were individually housed in elevated stainless steel wire mesh cages
Paradigm for dietary restriction:	NA
Dual control employed:	No
Interim sacrifice:	No
Satellite groups:	No
Deviation from study protocol:	Due to mortality, animals were sacrificed as follow: mid-dose and high-dose males at month 13, control and low-dose males at month 18; control and low dose females at month 23.

Observations and Results

Mortality

Mortality was observed in all treatment groups beginning at week 7 in males and week 11 in females. Mid and high dose males were sacrificed at month 13, when the percent survival was 12 and 10%, respectively, whereas the last 4 females in each group died during month 19. The study was terminated at month 18 and 20 in males and females, when the low dose survival reached 8% and 10%, respectively. Mortality was due to compression of the hypothalamic area of the brain due to the presence of neoplasms (adenoma or carcinoma) of the pars distalis of the pituitary gland.

Table 33. Summary of mortality in the rat

Mortality Summary[a]

Group mcg/kg	Initial Number on Test	Month 1	2	3	4	5	6	7	8	9	10	11	12	13[b]	14	15	16	17	18[c]	19	20	21	22	23	24[d]	Total Number Dead	Total Number of Survivors	Percent Survivorship
Males																												
I 0	50	0	0	0	0	0	0	0	0	0	0	0	0	2	1	1	1	0	4	-	-	-	-	-	-	9	41	82
II 120	50	0	0	0	0	0	0	0	0	0	2	1	8	13	9	1	6	3	3	-	-	-	-	-	-	46	4	8
III 600	50	0	0	0	0	1	0	2	5	7	10	10	6	3	-	-	-	-	-	-	-	-	-	-	-	44	6	12
IV 3000	50	0	0	0	0	0	1	3	4	10	5	12	7	3	-	-	-	-	-	-	-	-	-	-	-	45	5	10
Females																												
I 0	50	0	0	0	0	0	0	0	0	0	0	0	0	0 (1)	0	3	1	0	0	0	1	2	2	1	-	10 (1)	39	81 (78)
II 120	50	0	0	0	0	1	0	0	0	0	0	0	1	0	2	1	6	4	8	9	4	4	5	0	-	45	5	10
III 600	50	0	0	0	0	0	0	1	0	0	1	1	2	4	14	10	8	5	0	4	-	-	-	-	-	50	0	0
IV 3000	50	0	0	0	0	0	0	0	0	0	1	6	3	5	11	8	4	6	2	4	-	-	-	-	-	50	0	0

[a] Includes animals found dead or sacrificed in a moribund condition. Animals dying accidentally are presented in parentheses.
[b] All remaining survivors in Groups III and IV males were sacrificed during Month 13 (2/20/91) as per sponsor request.
[c] All remaining survivors in Groups I and II males were sacrificed during Month 18 (7/29 or 7/30/91) as per sponsor request.
[d] As a result of high mortality it was decided to sacrifice the remaining animals early (in Month 23) as per sponsor's discussions with the USFDA.

ORGAN/TISSUE EXAMINED	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	50	50	50	50	50	50	50	50
BRAIN	NUMBER EXAMINED:	50	50	50	50	50	50	50	50
COMPRESSED		2	49	37	37	4	41	48	47
FRANGIBLE		0	6	2	3	0	1	2	2
DILATED VENTRICLES		0	1	0	0	0	1	0	0

Clinical Signs

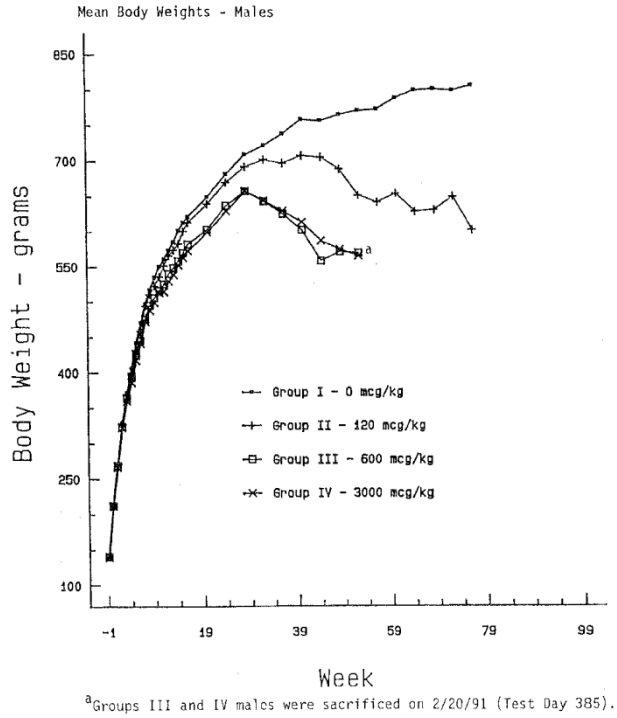
Lethargy, decreased food consumption, emaciation, no stool or decreased fecal volume, soft stool, abnormal posture, hypothermia and dyspnea. These findings are most likely due to the compression of the hypothalamic area of the brain.

Body Weights

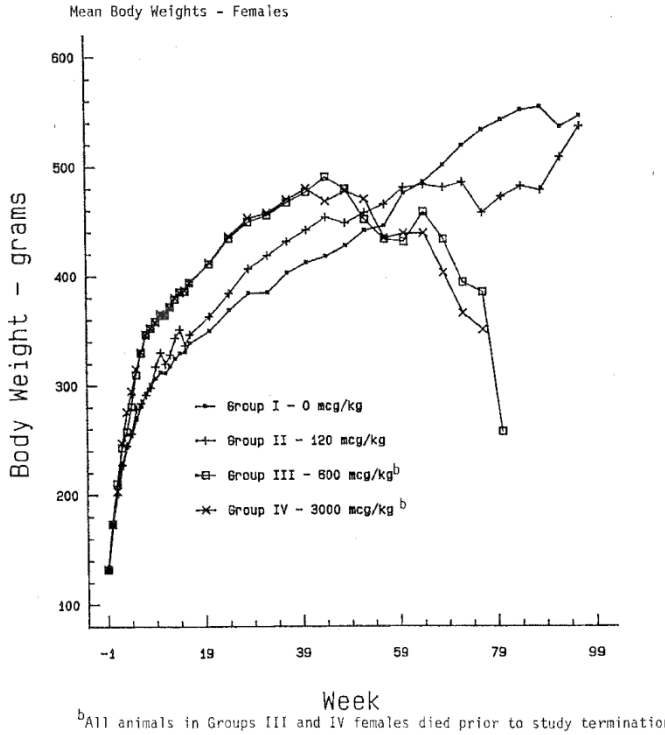
Decrease in body weight gain was observed in mid-dose and high-dose males starting at week 3 with frank body weight loss starting at week 30. In the low-dose male group, decrease in body weight gain and weight loss started at week 36 and 50, respectively.

In female, a dose related increase in body weight and body weight gain was observed until approximately week 40 (3-8% at LD, 10-18% at MD and HD), followed by weight loss at MD and HD.

Figure 10. Body weight in the 2-yr rat study



[a]Groups III and IV males were sacrificed on 2/20/91 (Test Day 385).

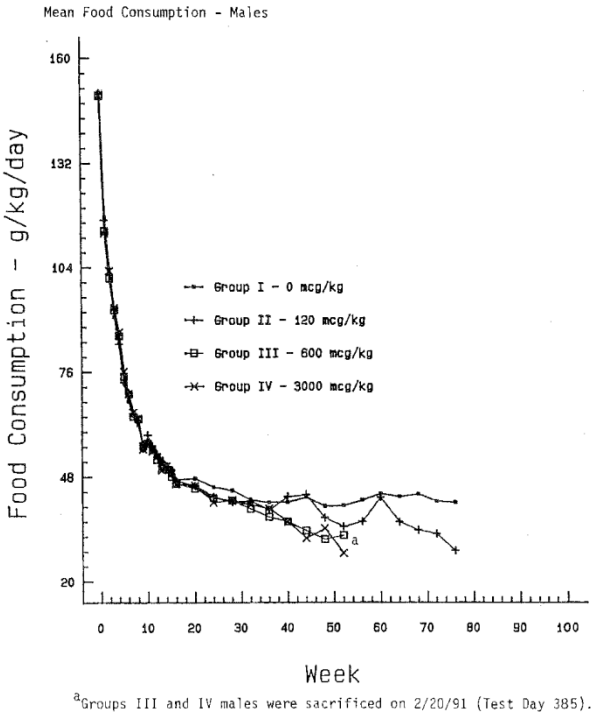


[b]All animals in Groups III and IV females died prior to study termination.

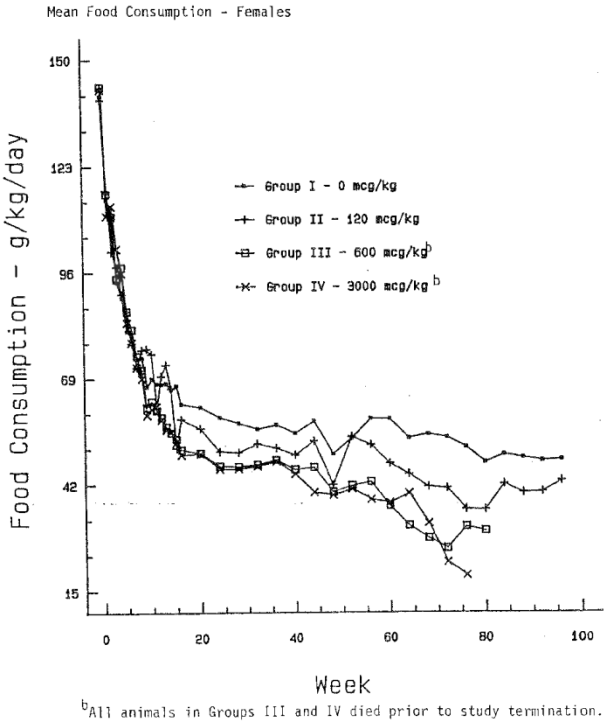
Feed Consumption

Decrease in food consumption was observed in mid- and high-dose females and males after week 10 and 40, respectively, and in the high-dose groups after week 20 and 50 in females and males, respectively.

Figure 11. Food consumption in the 2-yr rat study



[a]Groups III and IV males were sacrificed on 2/20/91 (Test Day 385).



[b]All animals in Groups III and IV died prior to study termination.

Hematology

Unremarkable

Gross Pathology

Brain compression, pituitary masses, small reproductive organs and small spleen were observed in all treatment groups.

Table 34. Macroscopic findings in the rat

Sex	Male				Female			
Group	1	2	3	4	1	2	3	4
Number examined	50	50	50	50	50	50	50	50
Organ								
Brain compressed	2	49	37	37	4	41	48	47
Epididymides small	0	4	2	0	-	-	-	-
soft	0	1	1	0	-	-	-	-
Liver nodules/mass	0	1	1	0	0	0	0	1
Ovaries cysts	-	-	-	-	11	6	0	0
small	-	-	-	-	2	8	23	17
Pituitary nodules or masses	3	48	45	47	16	44	48	48
cysts	0	1	3	3	1	0	1	0
Prostate small	0	5	2	2	-	-	-	-
Skin discolored	5	26	30	32	5	30	39	39
hair loss	0	4	4	4	6	6	16	13
swollen	3	15	7	8	6	15	11	9
Spleen small	0	7	8	6	0	9	13	18
Testes small	3	18	4	5	-	-	-	-
soft	11	15	4	3	-	-	-	-
Uterus small	-	-	-	-	0	12	32	25
General comments: Emaciated	3	18	15	15	3	23	28	31

Histopathology

Complete gross postmortem examinations and histopathological evaluation of selected tissues were conducted on all animals.

Peer Review: Not done

Neoplastic

Adenoma of the pars distalis was seen in almost all treated males and females, with a dose related onset. Males appear to be more susceptible. Pituitary carcinomas were noted at lower incidence. Pituitary adenoma is one of the most common spontaneous tumors observed in SD rats (Baldrick P, Tox Pathol 2005). However, treatment with triptorelin dose-dependently accelerated the onset of this tumor. The carcinogenic profile of triptorelin was similar to that observed for other approved GnRH agonist analogs.

Pituitary tumors are known effects of castrations and exposure to compounds which cause gonadal atrophy and concomitant defects in gonadal hormones production leading to histopathological changes in the pituitary. In absence of negative feedback control, hypothalamic hyper-physiotropic factors hyper-stimulate the pituitary causing castration cells to appear in the pars distalis (Gopinath et al 1987). Experimentally induced hypertrophy and hyperplasia of the pars distalis have been observed to progress to tumor formation in rats (Furth et al 1976) and mice (Leibelt 1979). The relevance of rat pituitary adenoma to humans has not been established.

Table 35. Tumors in the rat

	--- NUMBER-OF-ANIMALS -							
SEX:	-------MALE-------				------FEMALE------			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION NUMBER:	50	50	50	50	50	50	50	50
PITUITARY GLAND ..... NUMBER EXAMINED:	49	49	49	50	50	48	50	50
--B- PARS DISTALIS: ADENOMA	20	43	44	46	22	42	44	43
--M- PARS DISTALIS-CARCINOMA	1	6	3	4	3	5	5	6
--B- PARS INTERMEDIA: ADENOMA	0	0	0	0	1	0	0	0

Non Neoplastic

Non neoplastic findings were limited to the reproductive organs and were consistent with triptorelin pharmacologic activity.

Reproductive organs

Minimal to severe maturation arrest of the germinal epithelium, oligospermia, minimal to moderate atrophy and a decrease in the amount of secretory product in the prostate were observed mostly in the high dose group.

Dose related increase in the incidence of slight to marked atrophy, characterized by the absence of developed follicles or corpora lutea, and minimal to moderate Sertoliform cell hyperplasia, characterized by the presence of tubular structures lined by cells similar to Sertoli cells in the seminiferous tubules of the testes, were observed in the ovary. Sertoli form hyperplasia has been occasionally described in atrophic ovaries and has been induced experimentally by hypohysectomy and by chemical or hormone treatment (Alison RH 1990).

Forestomach

Minimal to marked congestion, edema, erosion/ulcer, subacute (chronic active)/chronic inflammation, squamous cell hyperplasia and hyperkeratosis in all treatment groups. While clearly treatment related, the clinical relevance of these findings is questionable, given that humans lack an anatomical analogue to the rodent forestomach.

Mammary tissue

Increased incidence of female type mammary tissue was noted in males.

Injection site
Increased incidence of tan/granular necrosis and subacute/chronic inflammation was noted in all treatment groups as compare to controls.

Table 36. Non neoplastic findings in the rat

ORGAN/TISSUE EXAMINED		SEX: / GROUP:	-------MALE------- -1-	-2-	-3-	-4-
		NUMBER:	50	50	50	50
TESTES	NUMBER EXAMINED:		50	48	46	49
--U/ GERMINAL EPITHELIUM: MATURATION ARREST		2>	0	1	2	0
		3>	0	3	0	0
		5>	0	1	0	0
		TL>	0	5	2	0
--B/ GERMINAL EPITHELIUM: MATURATION ARREST		1>	0	1	0	0
		2>	0	1	2	2
		3>	0	1	1	0
		4>	0	0	0	1
		5>	0	2	0	0
		TL>	0	5	3	3
EPIDIDYMIDES	NUMBER EXAMINED:		50	47	45	49
--U/ OLIGOSPERMIA		3>	1	0	0	1
		4>	0	2	0	0
		TL>	1	2	0	1
--B/ OLIGOSPERMIA		2>	1	2	1	0
		4>	2	1	0	1
		5>	0	3	2	0
		TL>	3	6	3	1
PROSTATE	NUMBER EXAMINED:		50	47	46	49
--DECREASED SECRETORY PRODUCT		1>	7	6	3	5
		2>	5	11	19	8
		3>	2	5	6	6
		TL>	14	22	28	19
--ATROPHY		2>	0	1	4	1
		3>	1	5	1	2
		TL>	1	6	5	3
SEMINAL VESICLES	NUMBER EXAMINED:		50	47	46	49
--U/ DECREASED SECRETORY PRODUCT		3>	1	0	0	0
		TL>	1	0	0	0
--B/ DECREASED SECRETORY PRODUCT		2>	0	2	4	3
		3>	1	5	3	1
		4>	1	1	0	2
		5>	0	5	2	0
		TL>	2	13	9	6
--U/ ATROPHY		2>	0	1	0	0
		TL>	0	1	0	0
--B/ ATROPHY		1>	1	0	0	0
		2>	1	1	0	1
		3>	0	1	1	2
		4>	0	3	1	0
		5>	0	1	0	0
		TL>	2	6	2	3

ORGAN/TISSUE EXAMINED		SEX: / GROUP:	------FEMALE------ -1-	-2-	-3-	-4-
		NUMBER:	50	50	50	50
OVARIES	NUMBER EXAMINED:		50	46	44	44
--U/ ATROPHY		2>	0	0	1	0
		3>	0	1	0	0
		4>	0	1	6	6
		5>	0	1	13	6
		TL>	0	3	20	12
--B/ ATROPHY		2>	0	4	0	0
		3>	0	15	0	0
		4>	1	9	14	15
		5>	0	0	9	17
		TL>	1	28	23	32
--U/ SERTOLIFORM CELL HYPERPLASIA		1>	1	7	16	8
		2>	1	4	4	8
		3>	2	0	1	6
		TL>	4	11	21	22
--B/ SERTOLIFORM CELL HYPERPLASIA		1>	3	1	3	3
		2>	3	6	1	4
		3>	0	4	2	5
		TL>	6	11	6	12
UTERUS	NUMBER EXAMINED:		50	47	50	48
--ENDOMETRIUM: ATROPHY		2>	0	8	1	0
		3>	1	12	5	4
		4>	0	13	15	32
		5>	0	1	29	12
		TL>	1	34	50	48
--MYOMETRIUM: ATROPHY		2>	0	8	1	0
		3>	1	12	5	4
		4>	0	13	15	32
		5>	0	1	29	12
		TL>	1	34	50	48

ORGAN/TISSUE EXAMINED		SEX:	MALE				FEMALE			
		GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
		NUMBER:	50	50	50	50	50	50	50	50
STOMACH	NUMBER EXAMINED:		50	46	44	50	50	45	50	50
--FORESTOMACH: SQUAMOUS CELL HYPERPLASIA		1>	1	2	1	2	0	0	0	0
		2>	2	10	7	4	5	5	5	7
		3>	3	16	11	18	1	14	12	22
		4>	0	0	2	1	0	0	12	4
		5>	0	0	0	0	0	0	1	0
		TL>	6	28	21	25	6	19	30	33
--FORESTOMACH: HYPERKERATOSIS		1>	0	2	1	3	0	0	0	0
		2>	2	11	7	3	5	8	5	8
		3>	2	15	11	19	1	14	12	24
		4>	0	0	2	0	0	0	12	1
		5>	0	0	0	0	0	0	1	0
		TL>	4	28	21	25	6	22	30	33
--FORESTOMACH: SUBACUTE (CHRONIC ACTIVE)/ CHRONIC INFLAMMATION		1>	0	0	0	0	0	0	0	2
		2>	0	13	2	8	1	3	5	5
		3>	3	12	12	13	1	11	14	18
		4>	0	0	0	0	0	0	9	1
		TL>	3	25	14	21	2	14	28	26
--FORESTOMACH: CONGESTION		1>	0	0	0	0	0	0	1	0
		2>	0	20	15	7	3	12	10	13
		3>	1	4	2	7	1	3	14	3
		TL>	1	24	17	14	4	15	25	16
--FORESTOMACH: EDEMA		1>	0	0	0	0	0	0	2	2
		2>	0	4	4	3	1	2	4	7
		3>	2	16	10	15	2	11	14	13
		4>	0	0	0	0	0	0	0	1
		TL>	2	20	14	18	3	13	20	23
--FORESTOMACH: EROSION(S)/ULCER(S)		1>	0	0	1	2	0	6	2	2
		2>	0	3	3	7	0	1	1	4
		3>	0	3	4	1	0	3	6	2
		4>	0	0	0	0	0	0	0	1
		TL>	0	6	8	10	0	10	9	9

Severity Codes

1> - Minimal 3> - Moderate 5> - Severe
2> - Slight 4> - Marked TL> - Total Number of Lesions

sex	Male				Female			
group	1	2	3	4	1	2	3	4
number	50	50	50	50	50	50	50	50
Mammary								
female type mammary tissue	17	25	31	36	48	47	49	44
Ductal ectasia/galactocele	4	19	14	9	34	43	34	29
granulomatous inflammatory reaction	0	5	7	0	12	27	20	1
Injection site foreign material: Tan/granular	0	2	10	21	0	4	11	30
necrosis	0	0	0	3	0	0	0	3
subacute/chronic inflammation	5	4	3	8	2	3	4	11
granulomatous inflammation/granuloma	26	2	10	20	18	4	10	28

Toxicokinetics

NA

9 Reproductive and Developmental Toxicology

Reproductive and developmental toxicity studies of triptorelin were performed in mice, rats, and rabbits. In the fertility studies, administration of triptorelin to females before mating did not affect fertility in rats or ovarian parameters in rabbits. No maternal, embryo, or fetal toxicity was observed in mice at doses up to 200ug/kg/day (4-fold the clinical dose). In rats, maternal toxicity (reduced body weight gain) and embryo toxicity (increase in uterine resorptions) was noted at 100 ug/kg/day or 4 fold the clinical dose, based on body surface area. Triptorelin was not teratogenic in mice or rats.

9.1 Fertility and Early Embryonic Development

Study title: Fertility study of triptorelin acetate and triptorelin acetate microspheres in female SD rats

Study no.:	704-534/4
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 1988
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	D-TRP6-LH-RH, batches # P 80040 and P 015, 99%

Key Study Findings

Parental treatment with triptorelin did not elicit maternal or embryo-toxicity, teratogenicity, post-natal development of the offspring, or reproductive performance of the F1 generation. NOAEL: 200ug/kg/day, 1200ug/m^2, 7 fold clinical dose

Methods

Doses:	Triptorelin acetate: 2, 20, and 200 ug/kg/day for 60 days by SC injection Triptorelin microcapsules : 600 ug/kg on Days 1 and 31 by IM injection
Frequency of dosing:	Daily (SC), once a month (IM)
Dose volume:	Not indicated
Route of administration:	SC and IM injections
Formulation/Vehicle:	Triptorelin solution: Saline 0.9% Triptorelin microcapsule: 2% CMC, 1% Tween 80
Species/Strain:	SD rats
Number/Sex/Group:	35/group
Satellite groups:	NA
Study design:	Female rats (8-12 weeks old) received triptorelin acetate by SC injection at doses of 0, 2, 20, and 200 ug/kg daily for 60 days. An additional group of 35 female rats received 600 ug/kg of triptorelin acetate microspheres (slow release) by IM injection on days 1 and 31. After showing a minimum of four estrus cycles, the females were mated for maximally 14 days with fertile untreated males. Twelve to 19 females per group were sacrificed on Day 20 post-coitum and the fetuses examined. The remaining females were allowed to litter and to rear the pups to weaning. Pups were examined for physical and behavioral development. Reproductive performance of the F 1 generation was assessed after the growth period of 91 to 110 days: one male was mated with one female from the same dose group over a period of maximally 14 days in such a way that sibling mating was avoided.
Deviation from study protocol:	NA

Table 37. Fertility study design

Group number	Group designation	Dose level (µg/kg/day)	Number of females
1	Control	0	35
2	Low	2	35
3	Intermediate 1	20	35
4	Intermediate 2	20*	35
5	High	200	35

*) slow release

Dose selection: Based on pharmacological and kinetic studies in rats, the low dose of 2 ug/kg/day was chosen as a non-castrating dose, and the doses of 20 and 200 ug/kg/day as multiples of the castrating dose. 600 ug/kg for one month of the slow release formulation corresponds to a theoretical dose of 20 ug/kg/day but after the injection there is a "burst effect" due to a diffusion/hydrolysis phenomenon. Then the peptide release at the plateau is between 10 and 15 ~g/kg/day.

Observations and Results

Mortality

There was no treatment related mortality.

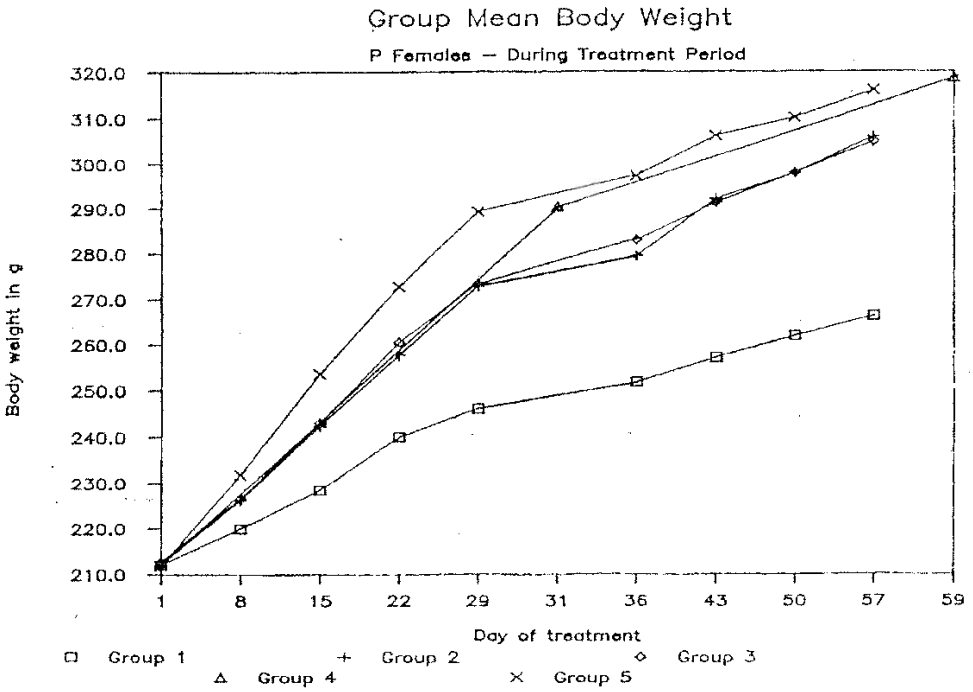
Clinical Signs

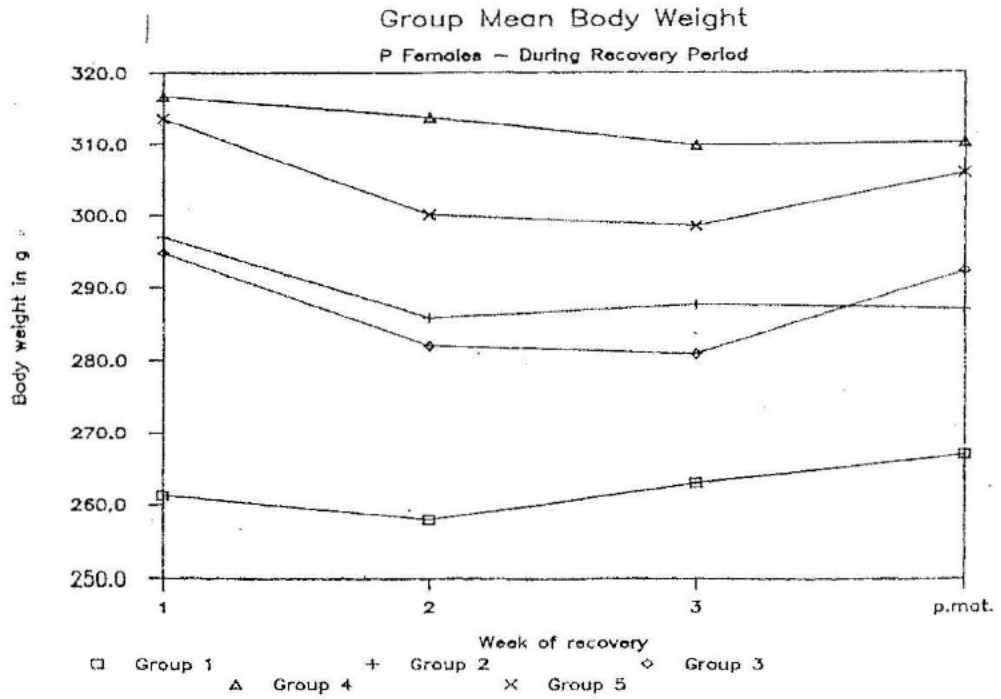
There were no treatment-related clinical signs.

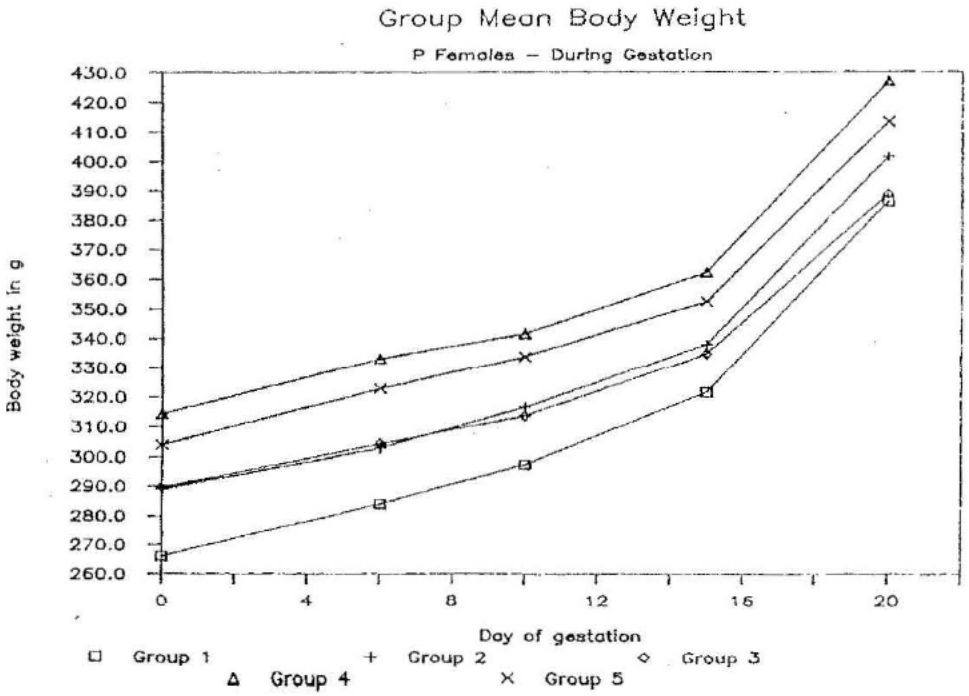
Body Weight

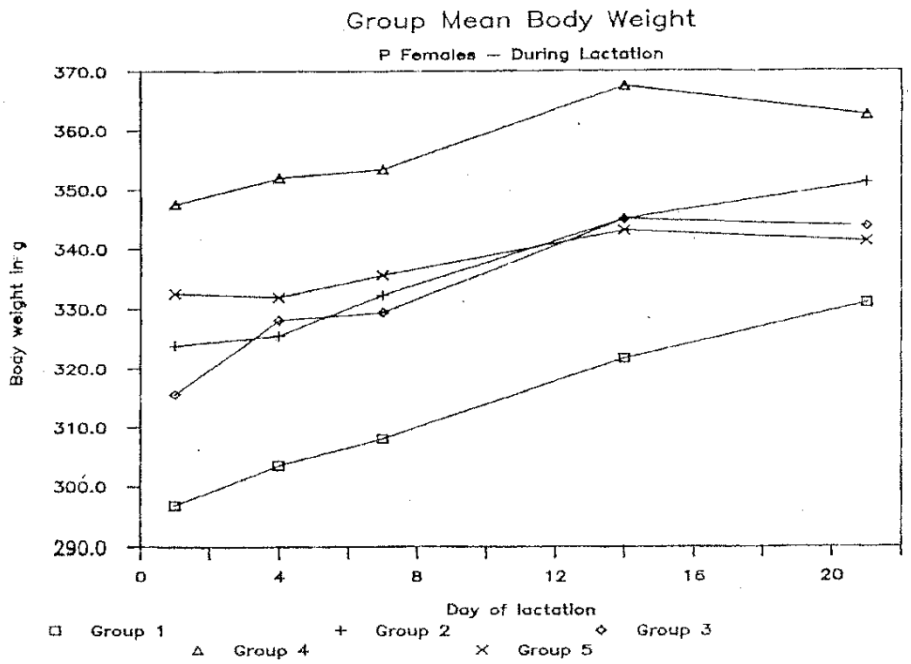
Body weight gain and body weight was increased in all treatment groups during dosing. Body weight remained higher during gestation and lactation; however weight gain was similar to that of controls.

Figure 12. Body weight during dosing, gestation, and lactation




Group Mean Body Weight
P Females – During Recovery Period
320.0
310.0
300.0
290.0
280.0
270.0
260.0
250.0
Body weight in g
1
2
3
p.mat.
Week of recovery
Group 1
Group 2
Group 3
Group 4
Group 5

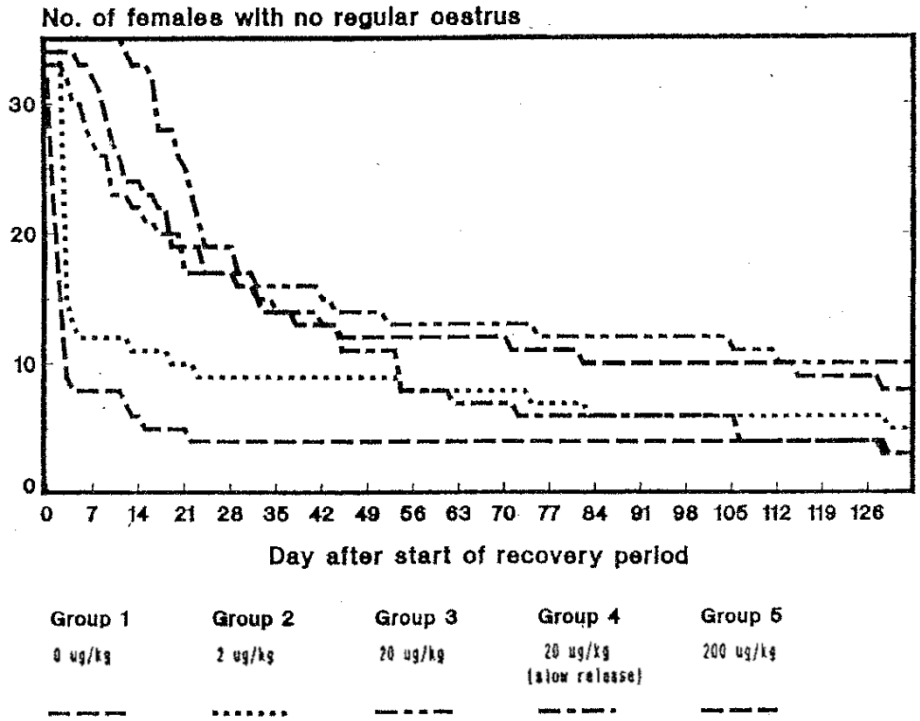

Group Mean Body Weight
P Females – During Gestation
430.0
420.0
410.0
400.0
390.0
380.0
370.0
360.0
350.0
340.0
330.0
320.0
310.0
300.0
290.0
280.0
270.0
260.0
Body weight in g
0
4
8
12
16
20
Day of gestation
Group 1
Group 2
Group 3
Group 4
Group 5



Estrous cyclicity

The recovery of regular cycles was dose-dependently delayed, and was longer with the monthly IM (7, 15, 28, 39 days) than the daily SC treatment (31 days). No changes in the cycle duration were observed.

Figure 13. Estrous cyclicity



Mating and fertility

No treatment related effect were observed.

Toxicokinetics

NA

Necropsy

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

There was no treatment related effect on implantation, post-implantation loss, number and sex of fetuses, fetal weight.

Offspring (Malformations, Variations, etc.)

There were no external or skeletal malformations in any dose group.

Dams-Littering subgroup

There were no treatment related effects on the duration of gestation, number of pups and sex distribution, pup weight, physical development (pinna unfolding, hair growth, incisor eruption, eye opening) or neurobehavior (pupillary reflex, auditory response, water maze test).

F1 generation

Reproductive performance

There was no effect of maternal treatment on F1 reproductive performance.

Caesarian data-F1 generation

There was no treatment related effect on implantation, post-implantation loss, number and sex of fetuses, fetal weight, or external malformation.

Pilot reproductive and developmental toxicity study of triptorelin acetate in rabbits

The object of this study was to investigate the effects of triptorelin on the ovaries of the New Zealand White rabbit when administered during two weeks prior mating.

Study no.:	691-534/3
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 1987
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	D-TRP6-LH-RH, batch # P 80040, 99%

Key Study Findings

There were no treatment related effects on the ovaries following two weeks of triptorelin treatment prior to mating.

Methods

Doses:	20 ug/kg/day for 2 weeks
Frequency of dosing:	Once daily
Dose volume:	Not indicated
Route of administration:	SC injections
Formulation/Vehicle:	Saline 0.9%
Species/Strain:	New Zealand White rabbits
Number/Sex/Group:	30/group
Satellite groups:	NA
Study design:	Female rabbits were administered triptorelin once daily during two weeks prior to mating and then mated at the first signs of estrus after termination of treatment. Group 1 animals were killed on day 8 post coitum and group 2 animals on day 28 post coitum and the fetuses obtained. The ovaries of the animals killed on day 8 post-coitum were examined. The number of atretic follicles and the existence of primary, secondary, tertiary and graafian follicles as well as corpus luteum were examined.
Deviation from study protocol:	NA

Mortality

There was no treatment related mortality.

Clinical Signs

No treatment-related changes were observed.

Body Weight

No treatment-related changes were observed.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

There were no treatment related effects on pregnancy incidence, pre- and post-implantations loss, number and sex of fetuses, fetal weight or external malformations.

Ovary-Histopathology

No treatment-related histopathology changes were observed in the ovary.

9.2 Embryonic Fetal Development

A segment II teratology study of triptorelin pamoate in mice

Study no.:	88-3368
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 1989
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	D-Trp6]-LHRH Pamoate, batch DPG 0389

Key Study Findings

Administration of triptorelin during organogenesis did not elicit maternal toxicity, embryotoxicity or teratogenic effects up to 200 ug/kg/day, 4 fold the clinical dose.

Methods

Doses:	0, 2, 20 and 200 ug/kg/day
Frequency of dosing:	Once daily from GD6 to15
Dose volume:	4 mL/kg
Route of administration:	SC injection
Formulation/Vehicle:	Propylene glycol
Species/Strain:	CD1 mice
Number/Sex/Group:	30 mated female/group
Satellite groups:	NA
Study design:	Triptorelin was injected subcutaneously to female mice from Gestation Days 6 to 15. Females were sacrificed on GD 18 and given a

gross postmortem examination. Ovaries were evaluated for number of corpora lutea and uterine implantation data were evaluated for number of live, dead and resorbed fetuses. Fetuses recovered at this time were weighed, sexed and evaluated for external, skeletal, and visceral malformations.

Deviation from study protocol: NA

Table 38. Segment II mouse study design

Group	Dose Level (mcg/kg/day)	Dose Volume (ml/kg/day)	Concentration of Dosing Solution (mcg/ml)	No. of Females Mated	Treatment Schedule (gestation days)	Fetal Evaluation: Proportion of Fetuses Examined/Litter for Malformations/Variations: External	Soft Tissue	Skeletal
I	0[a]	4.0	0	30	6-15	All	1/3	2/3
II	2	4.0	0.5	30	6-15	All	1/3	2/3
III	20	4.0	5.0	30	6-15	All	1/3	2/3
IV	200	4.0	50	30	6-15	All	1/3	2/3

[a]Propylene glycol.

Observations and Results

Mortality

None

Clinical Signs

Unremarkable

Body Weight

No treatment related changes were observed during gestation.

Feed Consumption

No treatment related changes were observed.

Toxicokinetics

NA

Dosing Solution Analysis

NA

Necropsy

No treatment related gross findings were observed.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

The numbers of implantations, resorptions, live and dead fetuses were comparable between drug-treated groups and the controls. The number of corpora lutea was slightly higher in the mid and high dose groups (15.6 and 15.9 compared to 14.1 in controls), but was not statistically different. Since ovulation occurred prior to initiation of treatment, no adverse effect of treatment was indicated from this slight increase in number of corpora lutea. The sponsor stated that treatment may have produced some stimulation in ovarian follicle maturation or accelerated the atresia of corpora lutea of pregnancy which would make it difficult to distinguish between the two structures at necropsy and thus elevate the corpora lutea count.

Offspring (Malformations, Variations, etc.)

No treatment related external, skeletal or visceral malformations were observed.

A segment II teratology study of triptorelin pamoate in rats

Study no.:	88-3369
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 1990
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	[D-Trp6]-LHRH Pamoate, batch DPG 0189

Key Study Findings

- Maternal (reduced gestational body weight gain) and embryotoxicity (increased resorptions and decrease viable fetuses) at 100 ug/kg, 4 fold the clinical dose based on BSA.
- No teratogenic effects were evident up to 100 ug/kg, although a limited number of fetuses were recovered at the high-dose level.

Methods

Doses:	0, 2, 10, and 100 ug/kg/day
Frequency of dosing:	Once daily
Dose volume:	Not indicated
Route of administration:	SC injection
Formulation/Vehicle:	Propylene glycol
Species/Strain:	SD rats
Number/Sex/Group:	25 mated female/group
Satellite groups:	NA
Study design:	Triptorelin was injected subcutaneously to female rats from Gestation Days 6 to 15. Females were sacrificed on GD 20 and given a gross postmortem examination. Ovaries were evaluated for number of corpora lutea and uterine implantation data were evaluated for number of live, dead and resorbed fetuses. Fetuses recovered at this time were weighed, sexed and evaluated for external, skeletal, and visceral malformations
Deviation from study protocol:	NA

Observations and Results

Mortality

None

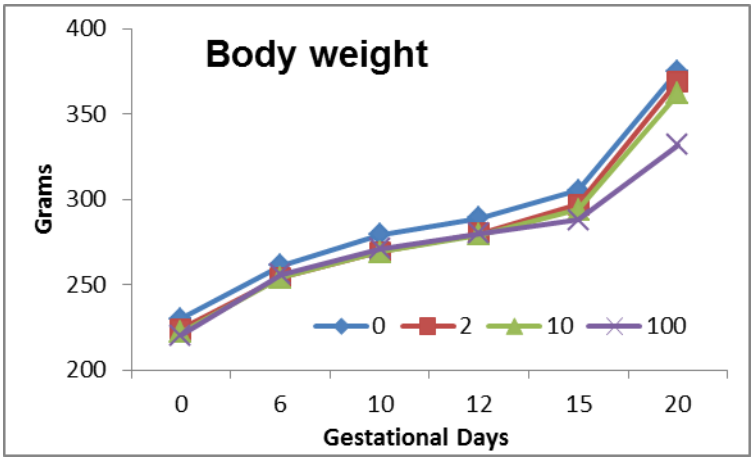
Clinical Signs

No treatment-related clinical signs were observed.

Body Weight

Decreased body weight gain in high-dose females compared to controls (-53% and -27% between GD 12-15 and GD6-15, respectively). Relatively to controls, body weight was decreased 6 and 11% on GD15 and GD20, respectively.

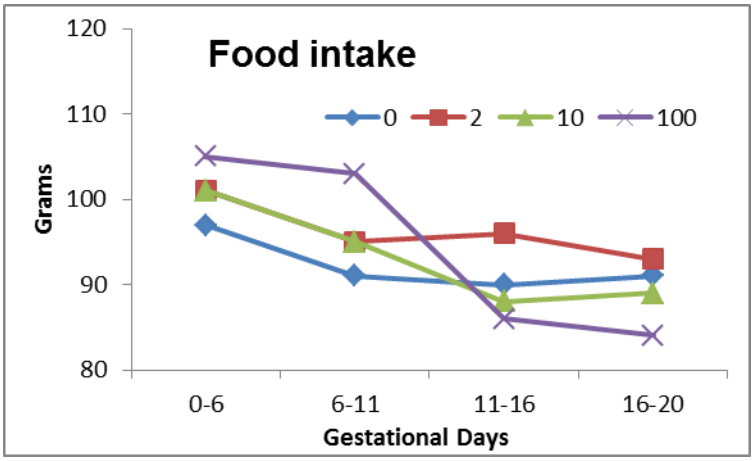
Figure 14. Gestational body weight in the rat



Feed Consumption

Compared to controls, food consumption in the high dose group was higher during GD 6-11, similar during GD 11-16 and lower thereafter.

Figure 15. Food consumption during gestation in the rat



Toxicokinetics

NA

Dosing Solution Analysis

NA

Necropsy

No treatment related adverse effects were observed.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

Increase in litters with all resorptions and decrease in litters with viable fetuses was observed in the high-dose group.

Increase in the number of corpora lutea in all treated groups, without dose relationship, may have been due to the difficulty in distinguishing between corpora lutea of pregnancy and mature ovarian follicles along the surface of the ovary, since ovulation occurred several days before treatment initiated. In addition similarity number of uterine implantations between the control and treated groups would also suggest that there was no effect on ovulation rate.

Increase in pre-implantation loss in all treatment groups attributable to an exaggerated corpora lutea count.

Decrease number of implantations in the high-dose group (13.2 vs. 14.7 for controls) was not statistically significant and within the historical control range (11.5-15.5).

Table 39. Fertility and C-section parameters in the rat

DOSE GROUP	0 mcg/kg/day	3 mcg/kg/day	10 mcg/kg/day	100 mcg/kg/day
#Females Mated	25	25	25	25
#Pregnant (%)	25(100.0)	22(88.0)	24(96.0)	24(96.0)
#Pregnancies Aborted	0	0	0	0
#Premature Births	0	0	0	0
#Litters with Viable Fetuses	25	22	23	6**
#Litters with all resorptions	0	0	1	7**
Female Mortality #(%)	0	0	0	0
#Corpora Lutea	421	510	658	280
Mean ± S.D.	16.8 ± 2.7	23.3 ± 6.4**	27.4 ± 10.8**	21.5 ± 7.8
#Implantation sites	368	330	343	171
Mean ± S.D.	14.7 ± 2.6	15.0 ± 2.3	14.3 ± 2.2	13.2 ± 3.4
Preimplantation Loss				
Mean ± S.D.	0.120 ±0.132	0.314 ±0.175**	0.424 ±0.188**	0.354 ±0.193**
#Viable Fetuses	349	313	310	80
Mean Litter Size ± S.D.	14.0 ± 2.7	14.2 ± 2.0	12.9 ± 3.6	6.2 ± 7.2**
Mean # Males ± S.D.	6.8 ± 2.2	7.1 ± 2.4	6.7 ± 2.5	2.8 ± 3.4**
Mean # Females ± S.D.	7.2 ± 1.9	7.1 ± 2.3	6.3 ± 2.8	3.3 ± 3.9**
#Dead Fetuses	0	0	0	1
#Resorptions	19	17	33	90
Mean ± S.D.	0.8 ± 0.9	0.8 ± 0.9	1.4 ± 3.0	6.9 ± 6.3*
Resorptions / Implants				
Mean ± S.D.	0.053 ±0.061	0.049 ±0.052	0.095 ±0.203	0.576 ±0.481*
#Litters with Resorptions (%)	12(52.0)	13(59.1)	15(62.5)	10(76.9)
Mean Body Weight (g) of Viable Fetuses ± S.D.	3.43 ± 0.21	3.42 ± 0.21	3.43 ± 0.27	3.55 ± 0.25
Male Fetuses	3.48 ± 0.26	3.53 ± 0.21	3.54 ± 0.30	3.59 ± 0.34
Female Fetuses	3.31 ± 0.21	3.32 ± 0.22	3.29 ± 0.31	3.53 ± 0.17
Ratio of Viable Fetuses Total males / Total females	0.9	1.0	1.1	0.9

Offspring (Malformations, Variations, etc.)

No treatment related increase in the incidence of external, skeletal or visceral malformations were noted.

10 Special Toxicology Studies

Twenty-four hours after intramuscular injection of triptorelin acetate microspheres or triptorelin pamoate microgranules into young, adult female Sprague-Dawley rats (5 per group), the histologically detectable tissue reactions were characteristic of repair of damaged tissue. A minimal inflammatory reaction was seen, characterized by infiltration of lymphocytes, plasma cells, and histiocytes; infiltration was most noticeable around some muscle fibers apparently damaged during the injection. There was a fibrous connective tissue reaction around each microsphere and microgranule. Although there

was negligible cell proliferation in the area containing microspheres, there was a visible accumulation of inflammatory cells around the microgranules indicative of a marked foreign body reaction.

11 Integrated Summary and Safety Evaluation

Triptorelin is a synthetic analog of the endogenous gonadotropin-releasing hormone (GnRH), a hypothalamic decapeptide that stimulates the pulsatile secretion of gonadropins (LH and FSH) from the anterior pituitary. LH and FSH stimulate the gonadal production of sex steroid hormones, which in turn inhibit secretion of GnRH by a negative feedback mechanism. The rationale of continuous GnRH secretion for the suppression of pubertal development is that continuous stimulation of LH secretion results in the desensitization of GnRH receptors, thereby inhibiting the release of LH and FSH, resulting in gonadal suppression.

Triptorelin was evaluated in a standard nonclinical program conducted under the prostate cancer indication (NDAs 20715, 21288, and 22437, to which the Applicant has the right of reference). No new nonclinical studies were submitted for the CPP indication.

Pharmacodynamic and pharmacokinetics studies in rats showed that intramuscular injection of the triptorelin pamoate 6-month formulation resulted in a rapid decrease of testosterone levels which remained at castrate levels for at least 6 months. No adverse findings in the the central nervous, cardiovascular, digestive, and renal systems were observed following acute administration of triptorelin in a standard battery of safety pharmacology studies.

General toxicity studies were conducted in rats, dogs, and monkeys for up to 6-month duration, with a recovery period of 2-month in monkeys and 4-month in male rats. In all species tested, toxicity was consistent with the expected physiological action of triptorelin: decrease in serum levels of LH (rat, monkey), testosterone in males (rat, dog), and estradiol and progesterone in females (monkey), and suppression of testicular (tubular atrophy,necrosis, maturation arrest, oligospermia in rat and prostate atrophy in the dog) and ovarian function (atrophy and absence of developed follicles in rats and monkeys) were observed starting at the clinical dose. All changes were reversible at dose cessation, except for the testicular changes in male rats (tubular atrophy, mineralization, and maturation arrest), which were partially reversible.

Triptorelin was not genotoxic in *in vitro* or *in vivo* testing. In a carcinogenicity study in rats, increased incidence and earlier onset of pituitary adenoma and carcinoma, leading to brain compression and subsequent mortality, were observed starting at the clinical dose. No tumors were observed in mice at doses up to 4 fold the clinical dose, based on body surface area. Pituitary tumors appear to be species specific, have been observed with other GnRH agonists at the clinical dose, and are related to hyper-stimulation of the pituitary in the absence of negative feedback control by the gonadotrope hormones.

No adverse effect on fertility was observed in female rats treated with triptorelin for two months or in the F1 females. In female rabbits administered triptorelin for two weeks prior to mating, there were no advserse effects on the ovaries examined on day 8 post-coitum. Maternal toxicity (decrease in maternal weight) and embryotoxicity (pre-implantation loss, increased resorptions, and reduced number of viable fetuses) were observed in a embryofetal toxicity study in rats at 8-fold the clinical dose; no adverse maternal or embryo effects occurred in mice at the same multiples to the clinical dose. Triptorelin was not teratogenic in mice or rats.

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

/s/

RONALD L WANGE on behalf of FEDERICA BASSO
05/25/2017
Recommend Approval.

RONALD L WANGE
05/25/2017
I concur with recommendation for approval.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208956 **Applicant: Arbor Pharmaceuticals, LLC** **Stamp Date: 8/19/2016**

Drug Name: Triptodur (triptorelin pamoate for (b) (4) suspension), 22.5 mg **NDA/BLA Type: 505(b)1**

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies (in accord with 505 (b)(1) and (b)(2) 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		The sponsor is relying on nonclinical data previously submitted and reviewed under (b) (4) NDA20715, triptorelin 6-month formulations, approved for the palliative treatment of men with advanced prostate cancer.
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		The formulation to be marketed is the same as for the approved Triptorelin NDAs.
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		The intended route of administration is via intramuscular injection, and the toxicology studies were conducted by intramuscular and subcutaneous injections.
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		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A No new nonclinical studies were requested during pre-submission discussions. Two in vitro drug-drug interaction studies were submitted to Module 5.3
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)			N/A
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		X	
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?			N/A

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

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

N/A

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

N/A

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

/s/

FEDERICA BASSO
10/18/2016

RONALD L WANGE
10/19/2016