CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-058

PHARMACOLOGY REVIEW(S)

Signed off in DFS on 4/17/07

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-058
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	6/30/2006
PRODUCT:	Supprelin LA (Histrelin acetate subcutaneous implant), a GNRH analog
INTENDED CLINICAL POPULATION:	It is indicated for the treatment of central precocious puberty (CPP) in children.
SPONSOR:	Valera Pharmaceuticals, Inc. Cranbury, NJ
DOCUMENTS REVIEWED:	Submitted in an electronic Common Technical Document (eCTD) format.
REVIEW DIVISION:	Division of Metabolism and Endocrinology Products.
PHARM/TOX REVIEWER:	Indra Antonipillai
PHARM/TOX SUPERVISOR:	Karen Davis Bruno
DIVISION DIRECTOR:	Mary Parks
PROJECT MANAGER:	Jennifer Johnson

Date of review submission to Division File System (DFS): 4/17/2007

TABLE OF CONTENTS

Executive Summary

I. Recommendations

A. Recommendation on approvability: Pharmacology recommends approval of NDA 22-058 for the treatment of central precocious puberty (CPP) in children.

B. Recommendation for nonclinical studies: Based on two previously approved NDAs, i.e. NDA 19-836 of Histrelin subcutaneous injection for the treatment of central precocious puberty and NDA 21-732 implant for palliative treatment of advanced prostate cancer, pharmacology considers that sufficient & adequate P/T information is available to establish safety of the proposed Histrelin implant for CPP in children.

C. Recommendations on labeling: Labeling is in general acceptable with minor revisions. New pharmacokinetic studies in rats and mice were submitted in the current application and almost all pharmacology/toxicity studies including carcinogenicity, fertility, and teratogenicity studies have been conducted under two previously approved NDAs; Shire (NDA 19-836) and Valera (NDA 21-732). Valera has a right of reference to NDA 19-836

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: Nonclinical studies reviewed under NDA 21-732 suggest that extracts of HEMA/HPMA copolymer placebo reservoir (Hydrogel implant reservoir) or that of Hydrogel/histrelin implants were not genotoxic. Also long term sub-dermal implant insertion had no significant adverse effects. This supports safety of the implant.

B. Pharmacologic activity: Histrelin acetate is an LH-RH agonist, and a potent inhibitor of gonadotropin secretion when given continuously. After an initial stimulatory phase, chronic subcutaneous administration of histrelin acetate desensitizes responsiveness of the pituitary gonadotrophs, which in turn causes a reduction in ovarian and testicular steroidogenesis and concomitant pubertal changes. This drug delivery system slows the sexual development and allows for appropriate growth and maturation in this population.

C. Safety issues relevant to clinical use: In light of the previous safe approval of histrelin acetate under NDA 19-836 (as a daily SC injection for CPP) and NDA 21-732 (an implant for the palliative treatment of prostate cancer), there appears to be no new non-clinical safety issues relevant to its clinical use.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: NDA 22-058
Review number: 1
Sequence number/date/type of submission: 000/ 6/30/2006/ Original submission. It is a 505(b)(1) application. Submission 9/15/06 (an amendment). The previous NDA (NDA 21-732) of this drug/device combination was approved in 2004.
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Valera Pharmaceuticals, Inc. Cranbury, NJ
Manufacturer for drug substance: [redacted] and Valera Pharmaceuticals, Cranbury, New Jersey b(4)

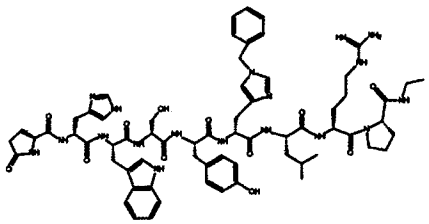
Reviewer name: Indra Antonipillai, Ph.D.
Division name: DMEP
Review completion date: 2/12/07

Drug:

Trade name: Supprelin LA (Histrelin acetate subcutaneous subdermal implant). The hisrtrelin acetate implant contains 50 mg of histrelin acetate and delivers approximately 65 ug/day of the drug over 12 months.
Generic name: LHRH (luteinizing hormone-releasing hormone).
Code name: LHRH factor, also known as gonadotropin releasing hormone (GnRH), [ImBz]-D-His^6, Pro^9,NE_t]-LHRH, H-9210, ORF 17070, LHRH-13
Chemical name: Histrelin acetate: 5-oxo-L-propyl-L-histidyl-L-tryptophyseryl-L -tyrosylN^t-benzyl-D-histidyl-L-leucyl-L-arginyl-N-ethyl-L - prolinamide acetate (salt)

CAS registry number: 76712-82-8
Molecular formula/molecular weight:
$C_{66}H_{86}N_{18}O_{12}$ (net histrelin), $C_{66}H_{86}N_{18}O_{12}.2CH_2CH_4O_2$ (Histrelin acetate)
MW: 1323.52 (net histrelin), 1443.7 (histrelin acetate)

Structural formula for drug substance Histrelin acetate:



Impurities: [redacted] synthetic impurities have been isolated and identified in histrelin acetate drug substance. [redacted] of the impurities are [redacted] and the [redacted] is the [redacted] b(4)

Following are the [redacted] impurities:

1.
2.
3.
4.
5
6

[redacted] b(4)

The sponsor has stated that drug substance assay is capable of resolving [redacted] impurities with a limited quantitation of [redacted] The impurity that is not resolved is [redacted] and this impurity along with and [redacted] have not been detected above [redacted] in the histrelin acetate drug substance. b(4)

Impurities/degradants: [redacted] have been isolated and identified in the implant drug product, all of which were [redacted] and were resolved using the drug product assay. All the above impurities/degradants mentioned here were also noted in the approved NDA 21-732. b(4)

Relevant INDs/NDAs/DMFs: Shire NDA #19-836 (approved for daily SC injection for clinical manifestation of CPP, the recommended dose was 10 ug/kg), NDA 21-732 (Vantas histrelin acetate implant to alleviate the symptoms of prostate cancer, the implant contains 50 mg of histrelin acetate and delivers approximately 50 ug/day of the drug or 8.3 ug/kg/day for 60 kg person), IND [redacted] IND 67,582. [redacted] DMF # [redacted] b(4)

Drug class: LHRH agonist

Clinical formulation: The Supprelin LA Histrelin Subcutaneous Implant is a reservoir type drug release device, where the release kinetics are controlled by the diffusion characteristics of the implant polymer. The implant contains the drug within its reservoir and the void volume is filled with water, which is saturated with the drug. The concentration gradient between the concentrations within the implant and the outside environment is the force driving the drug across the wall of the implant.

The drug/device combination is designed to provide a sustained release of a steady amount of histrelin over a period of one year or more, when inserted subcutaneously. The implant is hydrated, [redacted] polymer that contains histrelin acetate as the active pharmaceutical ingredient. b(4)

The system is composed of four hard packed histrelin pallets, [redacted] Histrelin acetate [redacted] Stearic acid) inserted into a polymer cartridge and submerged in 1.8% sodium chloride solution. Each implant contains a total of 51 mg histrelin acetate. The polymeric cartridges (i.e. devices) are packaged in 3.5 ml glass vials containing 2.0 ml of 1.8% Sodium Chloride solution. The yearly average rate of histrelin release is 65 ug/day, i.e., approximately 3.25 ug/kg/day for a 20 kg child. The composition of the implant is basically the same as NDA 21-732 (approved). b(4)

Route of administration: Subcutaneous/Subdermal

Proposed use: The implant is indicated for the treatment of children with central precocious puberty (CPP).

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Studies reviewed within this submission:

The safety information for the implant device is based on a number of studies performed over the last 30 years in support of products composed of [redacted] polymer. In addition sponsor has conducted a biocompatibility/toxicology program under NDA 21-732 to test the implant cartridge in its proposed commercial form. The pertinent studies related to present device formulation have been reviewed under the NDA 21-732. Only the new studies submitted in the present NDA (and that were not reviewed before under NDA 21-732), such as an in vitro safety pharmacology study on HERG current in transfected HEK293 cells, 29-day pharmacokinetic studies in rats and mice, as well as the safety of the current drug/device implant are reviewed here under appropriate sections.

b(4)

Studies not reviewed within this submission: None

2.6.1 INTRODUCTION AND DRUG HISTORY

Supperlin (histrelin acetate) subcutaneous implant is a luteininzing hormone-releasing hormone (LHRH) agonist for the treatment of central precocious puberty (CPP) in children. This is a non-biodegradable diffusion controlled reservoir drug delivery system designed to deliver histrelin acetate continuously for 12 months. Central precocious puberty (CPP) is the early onset of hypothalamic-pituitary-gonadal activity, which is generally acknowledged to be before the age of 8 in girls, and 9 in boys. If untreated, precocious puberty can result in short stature and significant psychosocial problems for children undergoing sexual maturation years before their peers.

The most common cause for early puberty in girls is an unexplained activation of the pubertal axis (ie, idiopathic CPP), which leads to increased secretion of gonadotropins followed by estradiol production and concomitant pubertal changes. In most girls 4 years of age or older, a specific cause for CPP cannot be identified, while in girls less than 4 years of age, a central nervous system lesion is more commonly found. In contrast, 60% of boys with CPP have an identifiable underlying disease. Intracranial tumors, specifically lesions of the hypothalamus (hamartoma) or pineal gland region (teratoma, pinealoma); neurofibromatosis and central nervous system gliomas may cause CPP in both girls and boys. The incidence of CPP is 10 to 1 times greater in girls than in boys. The objective of treatment is to stop or reverse sexual development so as to prevent the accompanying rapid growth that ultimately limits a child's height.

A diffusion-controlled reservoir drug delivery SC implant system is being developed for CPP. This is designed to deliver histrelin acetate, a GnRH analog, continuously for 12 months. A similar histrelin implant (Vantas) was approved for the palliative treatment of advanced prostate cancer on 10/12/2004 (NDA 21-732).

As indicated earlier histrelin acetate is a synthetic gonadotropin analog which acts by inhibiting gonadotropin secretion when administered daily at therapeutic doses. Animal and human studies have shown that following an initial stimulatory phase, chronic administration of histrelin acetate reversibly desensitizes responsiveness of the pituitary, which in turn down-regulates ovarian and testicular steroidogenesis and reproductive organ weights. The implant suppresses gonadotropin levels and maintain an acceptable degree of pubertal suppression in both boys and girls.

The current histrelin acetate SC implant contains approximately 50 mg of histrelin acetate [redacted] b(4)
[redacted] [redacted] The present drug-delivery system (nanapeptide GnRH agonist) is designated to provide a sustained release of the active drug, i.e. approximately 65 ug histrelin/day, over a period of one year when inserted beneath skin.

The drug product is composed of 4 histrelin acetate pellets [redacted] histrelin acetate and [redacted] stearic acid) inserted into polymer cartridge and submerged in 1.8% sodium chloride solution b(4)

1. Composition:

Table 1. All components of the dosage form, and their amounts are shown below based on a Per Unit Basis:

Ingredient	Function of components	Quality Standard	Amount per unit
Histrelin Acetate Pellet (4 pellets are inserted in one implant cartridge)			
Histrelin Acetate	Active	House	[redacted]
Stearic Acid	[redacted]	NF/EP	[redacted]
[redacted]			
Packaging Solution: 1.8% Sodium Chloride Solution (2.0 ml/vial) - Maintains hydration of cartridge and minimizes release of drug from the cartridge within vial			
(Sterile Solution)	-	USP	2.0 ml/vial
Sodium Chloride	-	USP/EP	0.018 g/vial
[redacted]			
Implant Cartridge-			
2-Hydroxyethyl Methacrylate (HEMA)	[redacted]	House	[redacted]
2-Hydroxypropyl Methacrylate (HPMA)		House	
Trimethylolpropane Trimethacrylate (TMPTMA)		House	
Benzoin Methyl Ether (BME)		House	
Perkadox-16 (P-16)		House	
Triton X-100		House	

b(4)

[redacted]

* Leaches out during manufacturing process.

The drug product consists of % Histrelin Acetate/ , Stearic Acid, compressed into pellets and incorporated in a small diameter, thin walled, cylindrical, polymeric cartridge. The polymer cartridge is a hydrogel composed of Hydroxyethyl methacrylate (HEMA) and Hydroxypropyl methacrylate (HPMA) which is biocompatible, swells reversibly in an aqueous environment, resists degradation, and does not support microbial growth. Four Histrelin acetate pellets are loaded into one polymer implant. The polymer implant is submerged in 2 ml of 1.8% sodium chloride solution.

Table 2. The composition of the Implant polymer cartridge (HEMA/HPMA/TMPTMA) is as follows:

Component	Qualitative Composition*
Implant Polymer Cartridge	**Hydroxyethyl Methacrylate (HEMA),** **Hydroxypropyl Methacrylate (HPMA),** **Trimethylolpropane Trimethacrylate (TMPTMA),** **Benzoin Methyl Ether (BME),** **Perkadox-16 (P-16),** **Triton X-100,**

b(4)

Polymer Cartridge

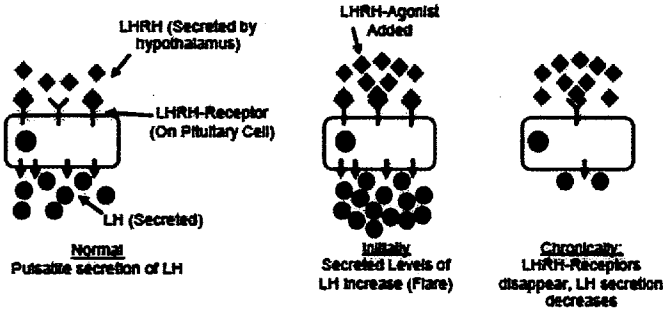
The monomer formulation as shown above consists of 2-Hydroxyethyl Methacrylate (HEMA or cartridge), Hydroxypropyl Methacrylate (HPMA or /implant cartridge), and Trimethylolpropane Trimethacrylate (TMPTMA). Based on the total weight of the uninitiated monomer mixture (the three monomers in the above ratio), Benzoin Methyl Ether (BME), Perkadox P-16 (P-16), and Triton X-100 are added at ratios of respectively. The formulation of the polymer allows it to absorb approximately of its weight in water. The active drug substance contained in the implant is then solvated and diffuses through the walls of the implant at a predetermined rate. T

b(4)

This LHRH agonist is approximately times more potent than natural LHRH. Histrelin Acetate initially causes the release of luteinising hormone (LH) and follicle stimulating hormone (FSH) from the pituitary gland. However, as indicated earlier if administered in large doses or administered continuously, the pituitary becomes desensitized and LH secretion falls well below normal. In addition, the pulsatile pattern of LH concentration in the blood required for end organ response is lost. This is shown in the figure below.

b(4)

Figure. LHRH mechanism of pituitary desensitization and LH suppression



Treatment with GnRH agonists is the current standard of care in the management of CPP. The goal of therapy is to suppress the pulsate secretion of GnRH from a subset of highly specialized neurons located in the hypothalamus, which set in motion a cascade of downward events which finally lead to the production of gonadal sex steroids inducing the development of secondary sex characteristics while maintaining regular reproductive function in children.

Histrelin acetate was first approved by FDA in December of 1991 (NDA 19-836, Shire Pharmaceuticals) for the treatment of CPP but as daily SC injections (10 ug/kg) vs the current drug which is a SC-dermal implant and delivers 65 ug/day or approximately 3.25 ug/kg/day, based on 20 kg child. The drug is supposedly also marketed in Canada and in Denmark.

The CPP implant is similar to the approved Vantas prostate cancer implant, as both contain ~50 mg of histrelin acetate in the implant. However, note that the average rate of release for the CPP implant is higher (i.e. 65 ug/day) than that for prostate cancer implant (which releases 55 ug/day in NDA 21-732). Thus, the histrelin implant for prostate cancer was redesigned to allow greater daily release of histrelin from 50 ug/day to 65 ug/day to treat children with CPP. This change is reported by sponsor to be achieved by changing the percentage of implants cartridge components to [redacted] 2-HPMA- [redacted] (vs [redacted] in NDA 21-732), HEMA- [redacted] (vs [redacted] in NDA 21-732) and trimethylolpropane trimethacrylate (TMPTMA- [redacted] in NDA 21-732). This change supposedly produces a more hydrophilic implant allowing a higher rate of drug release. The mechanism of the controlled release of the drug is by diffusion through a micro-porous structure of the implant wall. b(4)

2.6.2 PHARMACOLOGY

2.6.2.1

Histrelin Acetate (an LHRH analog) is a nonapeptide [redacted] b(4)

Like most analogs of LHRH, histrelin acetate causes the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary. These hormones stimulate the ovaries or testes to produce estrogens in girls and testosterone in boys, and these sex hormones cause the onset of pubertal maturation. The primary activity of histrelin acetate is the suppression of gonadotropin secretion to inhibit progression of puberty in CPP.

2.6.2.2 Primary Pharmacodynamics:

Most pharmacology/toxicity studies have been reviewed in two previous NDAs (NDA 19-836 and NDA 21-732). As stated earlier, agonists of LHRH can either stimulate or inhibit the reproductive system depending on the dosage and frequency of administration. In rats, short-term intravenous administration of histrelin acetate stimulates the release of LH and FSH from the anterior pituitary gonadotrophs. In male rats, daily subcutaneous injection of histrelin reduced reproductive organ

weight and sex hormone levels. However constant delivery of LHRH in rats produces suppression of the reproductive/endocrine system.

Similar studies in rhesus monkeys showed that when the drug was administered daily by subcutaneous injection for 40 weeks, only moderate effects on serum testosterone were seen, despite marked decreases in serum LH and FSH levels. However, when histrelin was delivered continuously by osmotic pumps, serum testosterone levels decreased to 10% of pre-treatment levels within 2 months of implantation in 3 of the 4 monkeys. Treatment was discontinued after 18 months and within a week of cessation of treatment, testosterone levels started to rebound.

Mechanism of action:
The continuous administration of histrelin via the implant drug/device results in pituitary gonadotrophs insensitization to GnRH with subsequent suppression of gonadotropin secretion & decreased ovarian and testicular steroidogenesis. The decreased production of estrogen in girls and testosterone in boys results in delayed sextual development or onset of pubertal maturation.

2.6.2.4 Safety pharmacology

The safety pharmacology studies have been reviewed under NDA 19-836 and NDA 21-732. However, a following new in vitro safety pharmacology study has been submitted in the current NDA.

Effect of Histrelin Acetate on HERG Tail Current in Stably Transfected HEK293 Cells

The purpose of this study was to assess the potential of histrelin acetate to inhibit HERG tail current in an in vitro system. This is because there have been some suggestions that drugs that cause androgen deficiency may be associated with QT prolongation. Compounds that inhibit HERG current have been shown to prolong the cardiac action potential and hence QT interval in man.

Histrelin acetate (1 μM) did not produce statistically significant inhibition of HERG tail current ($P > 0.05$, compared to vehicle) in HEK293 cells stably transfected with HERG cDNA. Sponsor states that the concentration of 1 uM tested here is well in excess of the anticipated plasma levels that may be achieved in humans (peak serum levels in the clinic are approximately 1.5 ng/ml which equates to approximately 1 nM). In contrast the reference substance (E-4031, at 100 nM after 10-15 min exposure) inhibited HERG tail current by 92 % (an effect consistent with its known activity).

In a 6-month monkey toxicity study, where more detailed electrocardiogram exams were performed in animals, no changes in QT or QTc were noted following daily bolus administration of histrelin to monkeys.

2.6.2.5 **PHARMACODYNAMIC DRUG INTERACTIONS:** The drug interaction studies have not been performed with this drug product.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

These have been submitted, and as indicated earlier, these have been reviewed under two previous NDAs.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

These have been reviewed previously as shown in the Table below:

The Table below shows the serum concentrations of the drug that were achieved in various animal species and in humans (using different doses).

Study	Species/ approx. weight	Dose type		Approx. daily dose µg/kg/day	Serum Histrelin concentration ng/mL
BAR-002-0591A-USA	Human ~70 kg	Single implant ~55-60 µg/day		0.8	0.19[a]
301	Human ~70 kg	Single implant ~55-60 µg/day		0.7	0.265[a]
01-2-001	Child ~37.4 kg	Single or Two implants ~65 µg/day		1.7 3.5	0.46 1.98
Study 8	Baboon ~16 kg	S.C.	25 µg/day	1.5	0.036[c]
			50 µg/day	3.0	0.185[c]
			100 µg/day	6.0	0.575[c]
Study 10	Dog ~12 kg	Implant	132: 80 µg/day	6.7	0.4[b]
			136: 60 µg/day	5.0	0.15[b]
Summary report only	Monkey ~16 kg	Implant 14-19 µg/day		1.0	0.4 – 2.1[a] (mean : 0.9)
Study 61	Mouse ~ 42 g	S.C, daily		20	3.81[d]
				200	47.91[d]
				2000	282.46[d]
Study 62	Rat ~ 470 g	S.C, daily		5.0	3.39[d]
				30	16.27[d]
				180	81.36[d]

[a] average concentration
[b] steady state concentration
[c] C_{max}
[d] C_{max} on Day 28

Following two new pharmacokinetics studies in mice and rats have been submitted in the current NDA.

1. A 29-Day Pharmacokinetic Study in mice

The pharmacokinetic parameters of histrelin acetate (20, 200, 2000 ug/kg) were examined in mice following SC administration (bolus, once a day) of the drug for 28 days. The results are shown below. The AUC values on day 28 in mice were 2, 41, 313, ng.ml/hr at 20, 200, 2000 ug/kg of histrelin.

Table. The pharmacokinetic parameters of histrelin acetate (20, 200, 2000 ug/kg) on day 28 in mice

PK Parameters	Group 1 – 20 µg/kg histrelin				Group 2 – 200 µg/kg histrelin				Group 3 – 2000 µg/kg histrelin			
	Study Day				Study Day				Study Day			
	0	7	14	28	0	7	14	28	0	7	14	28
AUC_{inf} (ng/mL.hr)	.	.	.	3.07	23.11	73.84	59.31	42.15	396.42	528.50	615.97	313.92
AUC_{last} (ng/mL.hr)	0.17	1.76	1.93	1.81	22.60	54.90	58.06	41.36	395.95	524.15	614.86	312.89
C_{max} (ng/mL)	0.67	2.37	3.83	3.81	20.78	41.86	55.11	47.91	359.58	554.43	703.14	282.46
T_{max} (hr) (Hr post-dosing on relevant Study Day)	0.50	168.5 (0.50)	336.50 (0.50)	672.25 (0.25)	0.50	168.25 (0.25)	336.50 (0.50)	672.25 (0.25)	0.50	168.25 (0.25)	336.50 (0.50)	672.25 (0.25)

Sponsor's conclusions are stated below:

The results of this study show that subcutaneous administration of histrelin acetate at 20 μg/kg, 200 μg/kg and 2000 μg/kg was well tolerated in mice for 29 days. Two animals were sacrificed pre-terminally, but this was due to injuries that were not treatment-related. There were no treatment-related changes in clinical condition or adverse effects on body weight. At necropsy, a low incidence of animals was observed with haemorrhage of one testis, but with a slightly higher frequency in the two highest dose groups. The biological relevance of this finding is not clear. There was a treatment-related reduction in mean seminal vesicle weight in animals treated at 2000 μg/kg and the weight of this organ was also less than in procedural controls and in animals treated at 20 and 200 μg/kg. This finding is consistent with the pharmacological effect of the test item in chronic studies in the mouse. The weights of the other reproductive organs measured were not affected.

Pharmacokinetic results indicate that subcutaneous administration of histrelin (20, 200 and 2000 μg/kg) generally resulted in an increasing extent and rate of absorption as determined by AUC and C_{max} respectively, with a very rapid time to reach peak concentrations and elimination half life. Based on the results from Study Day 28, the AUC_{last} was 1.81ng/mL.hr (20 μg/kg), 41.36 ng/mL.hr (200 μg/kg) and 312.89 ng/mL.hr (2000 μg/kg), the C_{max} was 3.81 ng/mL (20 μg/kg), 47.91 ng/mL (200 μg/kg) and 282.46 ng/mL (2000 μg/kg) and the time to peak concentration was within 30 minutes. No histrelin was determined in any of the samples from the untreated procedural control group.

Analysis of formulations of histrelin acetate at 5 μg/mL, 50 μg/mL and 500 μg/mL confirmed acceptable sterility, concentration and stability.

2. Pharmacokinetic Study in rats

Similarly, the pharmacokinetic parameters of histrelin acetate (5, 30, 180 ug/kg) were examined in rats following SC (bolus, once a day) administration for 29 days. The results are shown below. The AUC values on day 28 in rats were 3.9, 20.2, 139.2 ng.ml/hr at 5, 30, 180 ug/kg of histrelin

Table. The pharmacokinetic parameters of histrelin acetate (20, 200, 2000 ug/kg) on day 28 in rats.

PK Parameters	Group 1 – 5μg/kg histrelin				Group 2 – 30μg/kg histrelin				Group 3 – 180μg/kg histrelin			
	Study Day				Study Day				Study Day			
	0	7	14	28	0	7	14	28	0	7	14	28
AUC_{inf} (ng/mL.hr)	-	-	3.50	12.22	17.91	28.40	25.89	27.72	105.92	157.27	99.79	153.29
AUC_{last} (ng/mL.hr)	0.28	2.02	2.06	3.87	15.52	18.95	21.94	20.19	104.24	150.89	98.01	139.19
C_{max} (ng/mL)	1.12	2.55	2.85	3.39	16.37	23.68	19.45	16.27	68.17	65.84	63.31	81.36
T_{max} (hr) (Hr post-dosing on relevant Study Day)	0.50	169.00 (1.00)	336.25 (0.25)	672.25 (0.25)	0.50	168.25 (0.25)	336.25 (0.25)	672.50 (0.50)	0.50	168.50 (0.50)	336.25 (0.25)	672.50 (0.50)

Sponsor's conclusions are stated below:

The results of this study show that subcutaneous administration of histrelin acetate at 5 µg/kg, 30 µg/kg and 180 µg/kg was well tolerated in rats for 29 days. No animals died and there were no treatment-related changes in clinical condition or abnormalities at necropsy, although the mean body weights of animals treated at 30 and 180 µg/kg were slightly reduced from Study Day 13.

The weights of the reproductive organs in the treated groups at necropsy confirmed the expected pharmacological effect of histrelin acetate. When compared with Study Day 0, at the majority of all timepoints, a treatment related pattern of lowering of mean organ weights was evident. After Study Day 0, for each of the treated groups, the mean weights of the organs were considerably lower than the mean weights of the organs from the procedural control animals recorded on Study Day 28.

Pharmacokinetic results indicate that subcutaneous administration of histrelin acetate (5, 30 and 180 µg/kg) resulted in a broadly linear extent and rate of absorption as determined by AUC and C_{max} respectively, with a very rapid time to reach peak concentrations and elimination half life. Based on the results from Study Day 28, the AUC_{last} was 3.87 ng/mL.hr (5 µg/kg), 20.19 ng/mL.hr (30 µg/kg) and 139.19 ng/mL.hr (180 µg/kg), the C_{max} was 3.39 ng/mL (5 µg/kg), 16.27 ng/mL (30 µg/kg) and 81.36 ng/mL (180 µg/kg) and the time to peak concentration was within 30 minutes. No histrelin was determined in any of the samples from the untreated procedural control group.

Analysis of formulations of histrelin acetate at 5 µg/mL, 30 µg/mL and 180 µg/mL confirmed acceptable sterility, concentration and stability.

Discussion and conclusions:
Thus in both 29-day studies in mice and rats, a dose related increase in exposure was noted at low doses but this was not seen at higher doses. Detectable levels of the drug were found up to 8 hrs after administration. In these studies in rats, the 180 ug/kg dose produced Cmax of 81 ng/ml, while in mice the 2000 ug/kg dose produced Cmax values of 283 ng/ml. Sponsor states that these concentrations are 170-fold and 600 fold the human concentrations (based on 0.46 ng/ml serum concentrations of histrelin in children in a phase 2 study).

Dog studies demonstrated that formulations varying in the equilibrium water content of the implant, could regulate the release of the drug. Also, pre-hydrating the implant could avoid a lag period in achieving optimal histrelin release.

In addition, the pharmacokinetic studies demonstrated that histrelin is rapidly distributed and eliminated by first order kinetics, and that the hydrated hydrogel implant delivers a continuous dose of histrelin over a period of up to 48 weeks. The average histrein serum concentrations from a single histrelin acetate implant in a phase 2 study in children were 0.46 ng/ml. The implant is surgically removed at the time of replacement. Implant is inert and does not biodegrade.

2.6.6 TOXICOLOGY

Histrelin Acetate has been tested preclinically in chronic/sub-chronic studies as well as in carcinogenicity/reproductive toxicity studies, using daily subcutaneous injection. Also, the histrelin acetate hydrogel implant and the polymer (hydroxyethyl methacrylate co-polymer) by itself have been tested for tolerance in animal models. Comprehensive genotoxicity batteries have been performed on extracts of the histrelin acetate implant and on the implant cartridge alone.

2.6.6.1 Overall toxicology summary: As stated earlier, most toxicity studies have been reviewed under previous NDAs, i.e. NDA 19-836 (approved for CPP in 1991 as daily SC injections, see the pharmacology review) and NDA 21-732 (approved for palliative treatment of prostate cancer in 2004, as a SC implant). Additionally, the hydrogel polymer implant cartridge toxicity studies were also reviewed under NDA 21-732

2.6.6.2 Single-dose toxicity/ 2.6.6.3 Repeat-dose toxicity: Following single and multiple dose studies have been conducted with the drug (see Table 1).

Table 1. Single and multiple dose studies conducted with histrelin

Table number: 2.6.7.1			Toxicology Overview						Page 1 of 6
Type of study	Test Material	Species and Strain	Method of Admin.	Duration of Dosing	Doses (ug/kg*)	GLP	Testing Facility	Study No.	Location Section
Single-Dose Toxicity									
Haemolysis	NaCl extract of placebo implant	Rabbit NZW (donor of blood)	*In vitro*	Single dose	Standard extract	Yes		Study 13	4.2.3.1
Acute toxicity	NaCl and cottonseed oil extract of placebo implant	Mouse Albino, Swiss	Intravenous (NaCl extract) Intraperitoneal (CSO extract)	Single dose	50 mL/kg of extracts	Yes		Study 14	4.2.3.1
Pyrogenicity	NaCl extract of placebo implant	Rabbit NZW	Intravenous	Single dose	10 mL/kg of extract	Yes		Study 15	4.2.3.1
	NaCl extract of powdered implant polymer	Rabbit	Intravenous	Single dose	10 mL/kg of extract	No		Study 16	4.2.3.1
Repeat-Dose Toxicity									
General toxicology	NaCl extract of placebo implant	Mouse Albino, Swiss	Intravenous	14 day (10 doses)	25 mL/kg of extract	Yes		Study 17	4.2.3.2
	Histrelin	Rat Sprague-Dawley	Subcutaneous	90 day	0, 8[a], 40 and 200	No		Study 18	4.2.3.2
	Histrelin	Rat Sprague-Dawley	Subcutaneous	6 month	0, 5[b], 30 and 180[d]	Yes		Study 19	4.2.3.2
	Histrelin	Rabbit NZW	Subcutaneous	90 day	0, 8[a], 40 and 200[d]	No		Study 20	4.2.3.2
	Histrelin	Monkey cyno	Subcutaneous	6 month	0, 5[b], 30 and 180	Yes		Study 21	4.2.3.2

Following summary studies are from the sponsor's submission in the current NDA

Repeat-dose subcutaneous administration of Histrelin to the rat for 3 or 6 months, in monkeys for 6 months, and to the rabbit for 3 months found that Histrelin was well tolerated and without overt toxicity. Pharmacological effects are discussed below in males and females separately. Discussion of other changes, including secondary pharmacological effects, and also findings of uncertain etiology then follows.

Effects of histrelin in males: As would be expected following administration of a LHRH-agonist, there were marked changes in testosterone-dependent reproductive organs; most notably the testes, seminal vesicles, epididymides and prostate. The lowest dose at which these changes were evident in the toxicological and carcinogenicity studies and their potential for reversibility is tabulated below (Table 2.6.6.9.1).

Table 2.6.6.9.1 (Table 2) shows that the expected pharmacological effects of testosterone reduction on the reproductive organs were apparent in the rat, monkey and rabbit subcutaneous dosing studies, with a LOEL of 5 µg/kg/day. In the mouse, effects were less evident and only from a higher dose of 200 µg/kg/day. Although none of the studies included concurrent toxicokinetic assessment, results from recent 29-day subcutaneous bolus dosing toxicokinetic studies in the same rodent strains indicates that in the rat, a dose of 5 µg/kg/day is associated with an AUC (last) of 3.87 ng/mL.hr and a Cmax of 3.39 ng/mL and, in the mouse, a dose of 200 µg/kg/day is associated with an AUC (last) of 41.36 ng/mL.hr and a Cmax of 47.91 ng/mL at the end of the dosing period. The consistency of effects on pharmacological markers (reductions in weights of reproductive organs) included in the toxicokinetic studies serve to confirm both systemic exposure and similarity with the effects seen in the repeat dose toxicity/carcinogenicity studies at similar doses.

Table 2. Results of toxicity studies with histrelin in rats, rabbits, mice and monkeys

Table 2.6.6.9.1 Direct pharmacological changes related to testosterone reduction

Species	Observation	Lowest dose affected (µg/kg/day)	Evidence of reversibility	Study number (s)
Testis				
Rat	Weight (<)	8	-	18, 19
	Tubular atrophy (>)	5	yes	19, 31
	Tubular retention of contents (>)	180	yes	19
	Tubular degeneration and mineralization (>)	5	-	18, 31
	Leydig cell depletion (>)	180	yes	19
	Leydig cell tumor/ hyperplasia (>)	5 & 25 [b]	-	31
Mouse	Leydig cell hyperplasia (>)	20 & 200 [b]	-	30
Monkey	Weight (<)	5	yes	21
	Atrophy (>), degeneration (>)	5	-	21
Rabbit	Weight (<)	8	-	20
Seminal vesicles				
Rat	Weight (<)	8	-	18, 19
	Secretory activity (<), atrophy (>)	5	yes	19, 31
Mouse	Atrophy (>)	2000	-	30
Rabbit	Weight (<)	8	-	20
Monkey	Atrophy (>), weight (<)	5	-	21
Epididymides				
Rat	Cellular debris (>)	200 [a]	-	18
	Grossly small	30	yes	19
	Sperm (<)	5	yes	19, 31
	Atrophy (>), degenerated cells (>)	5	-	31
Monkey	Sperm (<) , sperm immature (>)	5	-	21
Prostate				
Rat	Weight (<)	30	yes	18, 19
	Atrophy (>), secretion (<)	5	no	19, 31
Mouse	Atrophy (>)	200	-	30
Monkey	Weight (<)	5	-	21
	Atrophy (>)	5	-	21
Rabbit	Weight (<)	8	-	20

(>) increase (<) decrease - not assessed
The underlined study number(s) are affected at the lowest dose
[a] lower dose levels not subject to histopathological examination
[b] inverted dose response

However in the rat, and to a lesser extent in the rabbit, a number of other changes were observed (see Table 3 below), some of which were secondary pharmacological effects.

Table 3. Other (non-neoplastic) changes in the male

Species	Observation	Lowest dose affected (µg/kg/day)	Evidence of reversibility	Study number(s)
Clinical Pathology				
Rat	Triglycerides (>)	200	-	18
	MCH (>),	30	yes	19
	Hb (>), PCV (>), MCV (>)	180	yes	19
Rabbit	PCV (>), MCH (>)	200	-	20
Histopathology				
Rat	Liver, vacuolization (>)	180 [a]	yes	19
	Bone marrow, fatty deposition (>)	5	yes	19, 31
	Skeletal muscle, fatty deposition (>)	25	yes	19, 31
	Pancreas, fatty deposition (>)	5	-	31
	Myocardial fibrosis (>)	5	-	31
	Mammary gland, hyperplasia (>)	180	yes	19
	Stomach (non-glandular), hyperplasia (>)	5	-	31
	Thyroid, C-cell hyperplasia (>)	5	-	31
	Skin, atrophy, adnexa (>)	5	-	31
	Parathyroid, hyperplasia (>)	5 & 25 [b]	-	31
	Pituitary, hyperplasia (>)	5 & 25 [b]	-	31
	Adrenal cortex, hyperplasia (>)	5 & 25 [b]	-	31
Rabbit	Pituitary, acidophils (<)	200 [c]	-	20

(>) increase (<) decrease - not assessed
The underlined study number(s) are affected at the lowest dose

a not increased at 150 µg/kg/day in Study 31
b inverted dose response
c lower dose levels not subject to histopathological examination

Note that:
study 18 was a 3-month toxicity study in rats using doses of 8, 40 and 200 µg/kg/day.
study 19 was a 6-month toxicity study in rats using doses of 5, 30 and 180 µg/kg/day.
study 20 was a 3-month toxicity study in rabbits using doses of 8, 40 and 200 µg/kg/day.
study 21 was a 6-month toxicity study in monkeys using doses of 5, 30 and 180 µg/kg/day.

Effects of histrelin in females:
As would be expected following administration of a LHRH agonist, with consequent disruption of LH and FSH levels and estrogen production, there were marked changes in the female reproductive organs; ovaries, uterus, mammary gland, cervix and vagina. The lowest dose at which these changes were evident in the toxicological and carcinogenicity studies, and where assessed, their potential for reversibility is tabulated below (Table 2.6.6.9.3) Table 4.

Table 2.6.6.9.3 shows that the expected pharmacological effect of atrophy of the reproductive organs was apparent in the rat, rabbit and monkey. For most endpoints, the effect was apparent at the lowest dosage and did not necessarily show a dose-response, indicating that the low dose was a maximal pharmacological effect level.

Table 4. (Table 2.6.6.9.3) Direct pharmacological changes related to LH, FSH and estrogen

Species	Observation	Lowest dose affected (µg/kg/day)	Evidence of reversibility	Study number (s)
Ovaries				
Rat	Weight (<), atrophy (>)	5	yes	18, 19
	Follicular development (<)	5	yes	18, 19, 31
	Corpora lutea (<)	200 [a]	-	18
	Estrus cycling, disruption (>)	200 [a]	yes	18
	Stromal proliferation (>)	5	-	31
Rabbit	Weight (<)	8	-	20
	Follicular development (<)	200 [a]	-	20
Monkey	Weight (<)	5	-	21
	Corpora lutea, mature (<)	5	-	21
Uterus				
Rat	Weight (<)	8	-	18
	Atrophy (>)	5	yes	18, 19, 31
Rabbit	Weight (<)	8	-	20
	Atrophy (>), glandular activity (<)	200 [a]	-	20
Monkey	Weight (<)	5	-	21
	Endometrium, inactive (>), menstrual or secretory activity (<)	5	yes	21
	Stroma/myometrium condensed (>)	30	-	21
Mammary gland				
Rat	Atrophy (>)	5	yes	18, 19, 31
	Fibroadenoma (<)	5	-	31
Rabbit	Ductal epithelial growth (<)	200 [a]	-	20
Mouse	Adenocarcinoma (>)	20	-	30
Cervix				
Rat	Atrophy (>)	5	yes	19
Vagina				
Rat	Atrophy (>)	5	-	19, 31
	Mucification (<)	5	-	31
Monkey	Hyperkeratosis (<)	5	-	21
Mouse	Mucification (>)	20	-	30
Pituitary				
Rabbit	Acidophils (<)	200 [a]	-	20
Mouse	Adenoma (>)	200	-	30
	Pituitary, foci of acidophils (>)	20	-	30

(>) increase (<) decrease - not assessed
The underlined study number(s) are affected at the lowest dose
[a] lower dose levels not subject to histopathological examination

A number of other changes were observed, some of which were secondary pharmacological effects and these are shown below in the Table 5.

Table 5. Other (non-neoplastic) changes in the females

Species	Observation	Lowest dose affected (µg/kg/day)	Evidence of reversibility	Study number(s)
Clinical changes				
Rat	Body weight (>)	5	yes	18, 19, 31
	Food consumption (>)	5	yes	19, 31
Mouse	Body weight (>)	20	-	30
Clinical Pathology				
Rat	Triglycerides (>)	5	yes	18, 19
	RBC (>), Hb (>), PCV (>)	8	-	18
	WBC (<)	200	-	18
	ALP (>)	5	yes	19
	ALT (>)	180	yes	19
Rabbit	RBC (<), Hb (<), PCV (<)	200	-	20
Organ weights				
Rat	Pituitary weight (<)	5	no	19
	Adrenal weight (>)	8	-	18
	Spleen weight (<)	8	-	18
	Thyroid weight (<)	200[a]	-	18
Macroscopic observations				
	Liver discoloration (>)	5	yes	19
Histopathology				
Rat	Liver, vacuolization (>)	5	yes	19, 31
	Bone marrow and skeletal muscle, fatty deposition (>)	5	yes	19, 31
	Pancreas, fatty deposition (>)	5	-	31
	Pancreas, Islet cell adenoma (>)	5	-	31
	Pancreas, Islet cell hyperplasia (>)	25	-	31
	Myocardial fibrosis (>)	25	-	31
	Parathyroid hyperplasia (>)	5	-	31
	Pituitary hyperplasia (>)	5	-	31
	Stomach hyperplasia (>)	5	-	31

(>) increase (<) decrease - not assessed
The underlined study number(s) are affected at the lowest dose
[a] lower dose levels not subject to histopathological examination

Note that study 18 was a 3-month toxicity study in rats using doses of 8, 40 and 200 µg/kg/day.
study 19 was a 6-month toxicity study in rats using doses of 5, 30 and 180 µg/kg/day.
study 20 was a 3-month toxicity study in rabbits using doses of 8, 40 and 200 µg/kg/day.
tudy 21 was a 6-month toxicity study in monkeys using doses of 5, 30 and 180 µg/kg/day

The average serum Histrelin Acetate concentration from a single Histrelin Acetate implant in children were 0.46 ng/mL. Although there were no concurrent toxicokinetic evaluations conducted on the repeat dose toxicity studies, it is known from pharmacokinetic work by the subcutaneous route in the baboon that the serum concentration (Cmax) was approximately 0.58 ng/mL at 100 µg/day (approximately 6 µg/kg for a 16 kg baboon). Assuming that the concentration was dose-proportional and consistent in different monkey strains, it would be expected that a high dose of 180 µg/kg/day, as used in the cynomolgus monkey toxicity study would give a maximal serum concentration approximately 30 times higher than the baboon and approximately 65 times higher than the human concentration. Similarly, at the end of the dosing period in 29-day SC bolus dosing toxicokinetic studies in rodents, a dose of 180 µg/kg/day in the rat was associated with a Cmax of 81 ng/mL and a dose of 2000 µg/kg/day in the mouse was associated with a Cmax of 283 ng/mL,

indicating that these high doses were equivalent to approximately 180-fold and 570-fold the human concentration, respectively.

The NOAEL doses in repeat dose toxicity studies are described by the sponsor below in these studies

Table. Repeat dose toxicity studies NOAELs and human equivalent doses (HEDs)

Species	Study	NOAEL[a] mg/kg/day	Km[b]	Equivalent dose in mg/m^2	Factor[c]	HED mg/kg
Rat	18	0.200	6	1.20	6.2	0.194
Rabbit	20	0.200	12	2.40	3.1	0.774
Mouse	30	2.000	6	6.00	12.3	0.488
Monkey (cynomolgus)	21	0.180	12	2.16	3.1	0.697

[a] excluding primary and secondary pharmacological effects
[b] see FDA draft 3814, 2000 for multiplying factor for mg/kg to mg/m2
[c] see FDA draft 3814, 2000 for dividing factor for mg/m2 to HED mg/kg

Sponsor further states that the average dose in children from a single Histrelin implant releasing approximately 65 µg/day is 1.7 µg/kg/day. The animal HEDs (in mg/kg) represent ~16000 times the expected human dose (NB FDA default safety factor is x10) for overt toxicological effects (excluding primary and secondary pharmacological effects).

However in the NDA 21-732 (see in DFS), a review of a 6-month study in male rats with two formulation of histrelin hydrogel implant (a study conducted by the Population Council in 1989) indicates that both formulations produced severe mineral deposits on the surface of the implant (that were removed at 210 days post administration of the implant) with adhesion between implants and their fibrous capsule. The degree of mineralization was less at 60 and 120 days in this study. A similar 6-month study in dogs (a study conducted by the Population Council in 1990) also showed that the intensity of mineralization increased with the length of the implant use. In contrast, a one year study of a mineral deposit of histrelin hydrogen implant in monkeys (a study conducted by the Population Council in 1995) showed no edema or erythema at the implantation sites in monkeys.

2.6.6.4 Genetic toxicology: See genetic toxicity studies under NDA 19-836 review (for precocious puberty) and NDA 21-732 review (for palliative treatment of prostate cancer). As stated in NDA 21-732, Extracts of HEMA/HPMA copolymer placebo reservoir (Hydrogel implant reservoir) or that of Hydrogel/histrelin implants were not genotoxic in a battery of genotoxicity assays.

Table. Geno-toxicity studies conducted with histrelin

Table number: 2.6.7.1 Toxicology Overview									Page 2 of 6
Type of study	Test Material	Species and Strain	Method of Admin.	Duration of Dosing	Doses (ug/kg *)	GLP	Testing Facility	Study No	Location Section
Genotoxicity									
Ames	NaCl extract of Histrelin implant	*S. typhimurium* and *E.coli*	*in vitro*	52 ± 4 hours	(± S9) 0, 25.0, to 200 (µL/plate)	Yes	[redacted]	Study 22	4.2.3.3.1
	NaCl extract of placebo implant	*S. typhimurium* and *E.coli*	*in vitro*	72 hours	(±S9) 0 and 100 (µL/plate)	Yes		Study 23	4.2.3.3.1
	DMSO extract of placebo implant	*S. typhimurium* and *E.coli*	*In vitro*		(±S9) 0 and 100 (µL/plate)				
	Hydron powder	*S. typhimurium* and *S. cerevisiae*	*In vitro*	48 hours	(± S9) 0, 0.1 to 500 (µg/plate)	No		Study 24	4.2.3.3.1
Cytotoxicity	MEM extract of placebo implant	L929 mouse fibroblast cells	*In vitro*	48 hours	(24 and 48 h) 0 and 3.0 mL	Yes		Study 26	4.2.3.3.1
Cytogenetic	NaCl extract of Histrelin implant	Mouse lymphoma L5178Y	*in vitro*	4 hours (±S9), 24 hours (-S9)	(±S9, 4 h) 0, 0.785 to 100 (µL/mL) (-S9, 24 h) 0, 0.785 to 100 (µL/mL)	Yes		Study 25	4.2.3.3.1
	Ham's F-12 complete medium extract of the placebo implant	CHO-Ki cell line of Chinese Hamster Ovary cells	*in vitro*	5 hours (+S9), 16 hours (-S9)	(-S9 16 h) 0, and neat extract (+S9 5h) 0 and neat extract	Yes		Study 27	4.2.3.3.1

b(4)

Table number: 2.6.7.1 Toxicology Overview									Page 3 of 6
Type of study	Test Material	Species and Strain	Method of Admin.	Duration of Dosing	Doses (ug/kg *)	GLP	Testing Facility	Study No	Location Section
Genotoxicity (cont)									
Micronucleus	NaCl extract of Histrelin implant	Mouse [redacted]:CD-1(ICR)BR	Intravenous	Single dose (sampled 24 and 48 hours)	0 and 50 mL/kg (neat extract)	Yes	[redacted]	Study 28	4.2.3.3.2
	NaCl extract of placebo implant	Mouse Swiss albino	Intravenous	Single dose (sampled 24 and 48 hours)	0 and 50 mL/kg (neat extract)	Yes		Study 29	4.2.3.3.2

b(4)

2.6.6.5 Carcinogenicity: Rat and mouse carcinogenicity studies have been conducted and reviewed before.

Table 3. Carcinogenicity studies conducted with histrelin. These were conducted under NDA 19-836 for precocious puberty

Carcinogenicity									
Life-time *in vivo*	Histrelin	Mouse [redacted]:CD-1(ICR)BR	Subcutaneous	18 months	0, 20*, 200, 2000	Yes	[redacted]	Study 30	4.2.3.4.1
	Histrelin	Rat Sprague-Dawley	Subcutaneous	23 months	0, 5*, 25, 150	Yes		Study 31	4.2.3.4.1

b(4)

2.6.6.6 Reproductive and developmental toxicology: See original NDA reviews (NDA 19-836, and NDA 21-732 in DFS).

Table. Reproductive toxicity studies were conducted with histrelin under NDA 19-836 for precocious puberty.

Reproductive and developmental toxicity									
Male Fertility	Histrelin	Rat Wistar	Subcutaneous	2, 4, 6 and 8 week	83.3 (2[b], 4, 6 and 8 weeks)	No	[redacted]	Study 3	4.2.1.1
Male and female return to fertility	Histrelin	Rat Sprague Dawley	Subcutaneous	6 month	0, 5[b], 30 and 180[f]	Yes		Study 19	4.2.3.2
	Histrelin	Rabbit New Zealand White	Subcutaneous	3 month	0 and 200[b,f]	No		Study 20	4.2.3.2
	Histrelin	Monkey Cyno	Subcutaneous	6 month	0, 5[b], 30 and 180[f]	Yes		Study 21	4.2.3.2

b(4)

Table number: 2.6.7.1					Toxicology Overview				Page 4 of 6
Type of study	Test Material	Species and Strain	Method of Admin	Duration of Dosing	Doses (mg/kg/day)	GLP	Testing Facility	Study No	Location Section
Reproductive and developmental toxicity									
Teratology	Histrelin	Mouse CD-1	Subcutaneous	GD 6 to 15	0, 100, 500 and 1000[b]	Yes	[redacted]	Study 32	4.2.3.5.2
	Histrelin	Rat Sprague-Dawley	Subcutaneous	GD 7 to GD19 or to PND 25	0, 1[b], 3, 5 and 15	Yes		Study 33	4.2.3.5.2
	Histrelin	Rabbit NZW	Subcutaneous	GD 6 to 18	0, 20[b], 50 and 80	Yes		Study 34	4.2.3.5.2

Note that study #33 was a segment II study in rats using doses of 1, 3, 5, 15 ug/kg/day.
Note that study #34 was a segment II study in rabbits using doses of 20, 50, 80 ug/kg/day.

APPEARS THIS WAY ON ORIGINAL

Following is the sponsor's summary on segment II study in rats (study # 33, 8/28/1986): These repro-toxicity studies were reviewed under NDA 19-836.

HISTRELIN (ORF 17070): REPRODUCTIVE FUNCTION AND TERATOLOGY STUDY IN THE RAT: FINAL REPORT b(4)

[redacted] , 3/27/86]

SUMMARY

The purpose of this study was to determine the embryotoxic and/or teratogenic potential of ORF 17070 when administered to mated female rats during gestation, and also to assess the subsequent development of the F_1 generation to maturity and that of the F_2 generation to weaning. The study was conducted at [redacted] according to [redacted] Live animal work was conducted from September 17, 1984, to November 2, 1984. Laboratory studies were completed on February 18, 1985. b(4)

Dosing solutions of ORF 17070 at concentrations of 0, 1, 3, 5, and 15 ug/ml were prepared by the [redacted] Concentrations of the 3, 5 and 15 µg/ml dosing solutions were confirmed before commencement of dosing to be 83.5 to 98.7 percent of the intended levels, and after the dosing period to be 88.8 to 102.2 percent of the intended levels, i.e. ±20% of label claim. The 1 µg/ml concentration was initially 83.5% of label claim. End-of-use assays on samples returned from [redacted] indicated some degradation or loss in the 1 µg/ml concentration only to [redacted] Thus, the animals assigned to this group received slightly less than the intended 1 µg/ml dosage [redacted] b(4)

Two hundred mated female Charles River CD rats (Sprague-Dawley origin) were assigned to five groups (40 per group). Control or test articles were administered by daily subcutaneous injection (1 ml/kg) beginning on day 7 post coitum.

Twenty-five females from each group were killed on day 20 of gestation and a necropsy performed. The reproductive organs were examined for the number of corpora lutea and the number and characterization of uterine implants. Each fetus was weighed, measured for crown-rump length, sexed, and examined for external abnormalities. Placental weights and gross observations were recorded. The viscera of two-thirds of each litter were examined as fresh tissue and these fetuses were later examined for skeletal anomalies. The remaining third of each litter was preserved in Bouins solution and examined for visceral abnormalities after sectioning.

The general condition of these control and compound treated dams was unaffected, and there were no deaths. Body weight gain in all compound treated groups was less than in the control group, but was statistically significant only in groups receiving 5 and 15 µg/kg/day.

After day 10 of gestation, a slight but statistically significant dosage related reduction in food consumption was seen in all ORF 17070 treated groups.

At necropsy on day 20 of gestation, all ORF 17070 treated females showed stimulation of follicular development of the ovaries, thereby precluding proper determination of the numbers of corpora lutea. There were no other maternal necropsy observations that could be attributed to treatment.

Post-implantation loss was significantly greater in groups receiving 3, 5, and 15 µg/kg/day than in controls. The 1 µg/kg/day group was unaffected.

Male and female fetal weights showed significant increases in all compound-treated groups when compared to controls. Crown-rump lengths were also increased in ORF 17070-exposed fetuses indicating that these fetuses were larger overall than the control fetuses. Reduced litter size may be a contributing factor.

ORF 17070 treated groups showed significant dosage-related increases in placental weights of male and female fetuses. Pale placentae were observed in all treated groups, but the cause was undetermined. In groups receiving 3, 5, and 15 µg/kg/day there was a dosage related increase in the occurrence of mottling and depressions of the placentae. The 5 and 15 µg/kg/day group showed placental cysts and discoloration of the amniotic fluid.

There were some variations in the degree of ossification of the fetal skeletons, but there was no evidence of treatment-related effects on morphological development.

Fifteen females from each group (75 total) continued to receive treatment through gestation and parturition, and post partum through study termination. Thirty-nine females died or were killed in extremis during parturition: 1 from the control group, and 10, 13, 12, and 9 from the groups receiving 1, 3, 5, or 15 µg/kg/day, respectively. The exact cause of death of these animals was not determined.

Length of gestation varied greatly within groups and between groups. The majority of females that began parturition exhibited some degree of dystocia. The ratio of the number of live litters born to number of pregnant females was reduced in all treatment groups, being one-third to one-half that of the control group.

No viable offspring were delivered in the group receiving 15 µg/kg/day. Only five females in the group receiving 1 µg/kg/day, and 2 each in the groups receiving 3 or 5µg/kg/day had live off-spring. Viability of offspring was further reduced in treatment groups through day 4 post partum.

Mean body weight of live offspring on day 1 post partum was reduced in the groups receiving 3 and 5 µg/kg/day, but not in the group receiving 1 µg/kg/day, when compared to the controls. The sex ratio varied greatly between groups, but is attributable to the low number of off-spring. There was no evidence of sex related differences in survival.

At necropsy, females in all ORF 17070 treated groups showed pale pituitaries, and pale livers, some with accentuated lobular patterns. Since histopathologic evaluation of these tissues was not performed, the cause of these changes was not determined.

Based on the results of this study subcutaneous administration of ORF 17070 to pregnant rats from days 7 through 20 of gestation at dose levels of 1, 3, 5, or 15 µg/kg/day resulted in reduction in maternal weight gain, stimulation of ovarian follicular development, increased placental weight, increased incidence of placental mottling and depressions, and an increase in fetal size. A dosage-related decrease in fetal survival occurred up to day 20 at dosages greater than 1 µg/kg. There was no evidence of teratogenicity. Continuation of treatment through parturition resulted in dystocia and high maternal and offspring mortality in all groups treated with ORF 17070. No offspring survived in the group receiving 15 µg/kg/day, and few offspring survived to day 4 post partum in other treated groups. Examination of the parental females at necropsy revealed pale pituitaries, and pale livers, some with accentuated lobular patterns, in all ORF 17070 treatment groups.

The reproductive results are consistent with an exaggerated pharmacologic effect of ORF 17070 on the pituitary-gonadal axis leading to a reduction of reproductive potential at these high doses. These observations are very similar to the decreased fetal survival and dystocia (with some attendant maternal mortality) which occur late in gestation as a consequence of ovariectomy in pregnant rats.

Unlike the rat, however, humans are not dependent on the ovary for maintenance of pregnancy beyond the early stages of gestation. Therefore, the reproductive effects noted for pregnant rats treated with ORF 17070 may not have direct relevance to the human condition.

Prepared by:
John W. Kille, Ph.D.
Group Leader
Toxicology II

Reviewed by:
G. James Davis, Ph.D.
Assistant Director
Toxicology II

Following is the sponsor's summary on segment II study in rabbits (study # 34, 12/26/1985):

TERATOLOGY (SEGMENT II) STUDY OF ORF 17070
IN NEW ZEALAND WHITE RABBITS

SUMMARY

The purpose of this study was to determine the embryotoxic and/or teratogenic potential of ORF 17070 when administered subcutaneously to pregnant rabbits once daily during the period of organogenesis. The study [redacted] was performed at the [redacted] from August 13, 1984 to September 24, 1984.

b(4)

Eighty timed pregnant New Zealand White rabbits were randomly assigned to the following 4 groups, 20 rabbits per group.

Group	Treatment	Dosage mcg/ml	Dosage ml/kg
1	Vehicle Control	0	1.00
2	ORF 17070 (Histrelin)	20	1.00
3	ORF 17070 (Histrelin)	50	1.00
4	ORF 17070 (Histrelin)	80	1.00

Animals received test or control articles (10% mannitol in 0.9% sodium chloride) subcutaneously for 13 days (days 6-18 of gestation). Body weights were recorded on days 6-18 and on days 24 and 30 of gestation. All rabbits were observed daily on days 5-30 of gestation. Food consumption was monitored daily. At necropsy, on day 30 of gestation, C-section was performed and the thoracic and abdominal viscera of all animals were examined. The uterine contents were examined, and live and dead fetuses, and early and late resorptions were numbered and their positions recorded. The ovaries were examined, and corpora lutea were counted. Fetuses were weighed, measured, and examined for external, visceral, and/or skeletal abnormalities. Approximately one half of the fetal heads were fixed in Bouin's fluid and a brain evaluation performed after serial sectioning.

One mid dose animal died on day 20 of gestation. This animal had raised red areas on the lungs with adhesions on all lobes, and hemmorhagic mastitis. The death was not considered to result from treatment with ORF 17070.

There were no meaningful differences in maternal body weight or maternal body weight gain between the control and the treated groups. Bloody vaginal discharges occurred in one animal in each of the low and mid dose groups and two in the high dose group, and early termination of pregnancy (between days 20 and 28 of gestation) resulted in three animals in each of the mid and high dose groups. Other clinical signs were noted in all dose groups (such as alopecia and scant feces), but did not appear in a dose related fashion.

Necropsy of females that completed full term gestation revealed no dosage related gross pathological changes. The pregnancy rate was low (60-70%) but consistent across all groups. Uterine examinations showed numbers of live and dead fetuses, and early and late resorptions to be comparable across groups. In each compound treated group, several does (three in the low dose, four in the mid dose, and two in the high dose) showed evidence of uterine implantations with no apparent corpora lutea.

Fetal body weights and crown rump distances were comparable across all groups. There were no dosage related differences in litter size or sex ratio. External, visceral, skeletal and head examinations revealed incidences of dysmorphogenesis in all groups, including the controls. These occurred in a low incidence, however, and the levels in the compound-treated groups did not exceed those found in the controls. In addition, rabbits have a higher background incidence of developmental aberrations than other species. These observations were, therefore, considered to be spontaneous and not related to treatment with ORF 17070.

Subcutaneous administration of ORF 17070 to pregnant rabbits between days 6 and 18 of gestation resulted in bloody vaginal discharge and/or early termination of pregnancy at dosage levels of 20, 50 or 80 mcg/kg per day (1, 4, and 5 does affected per group, respectively). At the same dose levels, 3, 4, and 2 does per group respectively showed implant sites without corpora lutea in the ovary. This apparent fetal death is likely to be the result of luteal regression, considered to be a pharmacological effect of ORF 17070.[5]

While fetal evaluations revealed no obvious compound related teratogenesis, there were too few fetuses available to make an assessment of the teratogenic potential of ORF 17070 in rabbits due to the reproductive sensitivity of rabbits to compounds of this type. Fetal resorption is generally recognized as almost an inevitable consequence of the action of LHRH analogues such as ORF 17070 when given to pregnant animals during the period of organogenesis.

Responsible Investigator:

STUDY DIRECTOR
John W. Kille, Ph.D.
Group Leader
Toxicology II

Reviewed by:

G. James Davis, Ph.D.
Assistant Director
Toxicology II

Summary of toxicity studies *(conducted during 1986-1989 by population council or WHO) from NDA 19-836 review.*

In summary, target organs of toxicity in a 3-month study in rats (8, 40, 200 ug/kg/day) were testes (mineral deposit), in 6-month study in rats (5, 30, 180 ug/kg/day by SC) were dose-related decreases in size and weights of several reproductive organs (uterus, ovaries, testes, prostate & seminal vesicles, but reversible after one month of drug free recovery period) and histopathology changes in the liver (perilobular vacuolation, which was sometimes not reversible after 6-months of drug free period at a HD of 180 ug/kg/day) and bone marrow (fat deposition).

In a 3-month toxicity study in rabbits (8, 40, 200 ug/kg/day), target organs of toxicity were ovary, uterus (atrophy) and mammary glands (decreased ductal epithelial growth in females), and pituitary (partial depletion of cytoplasmic secretory granules in both sexes). Most of the findings in rabbits appear to be reversible after 5-weeks of drug free recovery period.

In a 6-month study in monkeys (5, 30, 180 ug/kg/day by SC), target organs of toxicity were decreases in weights of several reproductive organs (uterus, testes, seminal vesicles, and ovaries) and dose-related atrophy of testes, prostate and S.V. In males, high dose had a complete absence of spermatocyte precursors, while LD had absence of mature spermatozoa. In treated females, uteri had inactive endometrium, none of the females had any evidence of ovulation. However, after cessation of the treatment the reproductive capacity of both sexes was intact.

In a segment I study (8, 40, 200 ug/kg/day) in rats (following a 3-month study in rats), when recovery males were mated with normal females, the drug produced decreases in the incidence of pregnancy (7/10 vs 10/10 in controls) and decrease in number of fetuses (7.6 vs 9.6 in controls). These were again reversible after 5-weeks of drug free recovery period.

In a segment 2 study in rats (0, 1, 3, 5, 15 ug/kg/day), animals died at all doses during parturition (1, 7, 13, 10, 8 in controls and all treated groups respectively). Females in all groups showed pale pituitaries and pale livers (with or without lobular patterns). Histopathology of organs was not performed. The exact cause of death was not determined but died of some degree of dystocia (abnormal labor or child-birth).

In a segment 2 study in rabbits (20, 50, 80 ug/kg/day), there were treatment related early termination of pregnancy in some rabbits and increases in fetal deaths. There were too few fetuses to make assessment of the teratogenic potential of the drug.

A Correlation study in dogs to show in vitro elution rate of the drug is predictive of in vivo release rate of histrelin:

Following correlation of in vivo release rates of histrelin from hydrogel implant were examined in a dog study which has been reviewed under NDA 21-732 (see DFS). Following summary is from the NDA 21-732 review.

This study was conducted by the l in 1995. The goals of this study were to determine the in vivo release rate of histrelin from hydrogel implants in dogs and to ascertain whether they differ from the in vitro release rate of the peptide from similar implants.

The results are shown below, for complete details see NDA 21-732 review in DFS:

In vitro release of histrelin: The maximum release rate was 45 ug/day at week 12. The release rate declined to about 20 ug/day at 48 weeks.
In vivo release rate of histrelin (A) average daily percentage rate: At 8, 16, 24, 32, 40 and 48 weeks, the mean +/- SE average daily release rate was estimated to be 39.6+/-3.2, 41.8+/-9.0, 33.7+/-5.0,

26.4+/-5.4, 33.7+/- 1.6, and 26.3+/-3.8 ug/day respectively. These results were considered in close agreement with in vitro release data except for the data obtained at 32 weeks.

In vivo release rate of histrelin (B) metabolic clearance rate and serum levels of histrelin: The estimated MCR ranged from 255 L/day to 430 L/day. The in vivo release rate in 6 dogs over a period of 48 weeks was estimated to be 55 ug histrelin at 8 weeks, slowly declining thereafter to about 22 ug/day at week 48. Dose-response curve: Data showed an excellent correlation between serum levels of histrelin and the number of implants used.

2.6.6.7 Local tolerance: Local tolerance studies of the hydrogel implant were investigated in the rat, dog, rabbit and monkeys. These studies have been conducted under two previous NDAs. As stated in NDA 21-732, primary subdermal irritation study of histrelin implants in rats and administration of HEMA/HPMA copolymer placebo extracts prepared in either saline of cottonseed oil in various toxicity studies i.e., intra-cutaneous injection test in rabbits, Kligman Maximization test in guinea pigs, systemic injection test in mice, and pyrogen test in rabbits did not exhibit any significant adverse effects.

The implant is removed upon replacement of new implant **after one year and dose't degrade in vivo.**

Table. Local tolerance studies conducted with histrelin

Table number: 2.6.7.1					Toxicology Overview				Page 5 of 6
Type of study	Test Material	Species and Strain	Method of Admin	Duration of Dosing	Doses (units)	GLP	Testing Facility	Study No	Location Section
Local tolerance (cont)									
Local pathological reaction	Placebo implant	Rabbit NZW	Subcutaneous	4 week	5 test implants per rabbit Non-toxic	Yes		Study 39	4.2.3.6
				12 week	5 test implants per rabbit Non-toxic	Yes		Study 40	4.2.3.6
				26 week	5 test implants per rabbit Non-toxic	Yes		Study 41	4.2.3.6
Muscle irritation	Histrelin	Rabbit NZW	Intramuscular	3 doses in 8 days	1.0 mL (1 mg) minimal/mild irritation	Yes		Study 42	4.2.3.6
Primary irritation	NaCl and cottonseed oil extract of placebo implant	Rabbit NZW	Intracutaneous	Single dose	5 x 0.2 mL per rabbit Negligible irritant	Yes		Study 43	4.2.3.6
Eye irritation	NaCl and cottonseed extract of hydron lens	Rabbit NZW	Intraocular	Single dose	0.2 mL neat extract Non-irritant	No		Study 44	4.2.3.6
	Hydron soft contact lens	Rabbit NZW	Intraocular	21 days	6-8 hours daily No significant primary irritation	No		Study 45	4.2.3.6
	Hydron soft contact lens	Rabbit NZW	Intraocular	21 days	Continuous wear Slight, probably transient, corneal damage	No		Study 46	4.2.3.6
Local tolerance									
Implant mineralization	Histrelin implant	Rat Sprague-Dawley	Implantation	30, 60, 120 and 210 day	Single implant Formulation 132 and 136. ~80 and 60 ug/rat/day	No		Study 5	4.2.1.1
	Placebo implant (polypropylene mandel)	Rat Sprague-Dawley	Implantation	1 and 2 month	2 implants/animal	No		Study 35	4.2.3.6
		Rabbit NZW							
		Monkey Rhesus							
Sub-dermal irritation	Components of Histrelin implant	Rat Sprague-Dawley	Sub-dermal	14 day	Single pellet Slight irritation	No		Study 36	4.2.3.6
Skin sensitization	NaCl extract of placebo implant	Guinea pig	Intradermal/ topical	NA	Weak allergenic potential	Yes		Study 37	4.2.3.6
	Cottonseed oil extract of placebo implant	Guinea pig	Intradermal/ topical	NA	Weak allergenic potential	Yes		Study 38	4.2.3.6

b(4)

Table number: 2.6.7.1			Toxicology Overview						Page 6 of 6
Type of study	Test Material	Species and Strain	Method of Admin	Duration of Dosing	Doses (units)	GLP	Testing Facility	Study No	Location Vol. section
Local Tolerance									
Implant mineralization	Histrelin implant (glass mould)	Dog Beagle	Implantation	2, 4, 6, 8, 10 and 12 month	4 implants per dog Minimal/mild mineral deposits	No		Study 47	4.2.3.6
	Placebo implant (polypropylene and glass mould)	Monkey Rhesus	Implantation	12 month	Single implant, Formulation 136. Slightly less mineralization on glass mould implant	No		Study 48	4.2.3.6
	Histrelin implant (believed to be glass mould)	Monkey Cyno	Implantation	2, 4, 8 and 12 month	2 implants per monkey. Little or no mineralization or cellular reaction.	No		Study 49	4.2.3.6
Other studies									
Local toxicity	Hydron monomer	Rat Albino	Subcutaneous implantation (in sponge)	2 week	8 sponges per rat, 2 each impregnated with 25 µL crude Hydron monomer, 25 µL pure Hydron monomer, 10 µL pure Hydron monomer or controls	No		Study 50	4.2.3.7.7
	Hydron monomer	Rat Albino	Subcutaneous implantation (in sponge)	2 and 4 week	4 sponges per rat, 2 each impregnated with > 100 mg Hydron monomer or controls	No		Study 51	4.2.3.7.7
Systemic toxicity	NaCl extract of Hydron polymers A, N and E	Rat Sprague-Dawley	Subcutaneous	5 day	4 ml/rat	No		Study 52	4.2.3.7.7

For Repeat-Dose Toxicity: the highest NOAEL (No Observed Adverse-Effect Level) is underlined

[a] - Unless otherwise specified
[b] - Lowest dose level where pharmacological effects, including adverse effects on fertility, were observed
[c] - Raw data not available
[d] - Changes in liver and bone marrow seen at all dose levels, but recovery apparent
[e] - Small increases in PCV & MCH in males only
[f] - Fertility re-established after cessation of dosing
[g] - Possible effects on fetal skeletal ossification
[h] - Lowest dose level for pharmacological effects and maternal toxicity

b(4)

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Supperlin (histrelin acetate) subcutaneous implant is a synthetic analog of luteininzing hormone-releasing hormone (LHRH) which is indicated for the treatment of central precocious puberty (CPP) in children. The current implant is a device that is designed to provide a sustained release of the active drug (approximately 65 ug histrelin/day) continuously over a period of one year when inserted beneath the skin.

No new toxicology reports were submitted in this NDA. The sponsor has a right of reference to non-clinical studies in NDA 19-836. As indicated earlier a similar implant was approved in 2004 for the palliative treatment of prostate cancer (NDA 21-732). This implant for the prostate cancer was redesigned to allow greater daily release of histrelin from 50 ug/day to 65 ug/day to treat children with CPP. This change was achieved by the sponsor by changing the percentage of **implant's cartridge components i.e.** [redacted] 2-hydroxypropyl methacrylate (HPMA) to [redacted], and purified 2-hydroxyethyl methacrylate (HEMA) to [redacted] and trimethylolpropane, while the percentage of trimethacrylate (TMPTMA- [redacted]) was not changed. This change produces a more hydrophilic implant allowing a higher rate of drug release. No new studies were conducted with the components of this implant cartridge, since the components in the implant cartridge are basically similar to the approved cartridge, i.e. HPMA component in the current implant cartridge is actually slightly lower (i.e. it has HPMA of [redacted] than in the previously approved implant (which had HPMA of [redacted] in NDA 21-732), although HEMA percentage was increased to [redacted] in the current implant (vs it was [redacted] before in NDA 21-732), this increase is small, and the implant is non-biodegradable and removed after one year. Thus this implant is intended to provide continuous release of histrelin acetate at a nominal rate of 65 µg/day over 12 months

b(4)

No new toxicity studies have been conduced. However under NDA 19-836, this drug was approved for higher daily SC doses of 10 ug/kg in pediatric subjects for the same indication. In contrast in the present NDA 22-058, it will be approved at doses of 65 ug/day for one year/implantation.

The Chemistry reviewer has stated that although the implant is intended to provide continuous release of histrelin acetate at a nominal rate of 65 micrograms per day over 12 months, the drug product specifications allow the *in vitro* elution rate to varv between [redacted] The *in vitro* elution rate has been shown to be predictive of the *in vivo* release rate (based on a dog study described in the NDA 21-732 review). The DMF on this drug (DMF [redacted]) substance was reviewed on 8/9/2004 and was found to be adequate. Thus, in vitro elution or release rate of the drug drastically increases from 150 [redacted] after storage for 24 **months at the proposed storage conditions of 2-8° C. A similar "initial burst" may occur in vivo in** children, while the week 3 and week 4 elution or release rates do not significantly increase upon storage. b(4)

The initial release rates of [redacted] are not a concern from the pharmacology/toxicity point of view. Animal studies have been conducted up to 180-200 ug/kg/day in rats and monkeys, and these established NOAELs provide a safety margins based on ug/kg/day as well as C_{max} to this three times increase in initial burst based on in vitro data. In contrast, the nominal release of 65 µg/day provide safety rates of 55-60 fold in rats and monkeys. See Table 1 below. b(4)

Table 1. Multiples in humans are based on ug/kg/day in rat & monkey toxicity studies respectively, and also on ug/kg/day doses in humans. Note that the established NOAEL doses have been used **(sponsor's Table on page 20). The established doses are stated from a 3-month study in rats.** However similar doses have been used in a 6-month study in rats (5, 30, 180 ug/kg/day)

Species	µg/kg/day	NOAELS	Safety margins in human children
			65 µg/day dose
3-Month Rat	8, 40, 200	200	60X
6-Month Monkey	5, 30, 180	180	55X
*Human dose			
1) 65 ug/day or 3.25 µg/kg/day			

*** Calculations are based on a child's weight (based on 20 kg child).**

As stated above, toxicity data in rats suggests that doses up to 180 ug/kg/day corresponding to a C_{max}=81 ng/ml were not associated with significant toxicity. Based on a 65 ug/day release in pediatrics a C_{max} = 0.5 ng/ml has been established at steady state. This results in a safety margin of 160-fold based on C_{max} (81/0.5=160X). Therefore even if the 3-fold increase in initial burst were to occur after 24 months in pediatrics, the non-clinical data would suggest there isn't a safety issue based on the absence of toxicity in rats at 160-fold higher acute exposures (Table 2). Therefore there is no safety concern with a 2-year shelf life from a non-clinical standpoint. Note that no plasma concentration or C_{max} values are available from the initial burst studies in humans.

Table 2. Multiples in humans are based on C_{max} in 29-day rat toxicity/TK study, and also on C_{max} doses in humans from phase 2 studies at steady state*.

Species (ug/kg/day)	NOAELS	C_{max} (ng/ml)	Safety margins in human children
			65 µ/day dose
29-day Rat (5, 30, 180)	180	3, 16, 81	160X
Human dose (C_{max} ng/ml)			
1) *65 ug/day (C_{max}= 0.5 ng/ml)		0.5	

* Calculations are based on a steady state Cmax levels obtained in children from phase 2 study.

Table 3 below shows the multiples in humans, based on body surface area (ug/m^2) in rat and monkey toxicity studies.

Table 3. Multiples in humans are based on µg/m^2/day in rat & monkey toxicity studies respectively, and also on µg/m^2/day in human children*.

Species	NOAELs µg/kg/day	µg/m^2/day	Safety margins in human children based on µg/m^2/day
			65 µg/day dose
3-Month Rat	200	1200	15X
6-Month Monkey	180	2160	30X
*Human dose			
1) 65 ug/day or 3.25 µg/kg/day		81	

*** Calculations are based on a child's weight (based on 20 kg child).**

Labeling Review: The pharmacology/toxicity studies including carcinogenicity and repro toxicity studies were conducted under previous NDA 19-836 in which the recommended dose of histrelin was 10 ug/kg for the treatment of CPP. The current label in general is similar to the one in the NDA 21-732 for the prostate cancer. Note that the draft labeling with supprelin (histrelin acetate SC implant) is provided in the new format i.e in SPL format

However the following change in labeling is recommended

Sponsor's label

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Pharm/Tox-__1__

b(4)

[redacted]

External Recommendation:
From the preclinical standpoint, approval of this application is recommended, pending labeling changes.

cc: IND Arch
HFD-510
HFD-510/davisbruno/antonipillai/roman/j.jhohnson
Review code: AP
File name: nda22058 (histrelin implant)

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/s/

Indra Antonipillai
4/17/2007 12:48:54 PM
PHARMACOLOGIST/TOXICOLOGIST
From the pharm/tox point of view, approval of this application is recommended, pending labeling changes
This application is recommended for approval, pending lableing changes.

Karen Davis-Bruno
4/17/2007 01:37:51 PM
PHARMACOLOGIST/TOXICOLOGIST
concur w/recommendations