CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-058

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	22-058
Submission Date(s)	June 30, 2006
Brand Name	Supprelin® LA
Generic Name	Histrelin acetate subcutaneous implant 50mg
Reviewer	Sang M. Chung, Ph.D.
Team Leader	Johnny Lau, Ph.D. (Acting)
OCP Division	Division of Clinical Pharmacology II
OND Division	Division of Metabolism and Endocrinology Products
Sponsor	Valera Pharmaceuticals, Inc.
Submission Type	Standard
Formulation Strength(s)	Implant, 50mg
Indication	Treatment of children with central precocious puberty
Dosage & Administration	One implantation with 50 mg histrelin over 12 months

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed NDA22-058 for Supprelin® LA and finds it acceptable. The Recommendation should be sent to the sponsor as appropriate.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The sponsor submitted the NDA 22-058 for Supprelin® LA (histrelin acetate subcutaneous implant, 50 mg) and the proposed indication is for the treatment of central precocious puberty (CPP). Histrelin acetate is a luteinising hormone-releasing hormone (LHRH) agonist with about 4 hours terminal half-life in adult. With chronic administration of histrelin, pituitary is desensitized from LHRH stimulation and thus secretion of gonadotropins (i.e., luteinising hormone; LH and follicle stimulating hormone; FSH) and sex hormones (estradiol in female and testosterone in male) is reduced.

Histrelin was approved for the treatment of CPP under the NDA 19-836 for Supprelin® (Shire Laboratories) in 1991 and the NDA was withdrawn in 2002 because of no marketing activity. The dosing regimen of Supprelin® was 10 μg/kg daily subcutaneous injections. Supprelin® LA was slightly modified from the approved Vantas®, which is for the indication of palliative treatment of metastatic prostate cancer and marketed by the same sponsor. Supprelin® LA and Vantas® were designed to release histrelin 65 μg/day and 50 μg/day, respectively.

The sponsor conducted two clinical studies for efficacy, safety and pharmacokinetics with Supprelin® LA. One was a Phase II study for dose ranging in 11 children with CPP who were receiving a LHRH agonist subcutaneous monthly injections and the other was a Phase III in 36 children with CPP who were naïve to LHRH agonist treatments or were receiving a LHRH agonist subcutaneous monthly injections.

There was no reliable dose-response characterization for Supprelin® LA primarily due to small number of subjects per treatments in the Phase II study. However, the sponsor concluded that there was no additional benefit of 2 implants compared to that of 1 implant according to the Phase II study results and thus Supprelin® LA 1 implant was evaluated in the Phase III study. Histrelin serum concentrations were not proportionally increased with number of implants, which was one of the confounding factors in the dose-response relationship. Pharmacokinetics was characterized over 13 months

treatment period in both studies and it was concluded that mean serum histrelin concentrations (Cave) in CPP children were comparable to those in adult prostate cancer patients. Suppression of gonadotropins and sex hormones after Supprelin® LA implant seemed to be acceptable. There was no apparent histrelin pharmacokinetic difference after Supprelin® LA implant between subjects who were naïve to LHRH agonist treatment and subjects who were receiving LHRH monthly subcutaneous injections.

Supprelin® LA was predicted to show a maximum histrelin serum concentration in a few days after subcutaneous implant according to *in vitro* elution rate and human study results with Vantas®. The sponsor sparsely collected blood samples in a few subjects for the preliminary evaluation of the initial *in vivo* release characteristics of Supprelin® LA and there was no apparent signal for unusually high initial histrelin concentrations. In addition, there was no preclinical safety concern for the estimated Cmax up to 81 ng/ml. Therefore, it was concluded that there was no major clinical concern for the initial release.

The sponsor did not address the QTc prolongation effect of Supprelin® LA in this application. However, the sponsor concluded no further study to investigate the effect of Vantas®s on QT prolongation and the Agency agreed on the conclusion.

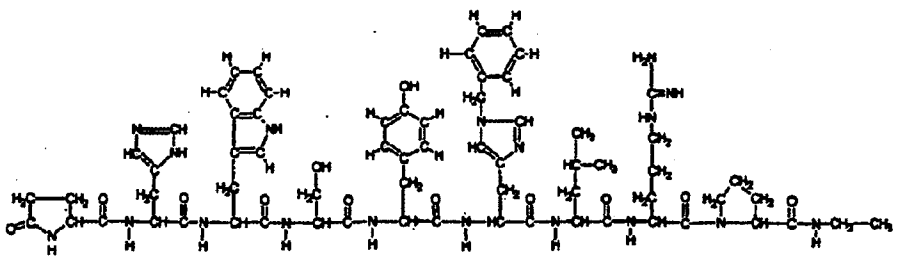
There was no formulation change for the to-be-marketed formulation from the formulation used in the Phase III study.

2 Question Based Review

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology review?

Histrelin acetate is a synthetic nonapeptide LHRH agonist (Figure 1). It is known to be up to 200 times more potent than LHRH in stimulating of LH and FSH. Histrelin acetate is sparingly soluble (~ 13mg/ml) at pH 5 and very slightly soluble (~ 0.5 mg/ml) at pH 6-7.5. Histrelin acetate was stable at pH 5 and the stability was decreased as pH.



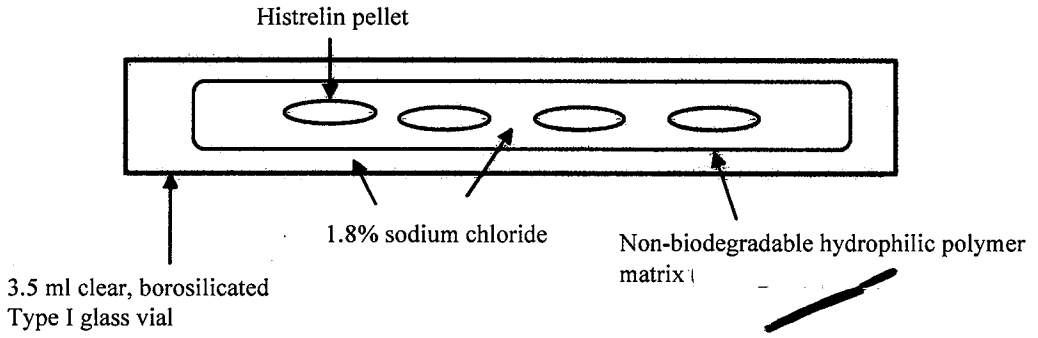
Molecular weight: 1323.52 (net) + 120.2 (diacetate) = 1443.7

Figure 1 Structural formula of Histrelin (From Figure 2.4.1.1-2)

Supprelin® (histrelin acetate) was used with the approved indication of CPP from 1991 and the NDA was withdrawn in 2002 because of no marketing activity. The dosing regimen of Supprelin® was 10 µg/kg daily subcutaneous injections and the labeling indicated that the metabolism, distribution, and excretion of histrelin in human were not determined.

Supprelin® LA is a diffusion-controlled reservoir drug delivery system designed to deliver histrelin for 12 months after subcutaneous implant. The drug product consisted of 4 histrelin acetate pellets inserted into a non-biodegradable polymer cartridge, and submerged in 1.8% sodium chloride solution (Figure 2). Supprelin LA® implant was designed to have a target *in vitro* release of 65 µg histrelin daily and *in vitro* elution rate was about [redacted] b(4)

[redacted] Supprelin LA® is modified to slightly increase histrelin releasing from the approved drug product (NDA 21-732 for Vantas®). Vantas® (12 month histrelin implant) was approved for the palliative treatment of [redacted] prostate cancer in October 2004 with the target *in vitro* release rate of 50 µg daily and *in vitro* elution rate was [redacted] daily. The release rate of histrelin for CPP subjects were increased due to higher histrelin clearance in children compared to that for adult prostate cancer patients.



b(4)

Figure 2 Drug product (3cm long and 3.5 mm in diameter, not to scale) and the container closure system (not to scale)

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Histrelin is an LHRH agonist for the pituitary desensitization and the proposed indication is the treatment of CPP.

The CPP is the early onset of hypothalamic-pituitary-gonadal activity and it is generally acknowledged to be before the age of 8 in girls and 9 in boys. Children with the precocious puberty look noticeably different than their peers and have short stature with

significant psychosocial problems. A common cause of the CPP is a central nervous system lesion in girls less than 4 years of age and intracranial tumors in both girls and boys. The incidence of CPP is 10 to 1 times greater in girls than in boys.

The currently available approaches to the CPP are surgical treatment and change the hormonal balance to stop sexual development. A standard dosage regimen for the hormonal treatments is a four-week interval intramuscular injections of LHRH analogs (e.g., leuprolide).

Histrelin initially stimulates the release of LH and FSH from the pituitary gland but the pituitary will be eventually desensitized with continuous histrelin administration. Therefore, secretion of LH and FSH will be suppressed (Figure 3).

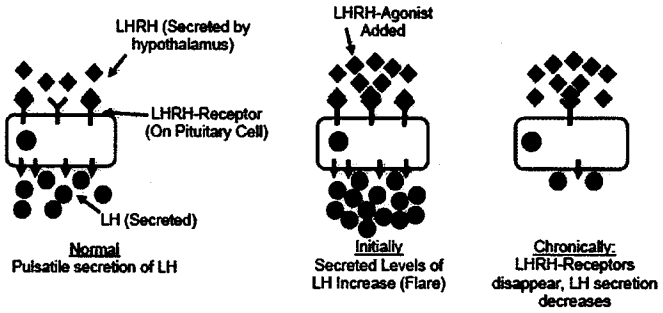


Figure 3 **Mechanism for pituitary desensitization by LHRH (from Figure 2.4.1.1-1)**

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The recommended dose of Supprelin LA® is one implant (50 mg) for 12 months and the implant is inserted subcutaneously in the inner aspect of the upper arm (Figure 4).

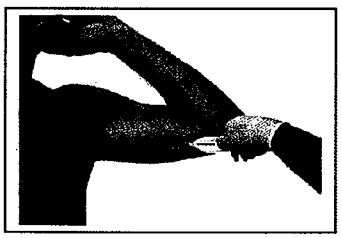


Figure 4 **Area of upper arm for subcutaneous implant (from Vantas® labeling)**

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

One Phase II study (Study 01-02-001) for efficacy, safety and pharmacokinetics was conducted in 11 female subjects with CPP who were receiving LH-RH analog intramuscular injections and pharmacokinetics was evaluated over 18 months during subcutaneous implant. Two doses were evaluated in the study and the evaluation of dose-response relationship was summarized in Section 2.2.3.

One Phase III study (Study 03-CPP-HIS-300) for efficacy, safety and pharmacokinetics was conducted in 36 subjects (male: 3, female: 33) with CPP over 24 months subcutaneous implant including extension period. Each subject received the new implant after removal of the first implant at 12 Month. Of the 36 subjects, 20 were LHRH naïve and 16 were receiving LHRH analog intramuscular injections. Study results were summarized in Section 2.2.4 for histrelin pharmacokinetics after Supprelin® LA implant.

The sponsor submitted historical histrelin pharmacokinetics in healthy adult males after histrelin subcutaneous injection and in patients with the prostate cancers after Vantas® administration as reference information.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Histrelin is to desensitize pituitary against LHRH stimulation and thus reduce gonadotropins and sex hormones (estradiol in female and testosterone in male) to below normal physiologic concentrations. Therefore, reductions of gonadotropins and sex hormones over the treatment period were the primary efficacy parameters. In addition, the noted changes in secondary sexual characteristics along with growth rates and skeletal maturation were measured. Secondary and observational measures of efficacy were suppression of estradiol or testosterone, TSH, DHEA-sulfate, and free T4, Tanner staging, bone age, and transabdominal pelvic ultrasound findings, Z-scores, growth velocity standard deviation scores, and investigator assessment of disease.

2.2.3 Exposure-response

2.2.3.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response)?

A preliminary Phase II dose finding study was conducted in female subjects with CPP. Subjects who weighed ≤ 40 kg received Supprelin LA 1 implant (Group 1) and subjects who weighed > 40kg received Supprelin LA 2 implants (Group 2). A total of 5 subjects (2 subjects from Group 1 and 3 subjects from Group 2) received replacement only for 1 implant at Month 9 (Track 1). For subjects who received 2 implants initially (Group 2), one implant was replaced with the new implant and the other was left in place. Otherwise, the original implant was left in place (Track 2, five subjects from Group 1 and 1 subject from Group2). The overall treatments were summarized in Table 1.

Table 1 Summary of treatments over 18 months

Screening	Visit 1	2	3	4	5	6	7	8	Extension Phase[c]
	Implantation	1 mo	3 mo	6 mo	9 mo	12 mo	15 mo	18 mo	
Within 14 days N=11	Group 1 (1 implant) N=7	→	→	→	Track 1[a] N=2	→	→	→	→
					Track 2[b] N=5	→	→	→	→
	Group 2 (2 implants) N=4	→	→	→	Track 1[a] N=3	→	→	→	→
					Track 2[b] N=1	→	→	→	→

[a] Day 1 implant(s) replaced with 1 new implant
[b] Day 1 implant(s) left in place
[c] Subjects who gave permission were allowed to continue treatment in the extension phase

The change of efficacy endpoints over 18 months was shown in Figure 5 (sex hormone changes) and 6 (gonadotropins changes). The sponsor concluded that suppression of sex hormone and gonadotropins were acceptable for both doses since reduction of sex hormone and gonadotropins were below therapeutic target as shown in the figures. In addition, there was no apparent efficacy benefit of 2 implants compared to that of 1 implant.

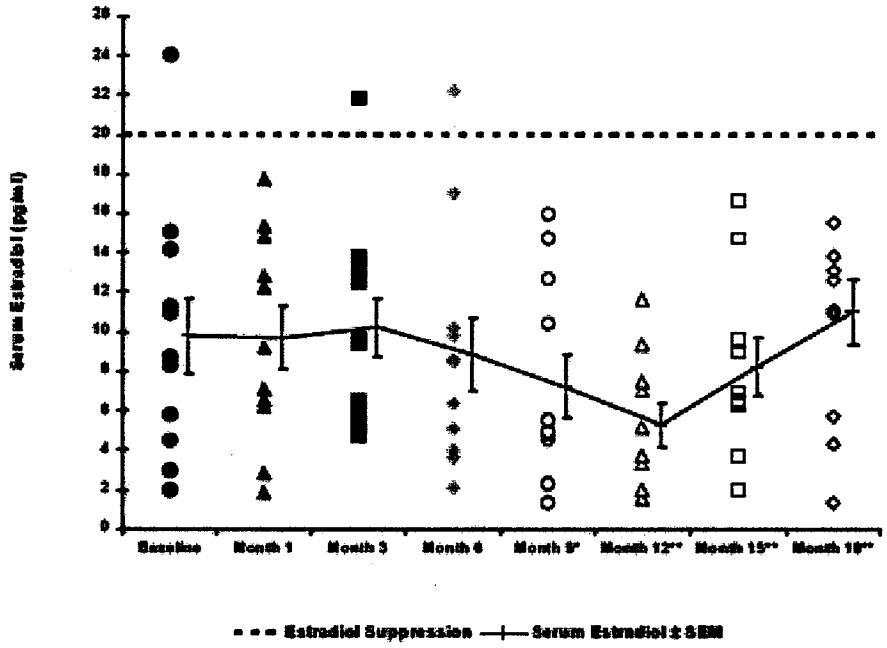


Figure 5 **Serum estradiol concentrations over the treatment period (the broken line indicates the therapeutic goal for estradiol reduction)**

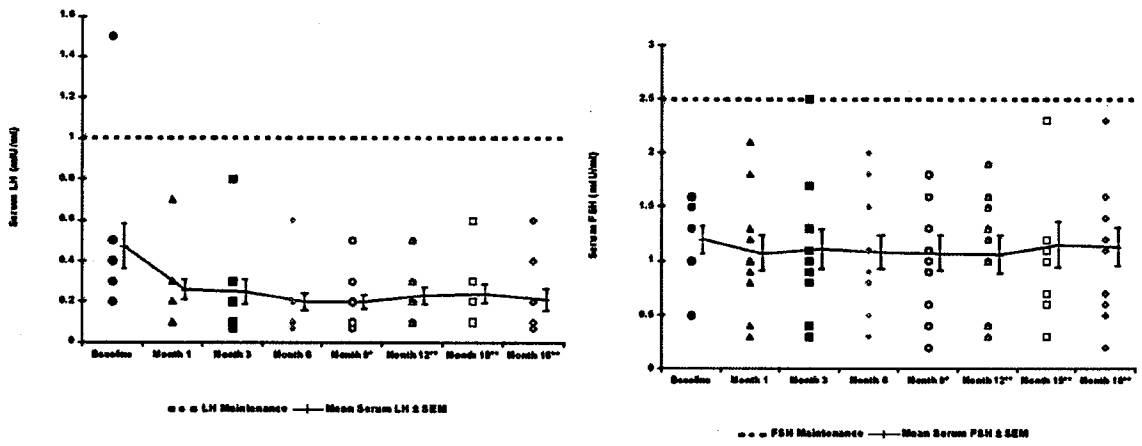


Figure 6 **Serum LH (left panel) and FSH (right panel) concentrations over the 18-Month (the broken line indicates the therapeutic goal for estradiol reduction)**

Reviewer's Comment: Dose-response characterization based on the study results was not reliable due to small number of subjects per treatment (i.e., n=7 for one implant and n=4 for two implants, Figure 7) and sub-groups (i.e., Group and Track).

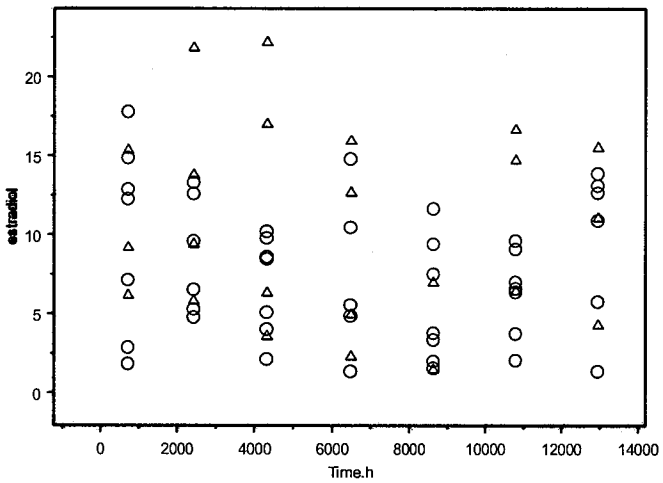


Figure 7 **Serum estradiol concentrations over the treatment period by dose: blue open circle for 1 implant and red open triangle for 2 implants**

In addition, correlation between histrelin concentrations and estradiol concentrations appeared to be flat (Figure 8) and the result indicated that a maximum effect was reached in the observed histrelin concentration range. However, the flat relationship might be confounded by pituitary desensitization from previous intramuscular injections of LHRH agonist.

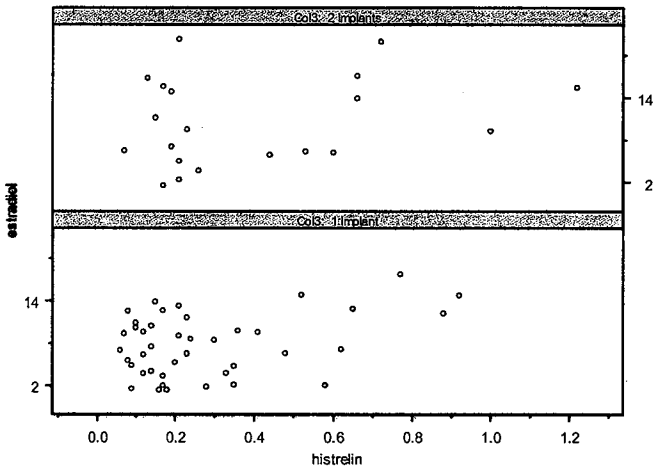


Figure 8 **Relationship between histrelin serum concentrations and estradiol concentrations: 1 implant (lower panel) and 2 implant (upper panel)**

Furthermore, serum concentrations of histrelin appeared to be not proportional to dose (i.e., number of implant) and it was a confounding factor for a lack of dose-response relationship in the results (Section 2.2.4).

Overall, there was no reliable exposure-response characterization in CPP subject after Supprelin® LA implant.

Vanta® label indicated that 2 or 4 implants did not show additional benefit compared to 1 implant even though serum histrelin concentrations were proportional to doses and it seems that the dose-response for Supprelin® LA was not well characterized due to a small number of subjects.

Histrelin *in vitro* elution rate decreased with time after the initial high rate and the serum histrelin concentrations may be below the efficacious levels after 12 months of implantation. However, the efficacy was not evaluated after 12 months for Supprelin® LA implantation without a new implant. In addition, there will be the initial pituitary stimulation after Supprelin® LA implantation if the pituitary is no longer desensitized to histrelin. Therefore, it is recommended to minimize the lag time for the replacement after 12 months of implantation. This issue was discussed during the OCP briefing from the clinical perspectives.

2.2.3.2 Does this drug prolong the QT or QTc interval?

There was no *in vitro* study or a thorough QT study. The reported QTc prolongation effect of Vantas® was about 6 msec and the magnitude is lower than other drug treatments for the prostate cancer patients. It is believed that androgen depression by histrelin is related to QTc increase. Therefore, the sponsor concluded no further study to

investigate the effect of Vantas®s on QT prolongation and the Agency agreed on the conclusion according to the review of Vantas®.

2.2.4 What are the PK characteristics of histrelin after Supprelin® LA subcutaneous implant?

Pharmacokinetics of histrelin was characterized after Supprelin® LA subcutaneous implant in two studies with CPP subjects (Study 01-02-001 and 03-CPP-HIS-300).

Study 01-02-001 was a Phase II study and blood samples were collected over 13 months (i.e., at Month 1, 3, 6, 9, 12, and 13) after 1 implant or 2 implants in 11 female subjects. Second implant (1 implant) was provided after removal of the first implant at Month 9 in 5 subjects. Treatments were summarized in Table 1. The serum concentration-time profiles were shown in Figure 9 and pharmacokinetic parameters were summarized in Table 2. It was concluded that mean peak histrelin acetate levels was observed at Month 1 and there was sustained histrelin release over the treatment period. Average concentration over the treatment (i.e., Cavg) was a representative pharmacokinetic parameter for histrelin after 12 month implant and median Cavg (i.e., 0.28 ng/ml) comparable to those in prostate cancer patients.

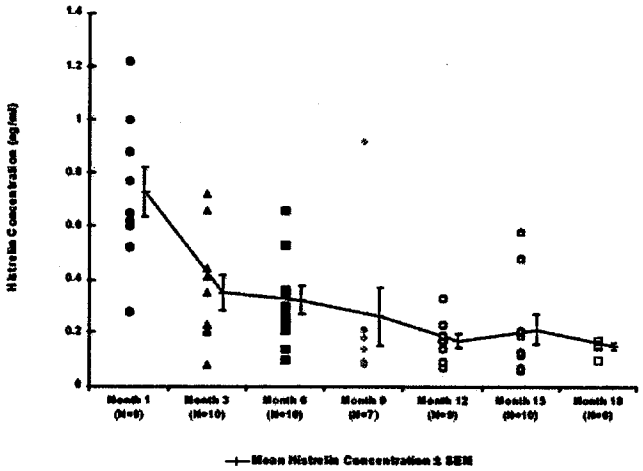


Figure 9 **Histrelin serum concentrations (ng/ml) over 13 months**

Table 2 **Histrelin pharmacokinetic parameters over 13 months**

	Cmax (ng/mL)	Tmax (months)	AUC(0-9 (hr*ng/mL)	Cavg (ng/mL)
N	11	11	11	11
Mean (SD)	0.75 (0.23)	3.50 (4.77)	4.67 (1.88)	0.34 (0.15)
Median	0.65	0.99	4.22	0.28

b(4)

Source: Table 2.7.3

NOTE: There were insufficient points or the elimination pattern was not linear in most subjects; therefore, the elimination rate constant could not be estimated.

* Subjects with histrelin concentrations below the level of quantification (BLQ ≤0.05 ng/mL) at any time point were not included in the analysis for that time point

• Cave: average of all the observed concentrations

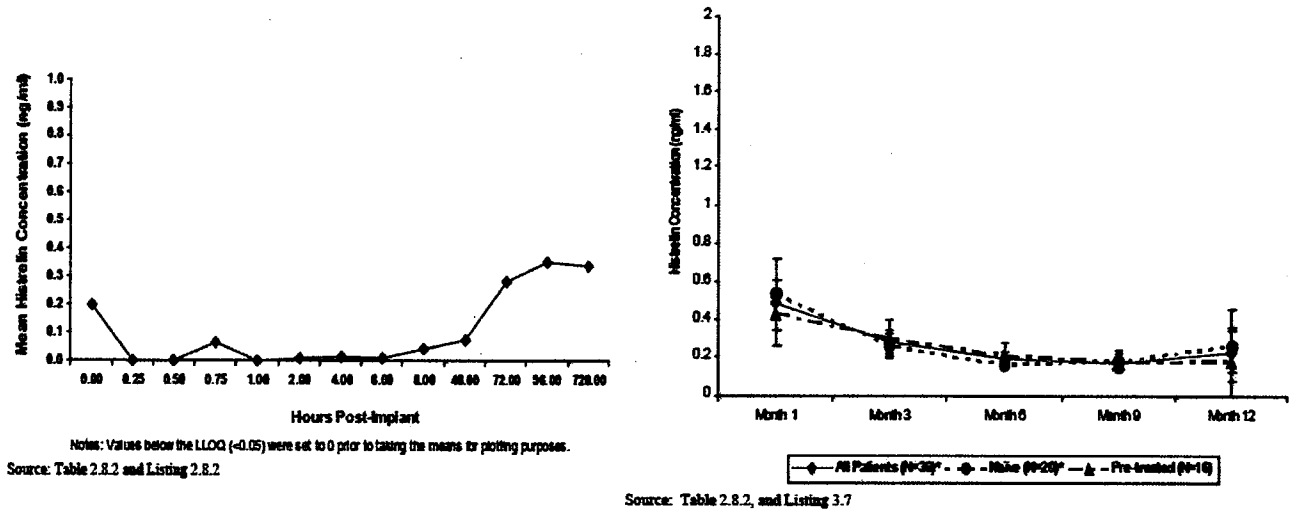
Study 03-CPP-HIS-300 was the Phase III study for the efficacy, safety, and pharmacokinetics of histrelin after Supprelin® LA implant in children with CPP. The subjects received 1 implant and pharmacokinetics was estimated primarily based on Visits over 13 months after the implant. Treatment and visit schedules are summarized in Table 3. A total of 36 patients finished pharmacokinetic study; 20 patients were naïve and 16 patients had received LHRH analog treatment before Supprelin® LA implant. Additional blood samples were collected on Day 1 through Day 4 in a subgroup of subjects to evaluate *in vivo* initial histrelin release of Supprelin® LA.

Table 3 **Treatment and Visit schedule**

Screening	Initial Phase							Extension Phase[a]			
Within 30 days	V1 Day 1	V2 1 mo	V3 3 mo	V4 6 mo	V5 9 mo	V6 12 mo	V7 13 mo[b]	V8 15 mo	V9 18 mo	V10 21 mo	V11 24 mo
Pretreated Group N=16	Initial implant	→	→	→	→	New implant[c]	→	→	→	→	Implant removal
Naïve Group N=20	Initial implant	→	→	→	→	New implant[c]	→	→	→	→	Implant removal

[a] Eligible subjects at Month 13 were allowed to continue treatment through Month 24 in the extension phase.
[b] Assessments were performed for subjects who received new implants at Month 12, after which they were allowed to enter the extension phase.
[c] The Day 1 implant was replaced with a new implant at Month 12 in eligible subjects.

The mean histreline serum concentrations-time profiles were shown in Figure 10, and pharmacokinetic parameters were summarized in Table 4.



Notes: Values below the LLOQ (<0.05) were set to 0 prior to taking the means for plotting purposes.
Source: Table 2.8.2 and Listing 2.8.2

Source: Table 2.8.2, and Listing 3.7

Figure 10 **Mean serum histrelin concentrations-time profiles: From Day 1 to Day 4 in a sub-group (left panel) and From Month 1 to Month 12 (right panel)**

Table 4 **Histrelin pharmacokinetic parameters over 12 months**

Statistics[a]	C_{max} (ng/ml)	C_{min} (ng/ml)	C_{av} (ng/ml)	T_{max} (months)	T_{min} (months)	AUC_{0-t} (months x ng/ml)
N	36	36	36	36	36	36
Mean±S.D.	0.51±0.35	0.13±0.05	0.27±0.12	2.96±3.31	8.40±3.43	2.65±1.38
Median	0.43	0.12	0.26	1.00	8.92	2.55
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b(4)

Source: Table 2.8.2, Listings 2.8.2 and 2.8.3

[a] Subjects with histrelin concentrations below the level of quantification (BLQ < 0.05 ng/mL) at any time point were not included in the analysis for that time point.

Notes: There were insufficient points or the elimination pattern was not linear in most subjects; therefore, the elimination rate constant could not be estimated.

Reviewer's Comments: According to the draft Chemistry Review by Dr. Elsbeth Chikhale, *in vitro* elution rate peaked at Day 1 [redacted] and the storage condition affected the initial elution rate; the longer the storage condition, the more variable and higher initial elution rate ([redacted] However, the storage condition did not affect *in vitro* elution rate at Week 3 or 4. The sponsor infrequently collected serum samples for histrelin determination from Day 1 to Day 4 in the Study 03-CPP-HIS-300 (Figure 10, left panel) and there was no signal for unusually high concentrations though the data were not reliable due to small number of subjects (about 4 subjects) with sparse sampling nature (Figures 11 and 12). In addition, the preclinical review concluded that there was no nonclinical safety concern in the projected Cmax up to 81 ng/ml. The median value of histrelin Cmax in children (Phase II study) was 0.75 ng/ml with the range of 0.52 to 1.22 ng/ml and the Cmax in adults was 1.10 ng/ml with SD of 0.375. Therefore, it was concluded that there was no major clinical concern for the initial release.

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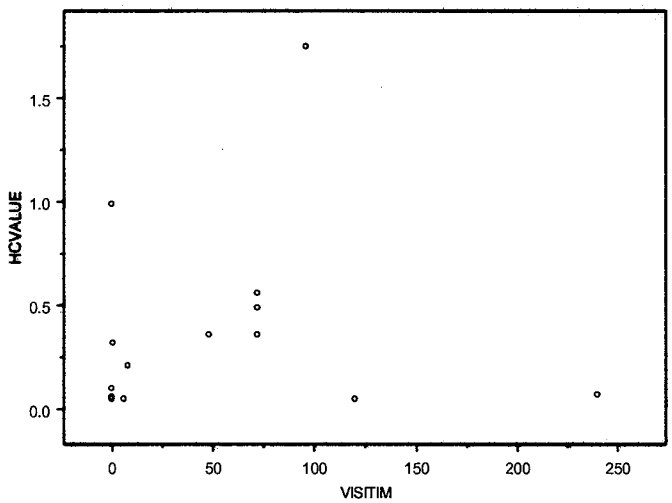

Figure 11 **Serum histrelin concentration in a sub-group from Day 1 to Day 4 (Study 03-CPP-HIS-300)**

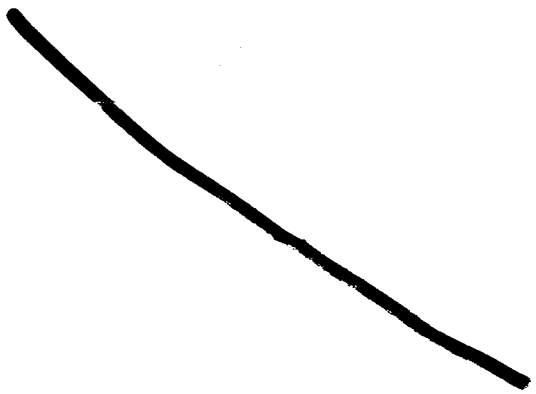

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Figure 12 **Individual serum histrelin concentration-time profiles in a sub-group (Study 03-CPP-HIS-300)**

Histrelin serum concentrations in children after Supprelin® LA implant were compared to those in adults from historical data after Vantas® implant to evaluate pharmacokinetic difference between the patients groups. Mean serum histrelin concentrations over treatment period in children were similar but variability was higher in children compared to that in adult cancer patients (Figures 13 and 14).

Variability of histrelin concentrations after the second implant was comparable to that after the first implant. Average concentration over the treatment period (Cave) were similar between children (0.27 +/- 0.12) and adults (0.265+/-0.0685, Table 5)

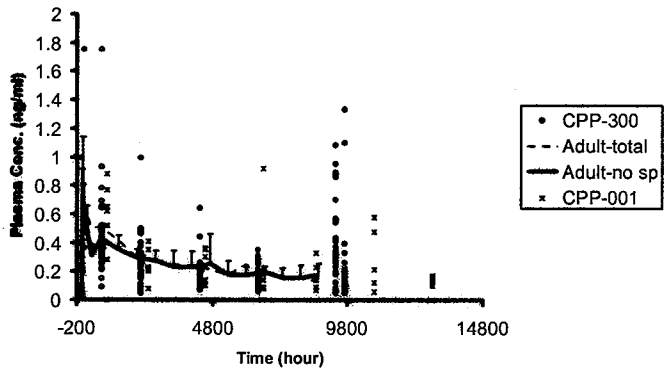


Figure 13 **Serum histrelin concentration-time profiles over 18 months: open circle for data from Study 300 (n=36), cross for data from Study 001 (n=11), broken line for data from Study 301 (adults; n=17), and solid line for data from Study 301 (adults without renal or hepatic impairment; n=5)**

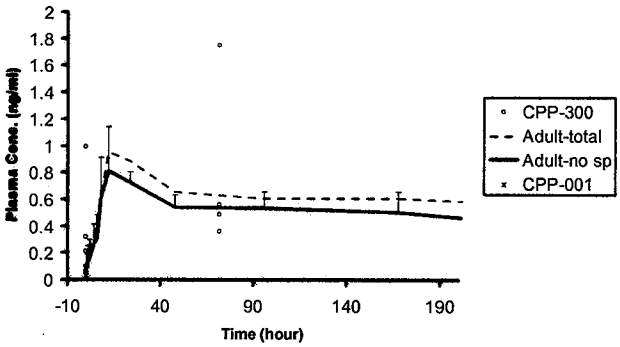


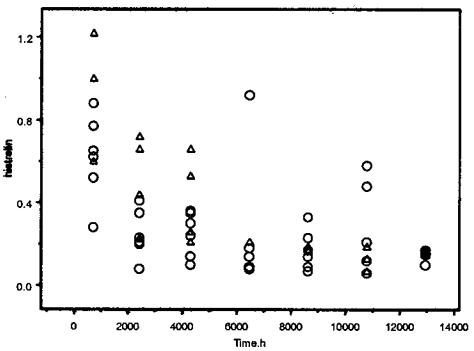
Figure 14 **Serum histrelin concentration-time profiles from Day 1 to Day 4: open circle for data from Study 300, broken line for data from Study 301 (adults; n=17), and solid line for data from Study 301 (adults without renal or hepatic impairment; n=5)**

Table 5 **Histrelin pharmacokinetic parameters in patients with prostate cancer following 50mg histrelin implant from the historical data**

Parameter	All Patients (N=17)		Normal Renal and Hepatic Function (N=5)		Renal Impairment (N=10)		Hepatic Impairment (N=2)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cmax, ng/mL	1.10	0.375	0.856	0.294	1.28	0.337	0.832	0.323
Tmax, hr[a]	12.00	6 hr-36 wk	12.00	12-24 hr	12.00	6 hr-36 wk	677.75	12 hr-8 wk
Cavg(0-96hr), ng/mL	0.697	0.226	0.576	0.114	0.802	0.178	0.472	0.438
Cavg(0-52wk), ng/mL	0.265	0.0685	0.247	0.0837	0.292	0.0527	0.193	0.0417
AUC(0-96hr), ng-wk/mL	0.398	0.129	0.329	0.0654	0.459	0.102	0.270	0.251
AUC(0-8wk), ng-wk/mL	3.99	1.24	3.36	0.692	4.58	1.31	2.91	0.127
AUC(0-16wk), ng-wk/mL	6.65	1.72	5.77	1.18	7.48	1.72	5.07	0.375
AUC(0-52wk), ng-wk/mL	13.8	3.55	12.8	4.35	15.2	2.71	10.0	2.20
SLP, wk[-1]	0.0350	0.0193	0.0259	0.00711	0.0426	0.0227	0.0232	0.00325

[a] Expressed as median and range.

Serum histrelin concentrations were not proportional to number of implant as shown in Figure 15 (Study 001) and it was one of the confounding factors in the estimation of dose-response relationship.



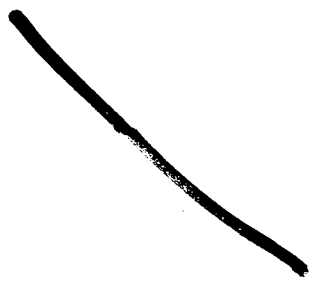


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Figure 15 **Serum histrelin concentrations over time by treatment group: all the subjects (left panel – circle for 1 implant, triangle for 2 implants) and individual profiles (right panel - circle for 1 implant, triangle for 2 implants**

There was no apparent difference in serum histrelin concentration-time profiles between naïve and previous IM treatments after Supprelin® LA (Figure 16).

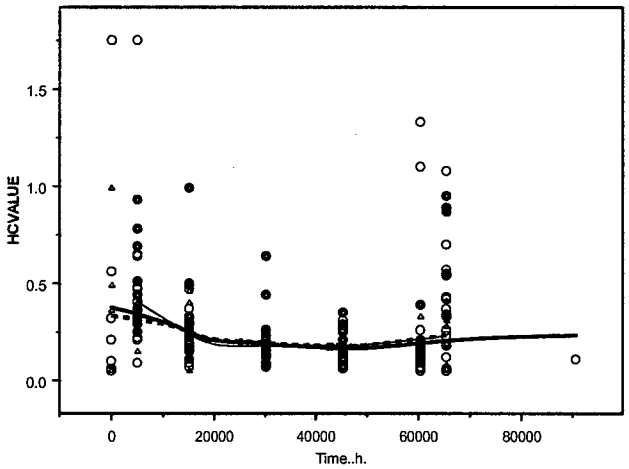


Figure 16 **Serum concentration time-profiles by sub-population: open circle is for naïve (n=20, line is for Loess fit), open triangle is for previous treatment (n=16, broken line is for Loess fit)**

2.2.4.1 What are the other pharmacokinetic characteristics (ADME and intrinsic factors) of histrelin?

Pharmacokinetics of histrelin in children was only available after Supprelin® LA implant. Histrelin pharmacokinetics of histrelin in adults was available from a historical study (6 healthy adults after 500 mg S.C.; Study 07-03-100). Serum concentration-time profiles were shown in Figure 17 and pharmacokinetic parameters were summarized in Table 6.

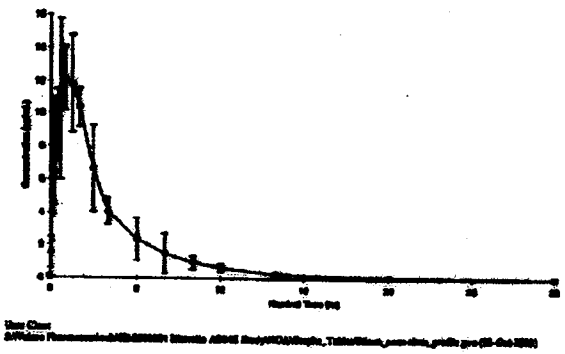


Figure 17 **Mean serum concentration-time profiles in healthy adults**

Table 6 **Pharmacokinetic parameters of histrelin in healthy adults**

	Mean	SD
Cmax (ng/mL)	13.50	3.00
AUC0-36 (hr ng/mL)	50.47	12.63
CL/F (mL/min)	171.26	36.13
V/F (L)	55.84	7.52
T1/2 (hr)	3.92	1.01

There was no mass balance study for histrelin. Relative bioavailability of Vantas® in adult prostate cancer patient to histrelin after SC in healthy adults was 92%. Metabolism of histrelin was not characterized but it is believed to be similar to LHRH or its agonists. According to the Vantas® labeling, histrelin exposure was increased up to 50 % in the cancer patients with renal impairment compared to that in healthy adults but the effect of renal insufficiency on histrelin exposure was not considered as clinically relevant and thus there was no dose adjustment. Vantas® labeling presents mean volume of distribution, clearance, and terminal half-life in healthy adults as 58.4 L, 179 ml/min, and 3.92 hour, respectively, and pharmacokinetic information of the Study 07-03-100 was comparable to that in Vantas® labeling.

2.3 Analytical Section

2.3.1 What bioanalytical methods are used to assess concentrations?

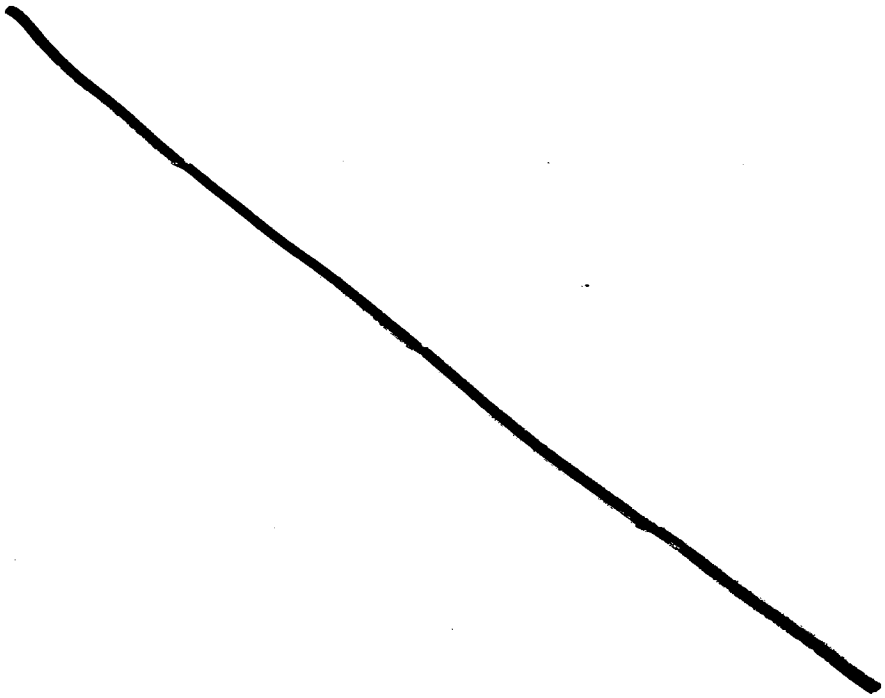
Serum histrelin concentrations were measured using an LC/MS/MS. Representative assay validation reports for Study 01-02-001 and Study 03-CPP-HIS-300 were summarized in Table 7 and it was acceptable.

Table 7 **QC run data from bioanalytical method validation report**

b(4)

The Optional Intra-Division Briefing was held on Monday April 16, 2007 and the attendees were Chandras Sahajwalla, Suresh Doddapaneni, Johnny Lau, Roman Dragos (Clinical Reviewer), Elsbeth Chikhale (Chemistry Reviewer), Indra Antonipillai (Preclinical Reviewer), Wei Qiu, David Lee, and Ting Ong.

3 Detailed Labeling Recommendations



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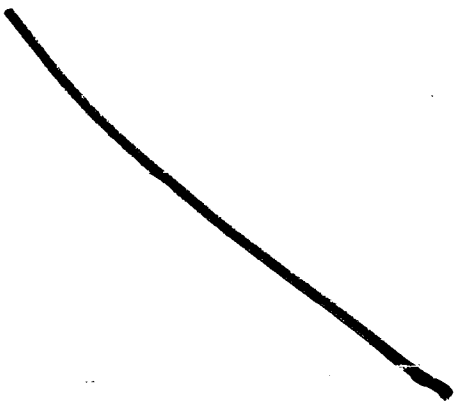

11 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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