CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-058

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-058
Submission Code	N-000
Letter Date	6/30/2006
Stamp Date	6/30/2006
PDUFA Goal Date	5/03/2007
Reviewer Name	Dragos Roman
Review Completion Date	4/19/2007
Established Name	Histrelin acetate
(Proposed) Trade Name	Supprelin LA
Therapeutic Class	Gonadotropin releasing hormone (GnRH) analog
Applicant	Valera Pharmaceuticals Inc.
Priority Designation	S
Formulation	Subcutaneous implant
Dosing Regimen	50-mg implant inserted once a year
Indication	Treatment of central precocious puberty

Intended Population Children with central precocious puberty

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Given that one 50-mg histrelin acetate implant is effective in suppressing the pituitary-gonadal axis and stabilizing clinical signs of precocious puberty, and it has an acceptable safety profile, it should be approved from a clinical perspective for the indication of central precocious puberty.

A pediatric waiver should be granted for children less then 4 years of age and over 12 years[1].

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The applicant has not presented a formal risk management plan. A need for risk management actions beyond the physician label does not appear necessary at this time (the adverse event profile of gonadotropin releasing-hormone agonists is, in general, well understood).

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

Adverse events related to the implant site should be collected in the postmarketing phase and presented in periodic safety reports. They should be characterized by the following categories: adverse events related to the procedure itself (i.e. implant insertion and implant removal) and to the implant site (i.e. implant site reactions).

1.3 Summary of Clinical Findings

1.3.1 Background and Brief Overview of Clinical Program

Histrelin acetate is a nonapeptide, synthetic analog of gonadotropin releasing hormone (GnRH). It is approximately 200 times more potent than endogenous GnRH. Histrelin acetate was approved in 1991 (NDA 19-836) under the brand name Supprelin as a daily subcutaneous

[1] The youngest children treated in the histrelin acetate clinical trials were approximately 4 years of age; age 12 is an age at which most children will be allowed to proceed through puberty without restrictions.

injection for the treatment of central precocious puberty (CPP). Due to the availability of other GnRH agonists with more convenient administration regimens (e.g. monthly or once every three months) the marketing of Supprelin was discontinued. A once-a-year subcutaneous implant of histrelin acetate was approved in October 2004 for the palliative treatment of [redacted] prostate cancer under the brand name Vantas™ (NDA 21-732). The Vantas implant is a drug-device combination. It consists of 50 mg of pelletized histrelin acetate forming a drug core inside a 3 cm x 3.5 mm polymeric (hydrogel) capsule which, following surgical insertion subcutaneously, delivers histrelin via diffusion at a rate of 55 micrograms per day. The histrelin acetate implant included in this submission is very similar to the Vantas implant but has been modified to deliver a higher rate of histrelin (65 micrograms daily) in order to accommodate the faster catabolism of children; the change in the *in vivo* histrelin diffusion rate has been achieved by altering the ratio of the two crosslinked copolymers that constitute the hydrogel cartridge (hydroxyethyl methacrylate and hydroxypropyl methacrylate). The implant is designed to be used for 12 months, at which time the old implant is surgically removed and a new implant is inserted during the same medical appointment.

b(4)

The clinical program for the current histrelin NDA (22-058) consists of two uncontrolled, single-arm, clinical trials conducted in children (mostly girls) with central precocious puberty. Study 03-CPP-HIS-300 is a multicenter, 12-month, Phase III trial conducted in the US and enrolled 36 patients (20 treatment-naïve and 16 pretreated). Study 01-02-001 is a single-center, 18-month, Phase II trial conducted in Israel and included 11 girls previously treated with another GnRH analog. Efficacy and safety evaluations in both clinical trials, although not identical, overlapped considerably. Each of the two clinical studies incorporated pharmacokinetic (PK) evaluations.

1.3.2 Efficacy

The main efficacy evaluations measured the histrelin effect directly at the level of the pituitary (i.e. gonadotropin levels) and indirectly (gonadotropin-mediated), at the level of the gonads (i.e. estrogen in girls and testosterone in boys). Additional efficacy endpoints were either clinical (e.g. evidence of stabilization or regression of signs/symptoms of puberty) or gonadal steroid-dependent (e.g. bone maturity, linear growth, uterine volume).

Analysis of the histrelin acetate clinical program indicates that a 50-mg histrelin implant was efficacious in suppressing the biochemical and clinical manifestations of central precocious puberty in a vast majority of patients. For the purpose of this review the term hormonal suppression (or simply suppression) is used to mean a serum concentration of gonadotropins or gonadal steroids below a protocol-defined threshold value that distinguishes between pubertal and prepubertal hormonal status. Thus, patients with gonadotropin or gonadal steroid levels below such a threshold are considered "suppressed" (conversely, patients with hormone concentrations above the threshold are considered non-suppressed). The evidence of efficacy in the histrelin clinical program is summarized next by study. For each study the efficacy data are presented first for the pituitary-gonadal axis endpoints and is followed by data for additional endpoints (refer also to Table 7 on page 55 for an integrated look of the HP axis efficacy analyses).

1.3.2.1 Study 03-CPP-HIS-300

1.3.2.1.1 Histrelin effects on the pituitary-gonadal axis

The primary efficacy endpoint for this study was the peak luteinizing hormone (LH) serum concentration measured during a GnRH stimulation test[2]. The primary efficacy analysis was the percentage of patients with suppressed peak serum LH at Month 3. All patients showed LH suppression at the Month 3 timepoint[3]. In fact, such suppression was observed for all patients at the first timepoint evaluated on trial (Month 1) and at all other timepoints through Month 12, inclusively, regardless whether patients were pretreated or treatment-naive.[4]

Similar observations (albeit less dramatic) were seen for the follicle-stimulating hormone (FSH) measurements. In the treatment-naïve group the mean values of peak FSH serum concentrations declined in the suppressed range and stayed so for up to Month 12; for the pre-treated group they were maintained suppressed up to Month 6. Although there was a trend that showed a discrete increase in mean FSH values with time and peak FSH levels were not below the predefined threshold in all patients, it should be recognized that LH and gonadal steroids (and not FSH) are the most important pharmacodynamic endpoints indicative of successful treatment in CPP[5].

Gonadal suppression was achieved in most patients (all but 3 patients were female). For treatment-naïve patients the mean estrogen levels were reduced four-fold on histrelin (a statistically significant finding for all timepoints assessed) and were brought in the suppressed range for the whole duration of the trial. For pretreated patients the mean estrogen levels were **maintained in the suppressed range. "Responder analyses" indicate that the vast majority of** patients had suppressed estrogen levels on histrelin (all pretreated patients through Month 12 and all treatment-naïve patients through Month 9 [6]). All three male patients had suppressed testosterone levels throughout the trial.

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[2] Serum LH concentration were determined before and at several timepoints up to 1 hour following a subcutaneous dose of the GnRH agonist leuprolide. The highest single LH value was considered the peak LH concentration. LH suppression was defined as a peak LH $\leq$ 4 mIU/ml.

[3] **Although patients were not formally 'washed out" of the previous GnRH analog, a potential carry-over effect is not** of significance in this situation because the primary analysis is conducted at a time (3 months) that exceeds any potential therapeutic effect of previous GnRH agonist medications and, most importantly, the effect in the treatment-naïve group was similar to that seen in the pretreated group.

[4] Histrelin suppressed the elevation in peak LH levels observed at baseline in treatment-naïve patients and maintained LH suppression in pretreated patients throughout the trial.

[5] LH is ultimately responsible for gonadal steroidogenesis.

[6] At Month 12 all but one of the treatment-naïve patients (95 %) had estrogen suppression. One patient had an estradiol level of 27 pg/mL at Month 12 (suppression was defined as < 20 pg/mL).

1.3.2.1.2 Other efficacy analyses

The following efficacy analyses indicate, in general, a favorable effect of histrelin therapy on bone age progression, growth rate, clinical signs of puberty, and uterine/ovarian size:

- Bone age progression through Month 12 slowed down during Histrelin treatment; specifically, the mean bone age advancement was less than the chronological age advancement[7] and the bone age/chronological age ratio decreased for both treatment-naïve and pretreated patients[8]. Most patients (28/36 or 78%) had advances in bone age that were smaller than the changes in chronological age.
- The mean height velocity on treatment was approximately 5 cm/yr, which is consistent with a prepubertal growth rate.
- Although transabdominal ultrasounds were used to evaluate the size and structure of the uterus and ovaries, the lack of standardizations of the readings and the absence of a control group limits the ability to draw firm conclusions; at Month 12, uterine and ovarian volumes were lower than baseline for each of the two ovaries in 73% and 56.5 % of the study population, respectively.
- The vast majority of patients had either arrest or reduction in the progression of clinical signs of puberty as judged by the investigators (82% of girls and two out of the three boys). All cases of progression of Tanner staging were by no more than one Tanner stage and tended to occur earlier during the treatment (i.e. at Months 1-3).

1.3.2.2 Study 01-02-001

In this Phase II clinical study patients received either one 50-mg implant or two 50-mg implants. Importantly, however, patients were not randomized but rather were assigned to receive different numbers of implants by the investigators. At Month 9, some patients had their implant(s) replaced with another one and were further evaluated for up to Month 18, while others were continued on the original implant(s) for up to Month 18 (to explore the durability of efficacy). All 11 patients enrolled in this trial have been previously treated with a GnRH agonist, which was discontinued upon the insertion of the histrelin implant. The comments regarding the absence of a carry-over effect made in footnote # 3 for Study 03-CPP-HIS-300 apply to this study as well.

[7] The mean change in bone age over one year was 0.91 ± 0.5 years for treatment-naïve patients, 0.43 ± 0.39 years for the pre-treated patients and 0.70 ± 0.51 years for the two groups combined.

[8] For pre-treated patients it decreased from 1.33 ± 0.16 to 1.24 ± 0.13 ($p<0.0001$). For treatment-naïve patients it changed from 1.42 ± 0.17 to 1.34 ± 0.13 ($p=0.0002$). For the whole group combined it changed from 1.38 ± 0.17 to 1.29 ± 0.14 ($p<0.0001$).

1.3.2.2.1 Histrelin effects on the pituitary-gonadal axis

The mean values for the peak LH and FSH levels were suppressed on Histrelin treatment through Month 9 regardless whether patients had one or two implants (the data at Months 1 and 3 were sparse) and continued so through Month 18[9].

Serum estrogen levels were the primary efficacy endpoint for this study. Through Month 9, 7/7 subjects with one implant (100%) had suppressed levels of estradiol and 3/4 (75%) of the patients who received two implants had suppressed serum estradiol levels at all timepoints[10]. All 6 patients who continued the original implant(s) up to Month 18 had suppressed estrogen levels.

Overall, there were no clinically meaningful differences in estrogen, LH and FSH whether patients received one implant or two. It is important to recognize that patients were not randomized to the two regimens (one vs. two implants) and the data set is exceedingly small.

1.3.2.2.2 Other efficacy analyses

As noted in the Phase III clinical trial, histrelin implant had, in general, favorable effects on several other (secondary) measures of efficacy such as bone age progression, clinical signs of puberty, growth rate and uterine/ovarian volume:

- Progression of bone age slowed down during histrelin treatment (the mean bone age advanced by 1 year relative to a mean chronological age advancement of 1.6 years and the mean bone age/chronological age ratio declined on treatment at Month 18[11].
- The mean annualized HV at 9 months of 4.6 cm is consistent with a prepubertal growth rate.
- Although transabdominal ultrasounds were used to evaluate the size and structure of the uterus and ovaries, the small size of the group, the lack of standardizations of the readings and the absence of a control group limit the ability to draw firm conclusions.

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[9] For this trial the criterion for peak LH suppression was ≤ 1 mIU/mL (the criterion for peak FSH suppression was ≤ 2.5 mIU/mL). The reason for which different thresholds were selected for LH suppression in Study 01-02-001 (≤ 1 mIU/mL) and Study 03-CPP-HIS-300 (≤ 4 mIU/mL) is related to the fact that gonadotropin stimulation was performed with different products that have different potencies (Factrel in the Phase II study and Lupron in the Phase III study).

[10] One patient had elevations above the pre-defined threshold of suppression of ≤ 20 pg/ml) at baseline (24.1 pg/ml), Month 3 (21.8 pg/mL) and Month 6 (22.2, pg/mL); this patient who terminated early the clinical trial due to a wound infection, had suppressed LH levels at the time of estrogen elevation.

[11] Inspection of individual patient data indicates that all but three patients had advances in chronological age (CA) exceeding advances in BA; in those few cases when BA changes exceeded the changes in CA, such changes were relatively small.

1.3.3 Safety

The 50-mg histrelin acetate implant had an acceptable safety profile that was, in general, comparable to that described for other GnRH analogs. The only adverse events that could clearly be attributed to the histrelin implant were those connected to implant insertion/removal or related to the implant site, and adverse events that could be attributed to the known mechanism of action of the drug (e.g. suppression of gonadal hormones).

There were no deaths reported in either clinical trial. Two serious adverse events (SAEs) were **recorded in the Phase III trial: amblyopia in a 7.4 year-old patient with Stargardt's disease**[12] **(judged to be "unrelated" to the study drug by** the investigator) and benign pituitary tumor in a 9.5 year-old patient previously treated for 7 years for CPP with other GnRH agonists (deemed as **"possibly related" by the investigator). One other** patient discontinued the Phase III trial due to a wound infection and spontaneous implant extrusion.

In the Phase II trial, 8/11 patients (73%) reported at least one treatment-emergent adverse event (TEAE); all TEAEs were mild in intensity and most represented common background childhood illnesses. Treatment-related TEAEs occurred in 6 (54.5%) patients and 4 patients (36.4%) reported an implant site related AEs (**preferred terms: "application site pain", "implant site irritation", "implant site reaction" and "wound infection"). Narrative** descriptions indicate difficulties related to the insertion and removal of the implant (e.g. inadvertent perforation of the implant during suturing, necessity for ultrasound exam to locate the implant, breakage of implant during removal, incomplete removal and need for removal under general anesthesia). The only other AEs which were deemed treatment-related were **"disease progression" and "influenza-like illness"** (one patient each or 9%). There was no evidence that patients with one or two implants had different patterns of adverse events but the datasets were exceedingly small for meaningful comparisons.

In the Phase III trial all 36 patients (100%) experienced at least one TEAE. Most TEAEs were mild or moderate in intensity and represented background childhood illnesses. The only TEAEs reported as severe were the two above-mentioned SAEs and migraine headache (reported in the same patient with the SAE pituitary adenoma). Twenty-two (61.1%) of patients experienced one or more **"treatment-related" adverse events with injection-site reactions (18 patients or 50%) being the** most frequent ones (preferred terms: discomfort, bruising, soreness, pain, tingling, or swelling). Scarring and keloid formation have also been described following implant insertion/removal. The narratives of patients who experienced implant-related problems include descriptions of difficult implant insertions while using the trocar (necessitating manual insertion), difficulty fitting the implant in the trocar, difficulty or breakage of the implant upon removal, need to use ultrasound exams to locate the implant, incomplete removal of the implant. Treatment-related AEs reported in two patients (5.6 %) were metrorrhagia, suture related complication, and scar. Treatment-related AEs reported in only one patient (2.8%) were: breast tenderness, dysmenorrhea, epistaxis, erythema, feeling cold [at the implant site], gynecomastia, headache, keloid scar, menorrhagia, migraine, mood swings, benign pituitary tumor, pruritus, and increased weight. Due to the lack of a control group and the small size of the dataset causality is difficult to establish with the exception of adverse events related to the insertion and removal of the implant itself or those

[12] **Stargardt's disease is the most common inherited form of juvenile macular degeneration.**

adverse events that can be plausibly related to the mechanism of action of the study drug (e.g. vaginal bleeding).

Over the 12-18 months of the Phase II-III trials there were no clinically meaningful changes in mean values of standard hematology and chemistry analytes, or in hormonal evaluations such as TSH and T_4. Mean prolactin levels decreased on treatment by approximately 1/3 in the Phase II trial but one does not expect this finding to have clinical significance in children[13]. Elevations in mean DHEA levels were observed in the Phase III trial wherein 9 patients exhibited elevated DHEA measurements[14]. There were no marked outliers in any laboratory values. The measurements outside the normal range were either small deviations from expected values or had clear explanations[15].

1.3.2.1.3 General comments

Taking into consideration that the active pharmaceutical ingredient in histrelin implant is an approved drug substance, the clinical experience provided in studies 03-CPP-HIS-300 and 01-02-001 was adequate to evaluate the efficacy and safety of this new drug product. Since the active moiety from the histrelin implant is already approved, the major focus of this clinical program has been to demonstrate that this new way of delivery (i.e. via an implant) is safe and effective. The duration of the clinical trials (18 months in the Phase II trial and 12 months in the Phase III trial) was adequate to establish efficacy and a reasonable benefit vs. risk profile. The efficacy assessments selected were appropriate for the proposed indication. The number of patients treated (47 patients *in toto* divided almost evenly between treatment-naïve and pre-treated patients) is also acceptable in view of the fact that central precocious puberty is a rare condition. The safety measures included (adverse events, standard analytes and a variety of hormonal changes, bone X-rays, etc.) were also adequate.

Across both clinical trials, adverse events related to the implant placement/removal or the implant site were clearly the most common drug-related adverse events. This issue and related issues has been discussed at the December 7, 2005 pre-NDA meeting where the sponsor **indicated that these adverse events were related in part to each surgeon's expertise accumulated** in inserting and removing the implant.

There were some limitations of the clinical program. Because the data on uterine and ovarian volume were not standardized they were difficult to interpret and only general assessments could be made. The height velocity data were also interpreted with some difficulty in the absence of baseline height velocity information. Another limitation was the absence of a control group. It is, however, unethical to withhold GnRH agonist treatment from children with central precocious puberty.

[13] Isolated prolactin deficiency is associated with puerperal alactogenesis. Although it has been suggested that prolactin is also an immunoregulatory hormone (prolactin receptors have been found on T lymphocytes and B lymphocytes) there is no evidence to support that prolactin deficiency is associated with an immunodeficient state.
[14] DHEA is a precursor of the sex steroids. The significance, if any, of this finding is not clear.
[15] e.g. a patient with ALT elevation> 2X ULN but < 3X ULN was taking anti-seizure medications known for causing LFT elevation.

1.3.4 Dosing Regimen and Administration

The dose effect was explored in trial 01-02-001 wherein some patients received either one 50-mg implant or two 50-mg implants (based loosely **on patients' weights** and ease of implant insertion). Although the lack of randomization and the small size of the dataset limit seriously the ability to draw firm conclusions, descriptive comparisons of efficacy between patients treated with one vs. two-implants do not suggest an efficacy benefit from higher histrelin doses. Despite variability in baseline body weight, the 50-mg implant was efficacious across the whole range of **patients' weights**[16]. It is theoretically possible that a lower histrelin dose may be as effective as the 50-mg implant over 12 months of treatment. However, the presence of a discrete time-dependent upward trend for the mean serum concentrations of LH, FSH, and estradiol observed in trial 03-CPP-HIS-300 argue against such an argument.

1.3.5 Drug-Drug Interactions

No drug-drug interaction studies were conducted.

1.3.6 Special Populations

The applicant did not conduct formal studies that evaluated the effect of age, gender, or race on the efficacy of the histrelin implant. Some of the efficacy analyses were presented by gender but there were only 3 boys enrolled in the clinical program (this is consistent with the known prevalence of CPP[17]). Despite this limitation, the different efficacy parameters evaluated in both clinical studies allow for a reasonable conclusion that the histrelin implant is efficacious in both boys and girls.

[16] There was a four-fold difference between the smallest patient weight of approximately 20 kg and the largest weight of approximately 80 kg.
[17] The prevalence of central precocious puberty has a striking female preference (3-23 to 1).

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Histrelin acetate is a synthetic nonapeptide analogue of the naturally occurring decapeptide gonadotropin-releasing hormone (GnRH) or luteinizing hormone-releasing hormone (LHRH)[18]. Histrelin acetate was initially approved as a daily subcutaneous injection for the treatment of precocious puberty on December 24, 1991 under the brand name Supprelin (the NDA applicant was Ortho Pharmaceutical Company). In 2002 Shire Pharmacetical Development Inc., who owned Supprelin at the time, withdrew the Supprelin NDA (19-836). Valera Pharmaceuticals **obtained the right of reference to Shire's NDA** in 2003 and developed a subcutaneous implant that contains 50 mg of histrelin acetate ([redacted] inside a nonbiodegradable, cylindrically shaped hydrogel reservoir. This new drug product was approved in October 12, 2004 under the brand name Vantas® for the palliative treatment of [redacted] prostate cancer (NDA 21-732). For the current NDA the applicant redesigned the histrelin implant to allow greater daily release of histrelin in order to treat children with central precocious puberty (CPP) [19]. Valera Pharmaceuticals plans to market the pediatric implant under the name Supprelin. [redacted] The hydrogel implant is drug-device combination. b(4)

2.2 Currently Available Treatment for Indications

GnRH agonists are the only class of drugs approved for the CPP indication. GnRH agonists that are currently approved for the treatment of central precocious puberty are nafarelin acetate (Synarel) and leuprolide acetate (Lupron).

2.3 Availability of Proposed Active Ingredient in the United States

Several GnRH agonists are approved and currently marketed in the US for a variety of indications, including CPP (Table 1). The list includes nafarelin, triptorelin, goserelin, and leuprolide. An important feature of these GnRH agonists is the frequency of administration (e.g. twice daily for Synarel, monthly to yearly for some of the other products).

[18] Histrelin acetate has approximately 200 times greater potency than endogenous GnRH.
[19] The implant contains a core of histrelin acetate included in 3.5 cm/3.1 mm cylindrical capsule made of a crosslinked copolymer of hydroxypropyl methacrylate and hydroxyethyl methacrylate. The ratio of the component polymers is responsible for the rate of release histrelin from the implant. The capsule (cartridge) is included in a sterile vial hydrated in 2 mL of 1.8 % saline, is be stored under refrigerated conditions (2-8 °C) and is inserted subcutaneously, under local anesthesia, into the upper arm with the use of an insertion tool. In contrast with the adult implant which was developed to release 50 μg of histrelin per day for 12 months, the pediatric implant releases 65 μg/day for 12 months (children metabolize histrelin faster than adults).

Table 1: Approved GnRH Agonists*

Name	Route and frequency of administration	Indication
Nafarelin acetate (Synarel)	Nasal spray, 400 -1600 micrograms daily	Endometriosis Central precocious puberty
Triptorelin pamoate (Trelstar Depot 3.75 mg)	3.75 mg IM monthly	Palliative treatment of advanced prostate cancer.
Triptorelin pamoate (Treslar LA Suspension 11.25 mg)	11.25 mg IM every 12 weeks	Palliative treatment of advanced prostate cancer.
Goserelin acetate (Zoladex 3.6 mg)	3.6 mg SC every 28 days	Treatment of localized prostate cancer (in combination with flutamide) and palliative treatment of advanced prostate cancer. Endometriosis. Advanced breast cancer in pre- and postmenaupausal women. Endometrial thinning prior to endometrial ablation for dysfunctional uterine bleeding.
Goserelin acetate (Zoladex 10.8 mg 3-Month)	10.8 mg SC every 12 weeks	Treatment of localized prostate cancer (in combination with flutamide) and palliative treatment of advanced prostate cancer.
Histrelin acetate (Vantas)	One 50 mg implant every 12 months inserted SC	Palliative treatment of advanced prostate cancer.
Leuprolide acetate (Lupron Depot 3.75 mg)	3.75 mg IM monthly	Endometriosis Uterine Leyomyomata (fibroids)
Leuprolide acetate (Lupron Depot 7.5 mg)	7.5 mg IM monthly	Palliative treatment of advanced prostate cancer.
Leuprolide acetate (Lupron **Depot – 3 Month 11.25 mg)**	11.25 mg IM	Endometriosis Uterine Leyomyomata (fibroids)
Leuprolide acetate (Lupron **Depot –PED 7.5 mg, 11.25 mg** and 15 mg.)	7.5 mg, 11.25 mg or 15 mg (weight based) IM monthly	Central precocious puberty
Leuprolide acetate implant (Viadur)	One implant (65 mg leuprolide) every 12 months.	Palliative treatment of advanced prostate cancer.
Leuprolide acetate (Eligard 7.5 mg)	7.5 mg SC monthly	Palliative treatment of advanced prostate cancer.
Leuprolide acetate (Eligard 22.5 mg)	22.5 mg SC every 3 months	Palliative treatment of advanced prostate cancer.
Leuprolide acetate (Eligard 30 mg)	30 mg SC every 4 months	Palliative treatment of advanced prostate cancer.
Leuprolide acetate (Eligard 45 mg)	45 mg SC every 6 months	Palliative treatment of advanced prostate cancer.

Source: ePDR, Orange book.
*Not all leuprolide acetate products currently listed in the Orange Book are listed in this table.

2.4 Important Issues With Pharmacologically Related Products

GnRH analogues have been marketed for approximately 20 years. Their safety profile has been recently reviewed[20]. Adverse events described in published literature include local reactions, allergic reactions, weight gain and expected effects of estrogen suppression (transient delay in mineralization, reduction of height velocity, withdrawal bleeding, moodiness, hot flashes, headaches, nausea). Although hyperandrogenism has been described during GnRH treatment for CPP in girls, this finding may represent coincidental morbidity.

Recently, DRUP formally requested all sponsors of LHRH agonist products (including Valera Pharmaceuticals) to place in the postmarketing section of the labels information regarding adverse events of pituitary apoplexy which have been rarely reported in association with this class of drugs.

Implant expulsions have been reported in safety updates for Vantas. This is a labeled adverse event. According to the applicant there have been approximately 11,500 implants placed in the last year in adults and the expulsion rate (reported expulsions/implanted units) is estimated to be 1 in 200 implants (0.5%). The applicant states that **the introduction of a new trocar** [redacted] as well as new insertion techniques and postoperative patient instructions appear to reduce the incidence of expulsions, but did not totally eliminate the problem. b(4)

2.5 Presubmission Regulatory Activity

Valera Pharmaceuticals' histrelin acetate implant received orphan drug designation on November 18, 2005 for the indication of treatment of central precocious puberty.

On December 7, 2005 a pre-NDA meeting took place between the Division of Metabolism and Endocrinology Products (DMEP) and representatives of Valera Pharmaceuticals during which, scientific and regulatory issues related to the future NDA were discussed, such as the format and content of the NDA and the issue of extrusion of implants in adult patients (see meeting minutes in DFS).

2.6 Other Relevant Background Information

None.

[20] Tonini G and Lazzerini M: Side effects of GnRH analogue treatment in childhood. Journal of Pediatric Endocrinology and Metabolism 13, 795-803 (2000).
Heger et al: Gonadotropin- releasing hormone analogue treatment for precocious puberty. Twenty years of experience. Endocr. Dev. Basel, Karger, 8, 94-125 (2005).
Antoniazzi F and Zamboni G: Central Precocious Puberty. Pediatr. Drugs, 4, 211-231 (2004).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Final recommendation from the CMC staff is pending. The chemistry reviewer (Elsbeth Chikhale, Ph.D.) noted that 24 month storage of the implant under the proposed storage condition of 2-8° Celsius resulted in an approximately 3-fold increase of the histrelin elution rate on Day 1. An important *in vivo* consequence of this observation is doubtful, however, if one takes into consideration the fact that histrelin has a 160-fold safety margin based on Cmax in rats (data reviewed and provided by Karen Davis, Ph.D.).

The microbiology review (in DFS) recommends approval.

3.2 Animal Pharmacology/Toxicology

The pharmacology/toxicology review recommends approval.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The main source of clinical efficacy and safety data are studies 01-02-001 and 03-CPP-HIS-300. The main features of these studies are summarized in section 4.2, Table 2.

4.2 Tables of Clinical Studies

The two clinical studies included in this submission in support of the CPP indication are summarized in Table 2.

Table 2: Summary of the histrelin acetate clinical program for the CPP indication

Study	Characteristics
01-02-001	**Single-arm, single-center (Israel), uncontrolled, "dose-response" (no initial randomization;** compared one vs. two 50-mg implants), single center study conducted in 11 pretreated girls with CPP for 18 months. Implants were replaced in some patients at Month 9, continued in other for up to 18 months. Primary endpoint: serum testosterone (males) and serum estrogen (females). Additional efficacy endpoints were either clinical (e.g. evidence of stabilization or regression of signs/symptoms of puberty) or gonadal steroid-dependent (e.g. bone maturity, linear growth, uterine volume).Included standard safety evaluations and PK assessments.
03-CPP-HIS-300	Single arm, open-label, multicenter (9 US centers) study conducted in 36 patients with CPP (3 males and 33 females; 16 pre-treated and 20 naïve) using one 50-mg histrelin implant for 12

	months. Primary efficacy analysis: the % of patients who reached or maintained prepubertal levels of stimulated LH at Month 3. Additional efficacy endpoints were either clinical (e.g. evidence of stabilization or regression of signs/symptoms of puberty) or gonadal steroid-dependent (e.g. bone maturity, linear growth, uterine volume). Included standard safety evaluations.

4.3 Review Strategy

This review focuses exclusively on the data from studies 01-02-001 and 03-CPP-HIS-300. Due to the differences in study duration, dose regimens and choice of efficacy endpoints between the two clinical trials, the applicant did not have to present an integrated summary of efficacy. Some of the safety data are integrated but there was no need for a formal integrated summary of safety either. Therefore, each study is summarized and reviewed in each section of the clinical review. References to the sources of data within the NDA are provided. Additional analyses are specified as such. The presentation of the data follows the format suggested by the Clinical Review Template.

4.4 Data Quality and Integrity

Study 01-02-001

The applicant states that the study was monitored, that CRFs and related source documents were reviewed at each study visit and identified discrepancies were resolved. There was no DSI audit.

Study 03-CPP-HIS-3000

The study was contracted to several Contract Research Organizations. According to the applicant the study was monitored by either the sponsor or its designee; direct access to source data/documents was provided by the investigator and the institution along with trial-related monitoring, auditing, review by the IRB, and regulatory agency inspections. The CRFs and **related source documents "were reviewed at each study visit, and identified discrepancies were resolved." Laboratory data were processed centrally. There was no DSI audit/investigation.**

4.5 Compliance with Good Clinical Practices

Study 01-02-001

The applicant states that

> the study was carried out in compliance with the protocol and in accordance with Good Clinical Practice (GCP), as described in the International Conference on Harmonisation

(ICH) Harmonised Tripartite Guidelines for Good Clinical Practice 2000 and the United States Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR including parts 50 and 56 concerning informed consent and IRB regulations). The study was conducted **according to the Nuremberg Code and the Declaration of Helsinki and its amendments."** The clinical monitor maintained regular contact with the investigational site, through telephone contact and on-site visits, reviewed accuracy and completeness of records, performed source document checks; evaluated study data (drug accountability, communication, and written records), monitored of site facilities and adverse events. In addition, investigator and institution provided direct access to source data and documents to IRB, and regulatory agency.

The applicant also states that "

in accordance with 21 CFR Part 50, a written informed consent was signed voluntarily by **each subject's parent or legal guardian after the** nature of the study was explained and prior to any study-related procedure being performed. Assent from minors was obtained when possible. The informed consent form was reviewed and approved by the Sponsor and the **Investigator's IRB/IEC prior to initiation of the study." The study received Institutional** Review Board (IRB) or Independent Ethics Committee (IEC) approval before it was initiated.

Study 03-CPP-HIS-3000

The applicant states that "Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approval was obtained for Protocol 03-CPP-HIS-300 before study initiation and that the study was carried out in compliance with the protocol and in accordance with Good Clinical Practice (GCP), as described in the International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines for GCP 2000 and the United States Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR including parts 50 and 56 concerning informed consent and IRB regulations). The study was conducted according to the Nuremberg **Code and the Declaration of Helsinki and its amendments." In addition, "[i]n accordance with 21 CFR Part 50, a written informed consent was signed voluntarily by each subject's parent or** legal guardian after the nature of the study was explained and prior to any study-related procedure being performed. Assent from minors was obtained in children ≥7 years of age, when possible. The informed consent form was reviewed and approved by the sponsor and the **investigator's IRB/IEC prior to initiation of the study."**

4.6 Financial Disclosures

The applicant submitted a signed FDA form 3454 that states that Valera Pharmaceuticals Inc. has not entered into any financial arrangement with clinical investigators whereby the values of compensation to the investigator could be affected by the outcome of the study as defined in 21CFR 54.2(a). The applicant also certifies that the investigators did not have a proprietary interest in the product as defined in 21 CFR 54.2(b) and were not recipients of significant

payments of other sorts as defined in 21 CFR 54.2 (f). A list of investigators and subinvestigators from all participating sites in Study03-CPP-HIS-300 is provided.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

For a critical review of the pharmacokinetic data please refer to the clinical pharmacology review. **This section briefly summarizes applicant's data.**

5.1.1 Study 01-02-001

All 11 subjects contributed data to the pharmacokinetic analyses. **Applicant's Table 2.7.4.1.2.2.1-1** summarizes the mean plasma concentrations through Month 9 by number of implants. The mean histrelin plasma concentrations peaked at Month 1 and declined subsequently. They were relatively constant between Month 3 and 9 for patients who received one implant, and showed a steady decline for patients with two implants. As expected, the mean serum concentrations were higher for patients with two implants albeit not proportional to the dose increase.

Table 2.7.4.1.2.2.1 - 1 Mean Histrelin Concentrations in the Phase II Study at Month 9

	1 Implant[a,b] N=7	2 Implants N=4	Overall N=11
Month 1			
N	6	3	9
Mean (SD)	0.62 (0.21)	0.94 (0.31)	0.73 (0.28)
Month 3[c]			
N	6	4	10
Mean (SD)	0.25 (0.12)	0.51 (0.22)	0.35 (0.21)
Month 6			
N	6	4	10
Mean (SD)	0.25 (0.11)	0.42 (0.22)	0.32 (0.17)
Month 9			
N	5	2	7
Mean (SD)	0.28 (0.36)	0.21 (0.00)	0.26 (0.30)

Source: Section 5.3.5.2 Study 01-02-001, Table 2.7.1

[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.

[b] Subject 105 initially received 2 implants, but 1 of the implants was removed during suture removal. This subject was included in the single implant group for pharmacokinetic analyses.

[c] Marginal statistical significance between the 1-implant and 2-implant groups was observed (p=0.0543) using the Wilcoxon Rank Sum Test

5.1.2 Study 03-CPP-HIS-300

All 36 treated patients contributed data to the **pharmacokinetic analysis. Applicant's Figure Figure 2.7.4.1.2.2.2 – 1 illustrates the mean h**istrelin concentration as a function of time. As

noted in Study 01-02-001, the mean serum histrelin concentration was highest at Month 1 and decreased through Month 12.

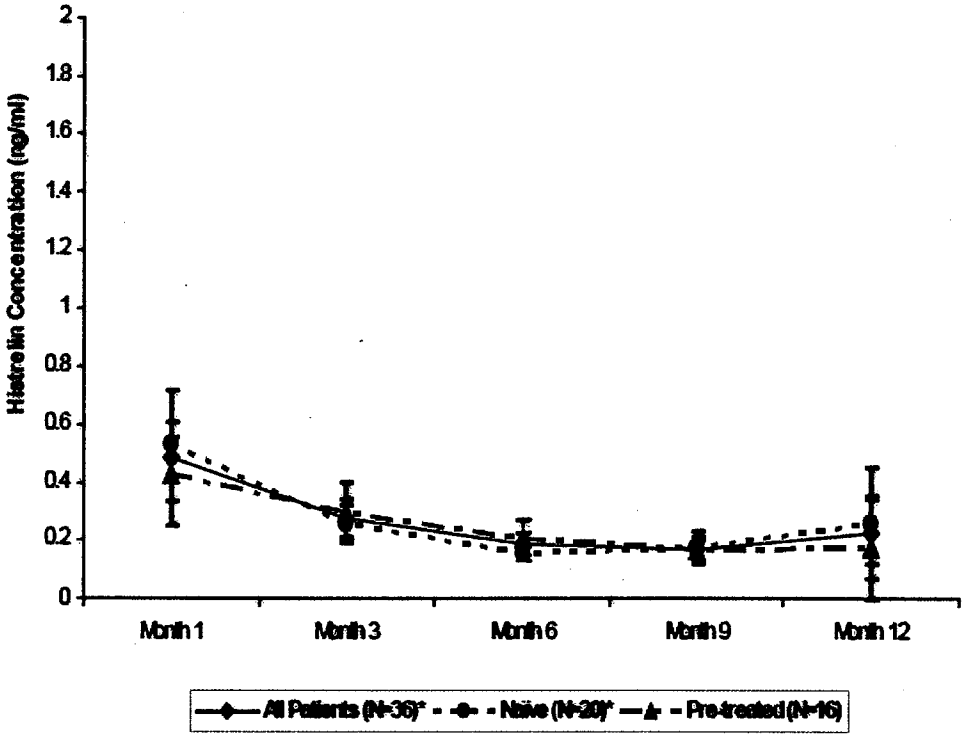

Figure 2.7.4.1.2.2.2 - 1 Plasma Histrelin Levels in the Phase III Study

The mean histrelin concentration is presented numerically in applicant's Table 2.7.4.1.2.2.2-1 for treatment-naïve and for pre-treated patients separately and combined. The data are, in general, comparable within the two groups[21].

[21] Some patients did not have detectable levels of histrelin. This observation was present in three situations: 1) at baseline (i.e. prior to histrelin administration), 2) occasionally on treatment (however, all patients had suppressed LH levels on the same days as the histrelin measurement), and 3) in patients off histrelin (patients who had the implant removed a month earlier).

Table 2.7.4.1.2.2.2 - 1 Mean Histrelin Concentrations in the Phase III Study at Month 12

	Pretreated Subjects N=16	Naïve Subjects N=20	All Subjects N=36
Month 1			
N	14	17	31
Mean (SD)	0.43 (0.21)	0.53 (0.38)	0.49 (0.31)
Month 3			
N	15	17	32
Mean (SD)	0.30 (0.23)	0.26 (0.12)	0.28 (0.18)
Month 6			
N	15	15	30
Mean (SD)	0.21 (0.15)	0.16 (0.05)	0.19 (0.11)
Month 9			
N	13	14	27
Mean (SD)	0.17 (0.06)	0.18 (0.10)	0.17 (0.08)
Month 12			
N	12	17	29
Mean (SD)	0.18 (0.09)	0.26 (0.37)	0.23 (0.29)

Source: Section 5.3.5.2 Study 03-CPP-HIS-300, Table 2.8.1
Note: 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.

5.2 Pharmacodynamics

Refer to the Efficacy Results Section (the pharmacodynamic endpoints are the main efficacy endpoints in both clinical trials).

5.3 Exposure-Response Relationships

The small size of the datasets made it difficult to conduct such analyses. The descriptive evidence coming from the Phase II clinical trial 01-01-001 suggests that two histrelin implants do not add more to the efficacy than a single implant.

6 Integrated Review of Efficacy

6.1 Indication

The proposed indication is the following:

> Supprelin® LA (histrelin acetate subcutaneous implant) is a gonadotropin releasing hormone (GnRH) analog indicated for the treatment of children with central precocious puberty (CPP).

6.1.1 Methods

6.1.2 General Discussion of Endpoints

The main efficacy endpoints in both studies were measurements of hormonal levels for pituitary hormones (LH, FSH) and gonadal sex steroids (testosterone in males and estrogen in females). These are all hormones whose basic physiology is well understood and who are responsible for the triggering and maintenance of central precocious puberty. In clinical practice they are standard measurements necessary for both the diagnosis and the confirmation of therapeutic success following interventions in children with CPP. Other endpoints and assessments such as Tanner sex maturity staging, bone age, and height velocity are standard endpoints/assessments in pediatric clinical trials that assess linear growth and puberty development.

6.1.3 Study Design

6.1.3.1 Study 01-02-001

Objective, design and patient population

This was a Phase II, open-label, single-center, **"dose-response" study (patients were not** randomized to dose) conducted in Israel in 11 girls with CPP who were already receiving GnRH analog therapy[22]. Patients were assigned to receive either **one ("Group 1") or two ("Group 2") histrelin implants (50 mg each) "depending on body weight and ease of surgical insertion". At the 9-** month visit, subjects within each group were divided into two **subgroups or "parallel tracks"; in** Track 1 patients had their implant(s) replaced with one implant. In Track 2, the original implant(s) were left in place for the remainder of the 18-month study if the child continued to have suppression of sex hormones (defined by serum testosterone concentration ≤0.2 ng/mL and serum estradiol concentration ≤20 pg/mL) and no signs of disease progression. At the 18-month visit, all subjects in Track 1 and Track 2 were given the option to continue treatment in the extension phase of the study. The design of the study is presented in applicant**'s Figure 1, below. The implant was inserted** surgically, after local anesthesia[23].

[22] Although the study was to enroll both boys and girls, it recruited girls only; this is not surprising since CPP is more frequent in girls

[23] Approximately 30 minutes before insertion of the implant a topical anesthetic cream a mixture of lidocaine and prilocaine) was applied on the inner surface of the upper arm. The site was then infiltrated with 2% lidocaine (oral administration of a sedative was optional). A <1 cm incision was made between the bicep and tricep, and a subcutaneous tunnel was created and the wound was sutured. b(4)

Table 1 Study Schematic

Screening	Visit 1 Implantation	2 1 mo	3 3 mo	4 6 mo	5 9 mo	6 12 mo	7 15 mo	8 18 mo	Extension Phase[c]
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

Baseline evaluations included medical history, physical examination (including height, body weight, vital signs and Tanner Staging), x-ray of the hand and wrist, transabdominal ultrasound, and a quality-of-life questionnaire. Follow-up visits were at 1 and 3 months after implantation, and then every 3 months through the 18-month study period. Efficacy evaluations included serial measurements of hormone concentrations (testosterone in boys, estradiol in girls, FSH, and LH), GnRH challenge testing, Tanner Staging, hand and wrist x-rays, transabdominal pelvic ultrasound[24], investigator assessment of disease progression, quality-of-life questionnaires, height and body weight. Histrelin plasma concentrations were measured before implant insertion and at each follow-up visit through Month 18. Safety evaluations included adverse events[25], clinical laboratory (standard hematology[26] and chemistry[27] analytes, urinalysis, TSH, prolactin, T4, IGF-I, IGFBP-3) and vital signs. The implant was inserted under local anesthesia.

Inclusion criteria

The main inclusion criteria were the following:

- boy or girl with central (gonadotropin-dependent) precocious puberty
- age range of 2 to 13 years
- advanced bone age relative to chronological age
- pretreatment serum testosterone concentrations of ≥0.2 ng/mL (≥0.7 nmol/L) in boys and pretreatment serum estradiol concentrations of ≥20 pg/mL (≥73 pmol/L) in girls
- pubertal-type response of LH and FSH following a standard GnRH stimulation test[28] before treatment initiation
- received GnRH analog treatment prior to implant insertion
- gave signed informed consent or assent

[24] To evaluate the ovaries and the uterus and any additional findings (eg, ovarian cysts, etc.).
[25] MedDRA Version 6.0) was used to classify all adverse events with respect to system organ class and preferred term.
[26] Hemoglobin, hematocrit, red blood cell count, total white blood cell count, differential count, and platelet count.
[27] Albumin, blood urea nitrogen, creatinine, AST, alkaline phosphatase, globulin, total bilirubin, total protein, uric acid, lactic dehydrogenase, glucose, calcium, phosphorus, and total cholesterol.
[28] GnRH dose: 100 μg/m^2 up to a maximum of 100 μg.

Exclusion criteria

Children were excluded from the trial if they had gonadotropin-independent precocious puberty, chronological age greater than 14, had evidence of hepatic impairment (AST >3 x ULN), or if their physician or parents planned to stop treatment in less than one year.

Statistical Analysis Plan

The primary efficacy endpoint was **"maintenance of prepubertal** levels of serum testosterone (boys) or estradiol (girls) up to 18 months after insertion of the histrelin **implant." Prepubertal** levels were defined as a serum testosterone concentration: **≤**0.2 ng/mL in boys and serum estradiol concentration: **≤**20 pg/mL in girls.

"Other endpoints" were:

- maintenance of prepubertal serum LH concentrations (≤1 mIU/mL)
- maintenance of prepubertal serum FSH concentrations (≤2.5 mIU/mL)
- prepubertal response to GnRH challenge testing[29]
- insulin-like growth factor 1 (IGF-1) and insulin-like growth factor-binding protein 3 (IGFBP-3) comparison with age- and sex-matched controls.
- absence of progression in signs of puberty as measured by Tanner Staging; absence of menarche; absence of pubertal growth spurt by serial Z-scores for body weight, height, and body mass index; and absence of inappropriate advancement of bone age (ie, beyond chronological age) as measured by serial hand and wrist x-rays.

Efficacy analyses were conducted in the following patient populations:

- intent-to-treat (ITT) population (included all subjects who received study drug)
- ITT subjects who received 1 implant on Day 1 (N=7)
- ITT subjects who received 2 implants on Day 1 (N=4)
- ITT subjects who received 1 new implant at Month 9 (Track 1, N=5)
- ITT subjects who did not receive a new implant at Month 9 (Track 2, N=6)

Safety and pharmacokinetic analyses were performed on the ITT population (all patients).

Protocol amendments.

There were 7 protocol amendments. They **are summarized in applicant's Table, below.**

[29] Defined as a peak LH serum concentration ≤1 mIU/mL and a peak FSH serum concentration ≤2.5 mIU/mL following stimulation.

Amendment	Date	Changes
1	14 Nov 2002	Changes to the timing of the GnRH stimulation test.
2	15 Dec 2002	Prophylactic antibiotics were prescribed on the morning of implant insertion and for 2 to 3 days following implant insertion to prevent infection at the implant site.
3	2 Mar 2003	Subjects were enrolled into 2 treatment groups instead of the original 3 groups. Group 1: children received 1 implant and Group 2: children received 2 implants. Generally, subjects who weighed >40 kg received 2 implants and those who weighed ≤40 kg received 1 implant. Assignment to Group 1 or Group 2 was determined by the principal investigator and the surgeon performing the insertion on a case-by-case basis and depended on the subject's body weight and the ease of inserting either 1 or 2 implants.
4	6 Jun 2003	After the first 9 months of the study, children were divided into 2 parallel tracks. In the first track, children continued the protocol as originally planned (ie, the Day 1 implant was removed after 9 months and a new implant was inserted). In the second tract, the Day 1 implant was not removed at 9 months to allow assessment of the biological life of the histrelin implant for a period >9 months.
5	9 Jul 2003	Surgeons were given the option to administer midazolam syrup to sedate children before implant insertion or removal.
6	1 Feb 2004	This amendment ended the study at 18 months and allowed subjects to enter an extension phase of the study. Subjects who did not have the implant removed at 9 months had their initial implant in for the entire 18 months and were then transferred to the extension protocol. The implant was then either removed or left in place for a total of 27 months. The subjects who had the initial implant removed and a new one reinserted at Month 9 were transferred to the extension protocol at Month 18. The implant (that was inserted at Month 9) was left in place for up to 27 months.
7	30 Jun 2004	All amendments were incorporated and a new protocol was issued.

Protocol violations

The applicant reports that there were no violations of the inclusion and/or exclusion criteria.

Study assessments

The study assessments are summarized in applicant's Table 2.

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Table 2 Schedule of Events

	Screening	Implant Insertion	Follow-up						
	Within 14 days	Visit 1 Day 1	Visit 2 Mo. 1[a]	Visit 3 Mo. 3	Visit 4 Mo. 6	Visit 5 Mo. 9[b]	Visit 6 Mo. 12	Visit 7 Mo. 15	Visit 8 Mo. 18[c]
PROCEDURE									
Informed consent	X								
Inclusion/ exclusion	X								
Medical history	X								
Physical examination	X		X	X	X	X	X	X	X
Tanner staging	X	X	X	X	X	X	X	X	X
Implant insertion		X							
Implant removal and reinsertion						X[b]			
Vital sign	X	X	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X	X
Bone x-ray	X					X			X
Pelvic ultrasound	X					X			X
Hematology		X				X			X
Chemistry		X				X			X
Urinalysis		X				X			X
TSH, prolactin, IGF-1, IGF-BP3, T4		X				X			X
Testosterone or estradiol concentrations		X	X	X	X	X	X	X	X
FSH &LH concentrations		X	X	X	X	X	X	X	X
GnRH test[d]		X		X[e]	X[e]	X	X[e]	X[e]	X
Histrelin concentrations		X	X	X	X	X	X	X	X
Quality of life questionnaire	X					X			X
Adverse events		X	X	X	X	X	X	X	X
Concomitant medications & procedures	X	X	X	X	X	X	X	X	X

Compliance

Compliance was measured by documenting in the CRF the date of administration, the number of implants administered, the amount of time required for implantation, the method of incision closure and any problems related to the implantation procedure.

Disposition of Subjects

One patient (103), discontinued treatment at Month 9 due to a wound infection at the insertion site after receiving a new implant. All 11 girls completed the first 9 months of treatment. Ten of the 11 subjects completed the 18-month study.

Demographics and baseline characteristics

All patients enrolled were girls. Mean age at baseline was 8.6 years (range: 3.7 to 11 years). Per protocol, all patients were receiving GnRH analogs at study entry[30]; the duration of GnRH therapy prior to enrollment ranged from <2 weeks to 39 months. Ten patients out of 11 had a suppressed serum estradiol level below 20 pg/mL (range: 1.99 to 24.05; mean ±SD: 9.83 ±6.39). The original diagnosis of CPP was first made at ages ranging between 10 months and 9 years.

6.1.3.2 Study 03-CPP-HIS-300

Objective, design and patient population

The stated objective of this study was to evaluate the efficacy and safety of the 50-mg histrelin implant in boys and girls with CPP. Study 03-CPP-HIS-300 was a 12-month open-label, single-arm, Phase III, multicenter[31] study. Forty patients were initially enrolled but four were screening failures. Of the remainder 36 patients 16 patients were already receiving a GnRH analog for ≥6 months and formed the "Pretreated Group"; the remaining 20 patients were naïve to treatment and formed the "Naïve Group". The study is summarized in applicant's Table 1, below.

Table 1 Study Schematic

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.

Baseline assessments included medical history, physical examination (including height, body weight, vital signs, and Tanner Staging), GnRH analog stimulation testing, an x-ray of the left hand and wrist, computed tomography scan or magnetic resonance imaging of the brain, a transabdominal ultrasound (for girls only), serum sex hormone levels (testosterone for boys or estradiol for girls), thyroid stimulating hormone, thyroxine, DHEA-sulfate, histrelin levels, and routine safety laboratory testing. Patients were re-evaluated at 1, 3, 6, 9, and 12 months. At the 12-month visit the initial implant was removed and those who met prespecified efficacy[32] and

[30] Decapeptyl embonate (9 subjects), diphereline (1 subject), and decapeptyl and diphereline (1 subject) were administered as intramuscular depot injections every 21 to 28 days.
[31] The study was conducted at 9 investigative sites in the United States (3 centers contributed 7 patients each; 2 centers contributed 5 patients each; one center contributed 3 patients; 2 centers contributed 2 patients each; two centers contributed one patient each).
[32] Prepubertal response to GnRH analog stimulation and no other signs of disease progression.

safety requirements were eligible to receive a new histrelin implant. The histrelin implant was inserted subcutaneously into the upper, inner aspect of the subject's nondominant arm (between the bicep and tricep) using an insertion tool. Implantation and/or explantation of the implant were performed under local anesthesia, conscious sedation, or general anesthesia as dictated by each site's IRB and standard operating procedures. The dose of histrelin was 50 mg (i.e. one implant). The lot number for the histrelin implants used in this study was 404. It they received a second implant, patients were re-evaluated at Months 13, 15, 18, 21 and 24 (at which time the second implant was removed). This NDA presents data up to the 12 month timepoint.

On-trial efficacy evaluations included serial GnRH analog stimulation testing, sex hormone concentrations (testosterone for boys or estradiol for girls), thyroid hormones, DHEA-sulfate, hand and wrist x-rays (to determine the bone age), growth velocity, Tanner Staging, transabdominal pelvic ultrasound, and investigator assessment of disease progression.

Inclusion criteria

The main inclusion criteria were the following:

- boy or girl with central (gonadotropin-dependent) precocious puberty
- age range of 2 to 9 years for boys in the "naïve group", 2 to 11 years for boys in the "pre-treated group", 2 to 8 years for girls in the "naïve group" and 2-10 years for girls in the "pretreated group"
- advanced bone age ≥2 standard deviations relative to chronological age
- duration of GnRH analog therapy for ≥6 months, if in the Pretreated Group
- pubertal-type response of LH to a standard GnRH stimulation test before initiation of treatment in naïve subjects[33]
- clinical evidence of puberty[34]
- informed consent (if the guardian), and assent, if the child was ≥7 years of age.

Exclusion criteria

Patients were not allowed in the study for any of the following:

- gonadotropin-independent precocious puberty
- if they planned to stop GnRH therapy within one year
- chronological age was <2 years,
- evidence of hepatic impairment (ie, bilirubin or AST>3 x ULN)
- inadequate hormone replacement for hormonal deficiencies
- inappropriate ages (see age inclusion criteria)

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as determined by the investigator.

[33] Defined as peak LH concentration of >7 mIU/mL after gonadarelin challenge, or peak LH concentration of >10 mIU/mL after leuprolide acetate challenge.

[34] Defined as Tanner Staging ≥2 for breast development for girls and testicular volume ≥4 cc for boys.

- major medical or psychiatric illness that would have interfered with the study or follow-up visits.

Efficacy assessments

Efficacy assessments included GnRH analog stimulation test, testosterone and estradiol concentrations, T4, TSH, DHEA, Tanner staging, bone age, transabdominal pelvic ultrasound, and investigator assessment of disease progression. Pharmacokinetic assessment was performed on blood samples collected from all patients; a subset of patients had more frequent pharmacokinetic sampling between Day 1 and Day 4.

Safety assessments

Safety assessments included medical history, physical examinations, adverse events, vital signs, and standard clinical evaluations (hematology[35], chemistry[36] and urinalysis). Adverse events were coded using MedDRA Version 7.1 with respect to system organ class (SOC) and preferred term.

Statistical plan

The primary efficacy endpoint was the percentage of children who showed LH suppression to prepubertal levels 3 months after histrelin implantation[37]. LH suppression was also measured for several timepoints through Month 12.

The secondary efficacy endpoints were the following:

- suppression of FSH (peak <2.5 mIU/mL)
- maintenance of suppressed prepubertal serum testosterone in (boys) or estradiol (in girls) level[38]
- serum TSH, serum DHEA-sulfate, serum free T4
- height velocity standard deviation score (SDS) <2.5 after 12 months of histrelin treatment
- bone age advancement of ≤18 months after 12 months of histrelin treatment
- lack of progression of disease in **investigator's assessment.**

[35] Hemoglobin, hematocrit, red blood cell count, total white blood cell count, differential count, and platelet count.
[36] Albumin, blood urea nitrogen, creatinine, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, total bilirubin, total protein, uric acid, lactic dehydrogenase (LDH), glucose, calcium, phosphorus, and total cholesterol.
[37] Suppression was defined as a peak serum LH concentration <4 mIU/mL after GnRH analog stimulation (Leuprolide was administered at a dose 20 mcg/kg); the peak LH was determined to be the maximum value among the results at 0, 30, and 60 minutes after implantation.
[38] Prepubertal serum testosterone levels were defined as: <30.0 ng/dL (<0.8 nmol/L); prepubertal serum estrogen levels were defined as <20 pg/mL (<73 pmol/L).

Other "observational efficacy endpoints" were: absence of progression in signs of puberty as measured by Tanner Staging and absence of menses after 4 to 6 weeks of histrelin implant therapy (for girls only).

The statistical and analytical plans in Amendment # 3 states that

> Data associated with the first 3 months will be the basis of a preliminary analysis. The preliminary analysis report will focus on the endocrine laboratory data and adverse event data as of the Month three visit. In addition, a summary of the demographic and baseline data will also be evaluated. Results from this preliminary analysis will be examined for administrative use only and will not result in early termination of the study. Data associated with 12 months of patient treatment will be the basis for final report of data summaries and statistical analyses. All such data will be documented and summarized via tables, data listings, and graphical appendices.
>
> Percentage of children with suppressed LH (at end of one month) will be estimated and 95% Confidence Interval will be calculated; Changes in LH (at all visits) from corresponding screening visit values will be estimated, tested and graphically presented; All data will be summarized via tables, listings and graphs; Tables with continuous variables will have will include N, mean, standard deviation and 95% confidence interval; Tables with counts will include the percentage and the 95% confidence interval; Statistical tests will be based on two-tailed tests with alpha = 0.05; All analyses will be conducted using SAS 6.12.

Protocol-defined analyses were to be conducted in the intent-to-treat (ITT) population. The patient populations analyzed in the Clinical Study Report were:

- safety population.(defined as all patients who received the study drug)
- efficacy population (defined as all patients of the safety population who had at least 1 valid assessment of serum LH after baseline (for any missing or invalid post baseline primary or secondary efficacy data a last observation carried forward (LOCF) approach was used
- acute-on-chronic (AOC) population[39] included all patients who completed 12 months of treatment and who received a second implant

Pharmacokinetic analyses were performed on all subjects in the safety population. A subset of subjects also had intermediate PK sampling on Days 1 through 4 after receiving the initial implant.

[39] The purpose of analyzing the AOC population was to determine whether there was an acute rise in LH, FSH, estradiol, or testosterone concentrations when the first implant was removed and replaced with a second implant, or whether suppressed levels were maintained.

Protocol amendments

There were three protocol amendments (summarized in applicant's table, below). The first subject was dosed on September 3, 2004 and the last visit date was March 31, 2006. The most significant changes to the protocol were made in Amendment # 1 (February 2004) and Amendment # 2 (July 2004), both before the dosing of the first patient. Among other changes, Amendment # 3 allowed for a preliminary analysis of the data during three first 3 months of the study; the amendment states that

Amendment	Date	Changes
1	04 Feb 2004	As a result of the Investigator's Meeting and FDA pre-IND meeting discussions, inclusion/exclusion criteria were added, deleted, or updated; primary, secondary, and observational efficacy endpoints were added and some were updated; PK was removed as an endpoint; and other clarifications were added to the appropriate sections throughout the protocol.
2	07 Jul 2004	The GnRH stimulation test was changed to GnRH analog stimulation test due to limited availability of [redacted] Instead, leuprolide 20 µg/kg was administered subcutaneously. This change was made to all appropriate sections of the protocol. Other minor clarifications were made as needed.
3	18 July 2005	An algorithm was added describing the process by which to locate difficult to palpate implants. A complete description of this algorithm may be found in the final protocol included in Appendix 16.1.1.

b(4)

Protocol deviations

The applicant reports that seven of the 36 patients had inclusion criteria deviations and none of **them "were expected to have an effect on the outcome of the study." The protocol deviations are** listed below:

- three patients (013, 030, 031) had a pretreatment bone age advanced <2 SD for chronological age
- two patients (010 and 038) received <6 months of treatment for CPP prior to enrollment
- two patients (011 and 036) had pubertal-type response of LH to standard GnRH stimulation testing before histrelin treatment.

Compliance

Histrelin implants were inserted surgically into **the inner aspect of the patient's upper arm. All information related to the implant's insertion (the date of administration, the type of anesthesia,** the amount of time required for implantation, the method of incision closure, and any problems related to the implantation procedure) **was documented on the subject's CRF.**

Study assessments

The study assessments are summarized **in applicant's Table 2.**

Table 2 Schedule of Events

Procedure	Screening Within 30 days	Visit 1 Day 1	Visit 2 Mo. 1	V3 Mo. 3	V4 Mo. 6	V5 Mo. 9	V6** Mo. 12	V7 Mo. 13	Telephone V8** Mo. 15	V9 Mo. 18	Telephone V10** Mo. 21	V11 Mo. 24
Informed consent/assent	X											
Inclusion/ exclusion	X											
Medical history	X											
Physical examination	X	X	X	X	X	X	X	X		X		X
Vital signs	X	X	X	X	X	X	X	X		X		X
Tanner Staging	X		X	X	X	X	X	X		X		X
Body weight	X		X	X	X	X	X	X		X		X
Height	X		X	X	X	X	X	X		X		X
Brain CT or MRI	X											
Bone x-ray	X						X					X
Pelvic ultrasound (girls)	X						X					
Hematology	X						X	X				X
Chemistry	X						X	X				X
Urinalysis	X						X	X				X
Testosterone or estradiol	X	X	X	X	X	X	X	X		X		X
TSH & Free T4	X						X			X		X
DHEA-sulfate	X			X	X	X	X	X		X		X
GnRH analog stimulation test	X	X	X	X	X	X	X	X		X		X
Histrelin concentration	X	X	X	X	X	X	X	X		X		X
Disease progression (by investigator)			X	X	X	X	X	X		X		X
Implant insertion		X										
Implant removal and/or reinsertion							X					X
AEs		X	X	X	X	X	X	X	X	X	X	X
Concomitant medications & procedures	X (prior)	X	X	X	X	X	X	X	X	X	X	X

Disposition of patients

Thirty-six patients received histrelin implants and were analyzed for efficacy and safety. Of these, 16 had a history of previous GnRH analog therapy for the treatment of CPP and formed the Pretreated Group; 20 patients were naïve to treatment and were included in the Naïve Group. One patient (042) was lost to follow-up. This patient had the first implant removed at Month 12 and a second implant inserted; the subject did not return for the 13-month visit.

Demographics and baseline characteristics

Demographics and baseline characteristics are presented in Table 3. The mean age at the beginning of the Histrelin treatment was almost 8 years. All patients displayed signs of pubertal development: none were Tanner stage 1 for breast or testicular development and most were Tanner stage 2-4. There were only three male patients (8.3 %) and most were females (33 patients or 91.7%).

Table 3: Demographics and baseline characteristics

	Safety population (N=36)	Efficacy population (N=36)	Pre-treated Group (N=16)	Naïve Group (N = 20)
Age (years)				
N	36	36	16	20
Mean (SD)	7.94 (1.66)	7.94 (1.66)	8.94 (1.47)	7.15 (1.37)

Min. Max.	4.5 to 11.6	4.5 to 11.6	5.6 to 11.6	4.5 to 9.1
Gender				
Male: N (%)	3 (8.3)	3 (8.3)	3 (18.8)	0 (0.0)
Female: N (%)	33 (91.7)	33 (91.7)	13 (81.3)	20 (100.0)
Baseline Tanner Stage (testicular/breast size)[#]				
Stage 1: N (%)	0 (0)	0 (0)	0 (0)	0 (0)
Stage 2: N (%)	8 (22.2)	8 (22.2)	6 (37.5)	2 (10.0)
Stage 3: N (%)	19 (52.8)	19 (52.8)	8 (50.0)	11 (55.0)
Stage 4: N (%)	8 (22.2)	8 (22.2)	1 (6.3)	7 (355)
Stage 5: N (%)	1 (2.8)	1 (2.8)	1 (6.3)	0 (0)
Baseline Tanner Stage (pubic hair development)				
Stage 1: N (%)	5 (13.9)	5 (13.9)	1 (6.3)	4 (20.0)
Stage 2: N (%)	13 (36.1)	13 (36.1)	3 (18.8)	10 (50.0)
Stage 3: N (%)	13 (36.1)	13 (36.1)	10 (62.5)	3 (15.0)
Stage 4: N (%)	5 (13.9)	5 (13.9)	2 (12.5)	3 (15.0)
Stage 5: N (%)	0(0.0)	0(0.0)	0 (0)	0 (0.0)
Baseline Peak LH (mIU/ml)				
N	36	36	16	20
Mean (SD)	16.57 (19.78)	16.57 (19.78)	2.09 (2.15)	28.16 (19.97)
Min. Max.	0.02 to 77.00	0.02 to 77.00	0.02 to 7.10	4.80 to 77.0
Baseline Peak FSH (mIU/ml)				
N	36	36	16	20
Mean (SD)	9.29 (7.79)	9.29 (7.79)	2.83 (2.12)	14.46 (6.70)
Min. Max.	0.11 to 30.0	0.11 to 30.0	0.11 to 7.10	7.10 to 30.0
Baseline testosterone level (ng/dl)				
N	3	3	3	0
Mean (SD)	10.63 (1.18)	10.63 (1.18)	10.63 (1.18)	
Min. Max.	9.90 to 12.0	9.90 to 12.0	9.90 to 12.0	
Baseline estradiol level (pg/ml)				
N	33	33	13	20
Mean (SD)	17.18 (19.53)	17.18 (19.53)	5.92 (2.22)	24.5 (22.27)
Min. Max.	5.0 to 72.0	5.0 to 72.0	5.0 to 13.0	5.0 to 72.0)

[#] Testicular size for boys and breast development for girls.
Source: Post-text Table 1.2.

6.1.4 Efficacy Findings

6.1.4.1 Study 01-02-001

Serum estradiol concentrations

Descriptive statistics for the estradiol serum concentrations through Month 9 are presented in Table 4 (ITT population). Data are presented by number of implants and for all patients. All subjects with one implant (100%) had suppressed levels of estradiol on Histrelin at all time points measured on trial (Months 1, 3, 6 and 9). Of the patients who received two implants all but one patient (75%) had suppressed serum estradiol levels (patient103 had serum estradiol levels slightly above the upper **limit of the "suppressed" threshold of 20 pg/mL on three** occasions through Month 9: 24.1 pg/ml at baseline, 21.8 pg/mL at Month 3 and 22.2, pg/mL at Month 6, respectively[40]).

Table 4: Serum estradiol concentrations and percentage of patients with estrogen suppression through Month 9 (ITT Population)

	1 implant	2 implants	All Patients
Estrogen (pg/ml)			
Baseline			
N	7	4	1
Mean (SD)	9.28 (4.82)	10.78 (9.37)	9.83 (6.39)
Range	3.00, 15.09	1.99, 24.05	1.99, 24.05
Month 1			
N	7	4	11
Mean (SD)	9.94 (6.10)	9.36 (4.24)	9.72 (5.27)
N (%) suppressed	7 (100.0)	4 (100.0)	11 (100.0)
Month 3			
N	7	4	11
Mean (SD)	8.82 (3.41)	12.76 (6.90)	10.25 (5.02)
N (%) suppressed	7 (100.0)	3 (75.0)	10 (90.9)
Month 6			
N	7	4	11
Mean (SD)	6.90 (3.14)	12.32 (8.79)	8.87 (6.05)
N (%) suppressed	7 (100.0)	3 (75.0)	10 (90.9)
Month 9			
N	7	4	11
Mean (SD)	6.14 (4.89)	9.01 (6.41)	7.19 (5.36)
N (%) suppressed	7 (100.0)	4 (100.0)	11 (100.0)

Source: Table 4 in Clinical Study Report (Study 01-02-001)

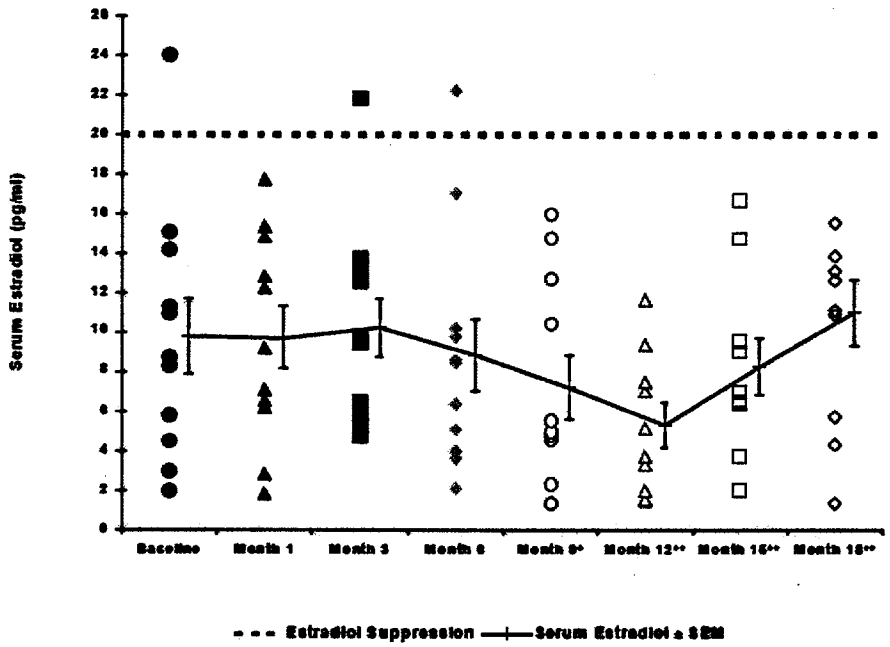
Six patients (five patients with one implant and one patient with two implants) were continued on treatment up to Month 18. They all showed suppressed estradiol levels at all time points assessed (i.e. Month 12, Month 15 and Month 18). Five of the initial patients had their

[40] **This patient had an "early termination" after the Month 9** visit due to a wound infection at the injection site after receiving a new implant (the new implant was removed 10 days after being inserted at month 9). Unstimulated basal LH levels measured only at Month 6 and Month 9 were in the suppressed range (ACCORDING TO FIG 5 HAD MONTH1,2,3,6,and 9 basal LH..

implant(s) replaced at Month 9 with only one new implant; one of them discontinued the trial due to a wound infection; the remaining four displayed continued suppression of estradiol through **Month 18. The applicant states that "there was no evi**dence of an acute-on-chronic effect (i.e., a flare in symptoms or interruption in suppression of hormone levels at 1 month after reimplantation) among **the 5 subjects who received a new implant at Month 9".**

Individual serum estradiol concentrations at baseline and at all visits on trial up to month 18 are **illustrated in applicant's Figure 1. As previously described, there were only three measurements** slightly above 20 pg/mL obtained at scheduled visits, all in patient 103 (at baseline, Month 3 and Month 6).

Figure 1 Individual Serum Estradiol Concentrations Over the 18-Month Treatment Period



Serum LH and FSH concentrations

Table 5 summarizes the mean values for the peak serum LH and FSH concentrations up to Month 9 (more than half of the patients did not have evaluations at Months 1 and 3). The mean values for the peak LH and FSH levels remained suppressed on Histrelin treatment (i.e ≤ 1 mIU/mL for LH and ≤ 2.5 mIU/mL for FSH). There were no clinically meaningful differences in the levels of suppression generated by one versus two implants.

Table 5: Mean values for the Peak Serum FH and FSH concentrations through Month 9 (ITT Population)

	1 implant	2 implants	All Patients
Peak Serum LH (mIU/mL)			
Baseline N	7	4	11

Mean (SD) Range	1.23 (1.46) 0.30, 4.50	1.43 (1.30) 0.40, 3.30	1.30 (1.34) 0.30, 4.50
Month 1 N Mean (SD)	0	1 0.10	1 0.10
Month 3 N Mean (SD)	3 0.33 (0.06)	2 0.20 (0.14)	5 0.28 (0.11)
Month 6 N Mean (SD)	6 0.23 (0.05)	4 0.14 (0.07)	10 0.20 (0.07)
Month 9 N Mean (SD)	7 0.33 (0.13)	4 0.14 (0.11)	11 0.26 (0.15)
FSH (mIU/mL)			
Baseline N Mean (SD) Range	7 1.74 (1.32) 0.60, 4.60	4 1.58 (0.62) 0.70, 2.10	11 1.68 (1.08) 0.60, 4.60
Month 1 N Mean (SD)	-	1 0.40	1 0.40
Month 3 N Mean (SD)	3 1.07 (0.15)	2 0.90 (0.57)	5 1.00 (0.32)
Month 6 N Mean (SD)	6 0.92 (0.33)	4 1.45 (0.67)	10 1.13 (0.53)
Month 9 N Mean (SD)	7 0.94 (0.38)	4 1.45 (0.71)	11 1.13 (0.55)

Source: Table 6 in Clinical Study Report (Study 01-02-001)

In five patients who continued with the original single implant beyond Month 9, the mean values for peak LH levels remained suppressed through Month 18 (0.28 ±0.04 at Month 9, 0.30 ± 0.07 at Month 12, 0.28 ±0.04 at Month 15, and 0.22 ± 0.04 at Month18), as was the case for one patient who continued with two implants for the same duration. In five patients who had their implant(s) replaced by one new implant at Month 9, the LH levels were suppressed at Month 18 (mean level: 0.35 ±0.26)[41].

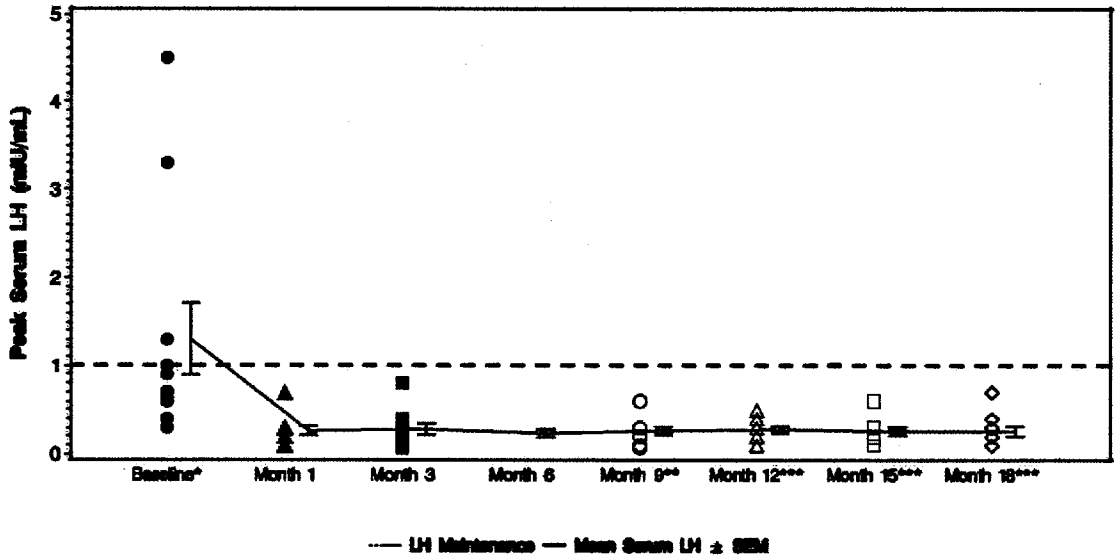
Concordant with the observations made for LH, the mean values for peak FSH levels were maintained suppressed through Month 18 in five patients who continued the original single implant to this timepoint: (1.08 ± 0.51 at Month 12, 0.98 ± 0.41 at Month 15 and 1.04 ± 0.57); this was equally true for the one patient with two original implants left in place and followed up to the same timepoint. Of the 5 patients who has their implant(s) replaced with one implant at Month 9, the data at Month 18 obtained form 4 patients indicated continued suppression (mean: 1.65 ±0.83).

[41] Only 4 patients contributed data at Month 18 due to the discontinuation of patient 103.

This reviewer inspection of Post-text Listing 2.2 entitled "LH and FSH Assessments - Efficacy Population" indicated that there were no individual peak LH levels > 1 mIU/ml on trial (except 4 baseline values) and no individual peak FSH level > 2.5 mIU/ml on trial except for one baseline value.

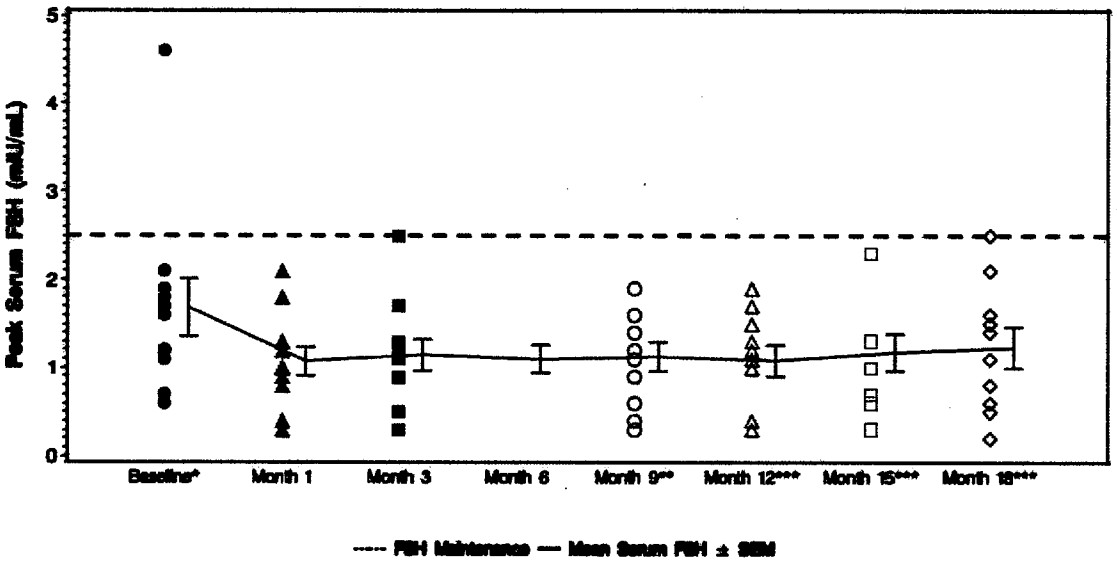
The individual peak LH serum concentrations at various timepoints on trial are illustrated in **applicant's Figure 2.2.1.1 from Amendment 8, which** indicates that all patients had suppression of LH (either induced or maintained) for entire 18-month treatment period.

Figure 2.2.1.1
Peak Serum LH Level Results (mIU/mL) Over 18 Month Period



The individual peak FSH serum concentrations at various timepoints on trial are illustrated in **applicant's Figure 2.2.1.2 from Amendment 8, which** indicates that all patients had suppression of FSH (either induced or maintained) for entire 18-month treatment period.

Figure 2.2.1.2
Peak Serum FSH Level Results (mIU/mL) Over 18 Month Period



Other efficacy evaluations

IGF-1 and IGFBP-3

There were small reductions in the mean IGF-I serum concentrations at Month 9 relative to baseline. The reductions were comparable between patients with one implant (11%) and patients with 2 implants (12%) for patients **with 2 implants (applicant's Table 2.3.1.1).**

Post-text Table 2.3.1.1
Summary Statistics on IGF-1 Results at Month 9 by Number of Implants
Secondary Efficacy Evaluation
Efficacy Population

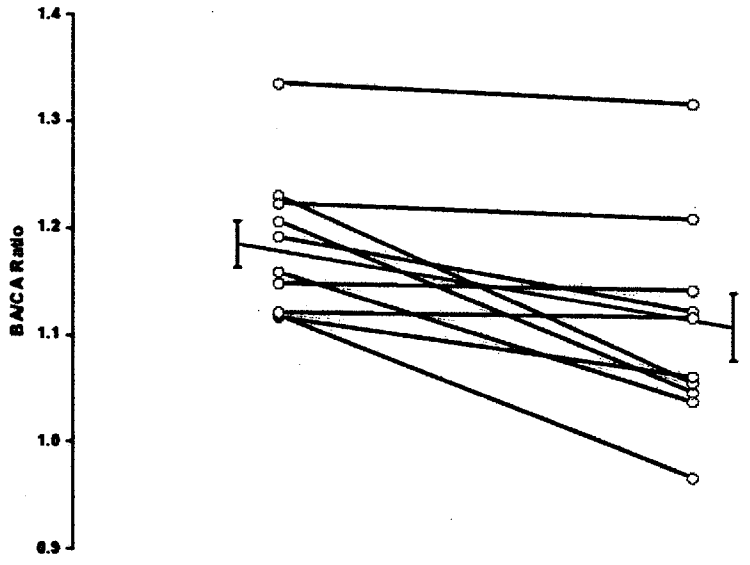
			Number of Implants*	
	Statistics	Efficacy N=11	1 Implant N=7	2 Implants N=4
IGF-1 at Baseline (Day 1 (Visit 1))*	N	11	7	4
ng/mL	Mean±S.D.	350.18±115.36	315.57±99.62	410.75±128.41
	Median	336.00	302.00	392.50
	Min, Max	162.00 , 577.00	162.00 , 459.00	281.00 , 577.00
IGF-1 at Month 9 (Visit 5)	N	11	7	4
	Mean±S.D.	311.82±96.38	283.29±80.19	361.75±135.04
	Median	297.00	273.00	366.00
	Min, Max	183.00 , 519.00	183.00 , 435.00	200.00 , 513.00
Change in IGF-1 from Baseline to Month 9	N	11	7	4
	Mean±S.D.	-38.36±60.96	-37.29±75.56	-40.00±27.07
	Median	-32.00	-5.00	-48.00
	Min, Max	-187.00 , 72.00	-187.00 , 72.00	-79.00 , -11.00
	95% CI	(-79.32 , 2.59)	(-102.17 , 37.60)	(-83.07 , -5.93)
	P-value	0.0634	0.3614	0.0362

Overall, there was a small increase in the mean IGFBP-3 from baseline at Month 9 of treatment from 5.47±1.51 to 6.51±1.56 (mean change: 1.04±1.61; p-value 0.0581). The change was similar whether patients received one or two implants.

Bone age

Bone age was assessed at baseline, Month 9 and Month 18 and was centrally read. The mean bone age for all patients was 10.1 ±2.90 years at baseline (approximately 1.5 years ahead of the chronological age of 8.62 ±2.57 years). The mean bone age for all patients advanced by approximately 0.3 years (to 10.4 ± 2.77 years) at Month 9 and by 0.8 years (to 10.9 ± 2.52 years) at Month 18. Overall, the bone age advancement was 1.00±0.78 from baseline to Month 18 relative to a chronological age advancement of 1.59±0.20 years for the same timepoint. The applicant reports that the bone age to chronological age ratio (calculated from 9 patients) **declined on treatment at Month 18 ($p<0.05$) as illustrated by applicant's Figure 6, indicating a** slowdown in bone age advancement relative to chronological age advancement.

Figure 6 Bone Age to Chronological Age Ratio – All Subjects



Mean bone to chronological age ratio at Month 18; $p<0.005$

This reviewers inspection of the changes in BA and CA calculated from the data provided in **Post-text Listing 2.7 entitled "Bone X-Ray Age and Chronological Age – Efficacy Population"**, indicates that all but three patients had changes in CA exceeding changes in BA; in those few cases where changes in BA exceeded the changes in CA, such changes were small.

Transabdominal pelvic ultrasound

Ultrasound evaluations of uterine and ovarian volumes were performed at baseline, Month 9 and **Month18. They were locally read. In this reviewer's assessment of Post-text Listing 2.6 4 the** Month 9 ovarian volumes were smaller (for both ovaries) in 5 patients; a sixth patient had one smaller ovary and a larger ovary at Month 9. The uterine volume at Month 9 was smaller in 4 patients, increased in 3 others and was about the same in one patient (all measurements relative to baseline). Patient 103 (early withdrawal for wound infection) was reported as having an increase in both uterine and ovarian volumes.

Investigator's assessment of disease progression

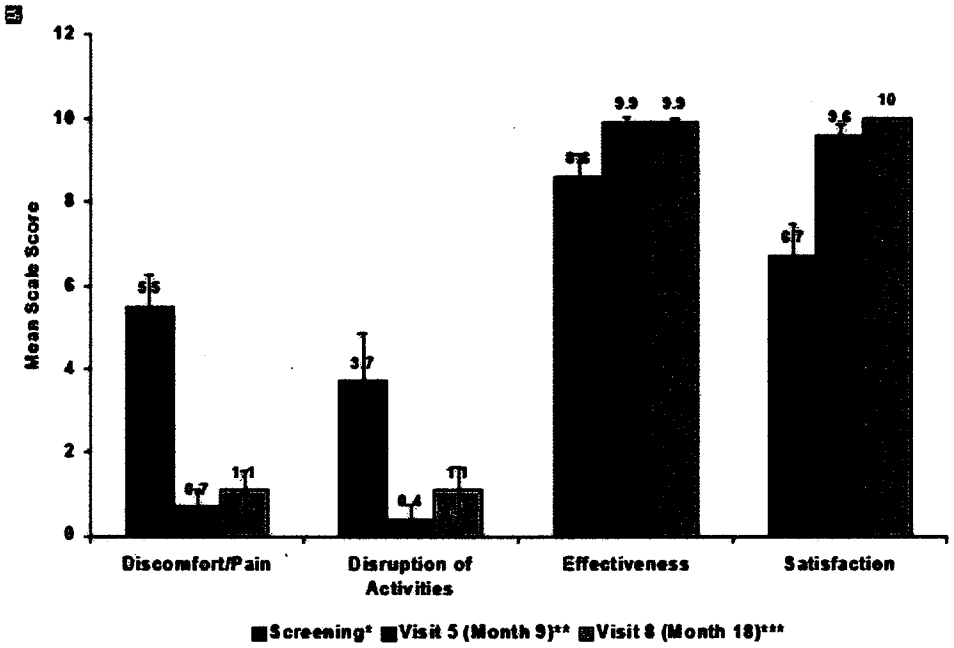
According to the investigator, two patients had progression of puberty:

- patient 101 advanced from a Tanner Stage 3 to a Tanner Stage 4 for breast development by the 12-month visit and from a Tanner Stage 2 to a Tanner Stage 3 for pubic hair development at Month 6 (Post-text Listing 2.5 and 3.7).
- **patient 109 "had a bone age of 13 years compared with a chronological age of 11.6 years at the 18-month visit" (review of Post-text listing 2.7 indicates that this patient had a bone age** advancement of 1 year at Month 18; for the whole duration of the trial (1.5 years) the BA advancement was slower (1 year).

Quality of life questionnaire

Patients were evaluated with an exploratory quality of life questionnaire at screening, Month 9 and Month 18. The results indicate reductions (i.e. improvements) in the mean scores for pain/discomfort and disruption of activities, and an increase (i.e. improvement) in the scores for **satisfaction and perceived effectiveness (applicant's Figure 7).**

Figure 7 **Mean (SE) Quality of Life Questionnaire Results at Screening, Month 9, and Month 18 – All Subjects**



Height velocity standard deviation score

Mean height (growth) velocity was calculated in cm/yr (4.6 ± 2.8) and SD score (-2.23 ± 3.03) at Month 9; at Month 18 it was 4.9 ± 2.3 (cm/yr) and -1.86 ± 2.32, respectively. The negative SD scores indicate a below average growth. Baseline height velocity information was not provided.

6.1.4.2 Study 03-CPP-HIS-300

Primary efficacy analysis and related efficacy analyses

The mean values for the peak serum LH concentration (absolute values and change from baseline by visit) are displayed in applicant's Table 6. All 20 patients in the treatment-naïve group had baseline peak LH concentrations above the protocol defined pubertal threshold of 4 mIU/ml (mean ± SD: 28.16 ± 19.97; range: 4.80 to 77.0). The mean values for peak serum LH concentrations during Histrelin treatment beginning at Month 1 and continuing through Month 12 were suppressed to prepubertal values ($p < 0.0001$ for all timepoints when compared to baseline). For the 16 patients in the pre-treated group, the mean peak LH concentration was

suppressed at baseline (2.09 ± 2.15)[42]. It decreased further at Month 1 and was maintained suppressed at all timepoints measured during the 12 months of Histrelin treatment (this finding was statistically significant for all timepoints). The primary efficacy endpoint was the percentage of children who had LH suppression to prepubertal levels at the Month 3 timepoint following histrelin implantation. All 36 patients had peak LH below the pre-defined threshold of suppression at Month 3[43].

Table 6 Mean Change from Baseline in Peak Serum LH Concentration (mIU/mL) Through Month 12 of Histrelin Implant Therapy – All Subjects

	Pretreated Subjects	Naïve Subjects	All Subjects
LH (mIU/mL)			
Baseline (Day 1/Visit 1)			
N	16	20	36
Mean (SD)	2.09 (2.15)	28.16 (19.97)	16.57 (19.78)
Median	1.80	24.00	9.20
Min, Max	0.02, 7.10	4.80, 77.00	0.02, 77.00
Visit 2 (Month 1)[a]			
N	16	20	36
Mean (SD)	0.51 (0.32)	0.82 (0.39)	0.68 (0.39)
Mean change (SD)	-1.58 (1.95)	-27.34 (19.96)	-15.89 (19.66)
95% CI	-2.61, -0.54	-36.68, -18.00	-22.54, -9.24
p-value[b]	0.0056	<0.0001	<0.0001
Visit 3 (Month 3)[a]			
N	16	20	36
Mean (SD)	0.53 (0.35)	0.80 (0.51)	0.68 (0.46)
Mean change (SD)	-1.56 (1.86)	-27.36 (19.89)	-15.89 (19.63)
95% CI	-2.55, -0.57	-36.67, -18.05	-22.53, -9.25
p-value[b]	0.0043	<0.0001	<0.0001
Visit 4 (Month 6)[a]			
N	16	18	34
Mean (SD)	0.62 (0.26)	0.85 (0.50)	0.75 (0.41)
Mean change (SD)	-1.46 (1.95)	-27.77 (21.02)	-15.39 (20.17)
95% CI	-2.50, -0.42	-38.22, -17.31	-22.43, -8.35
p-value[b]	0.0091	<0.0001	<0.0001
Visit 5 (Month 9)[a]			
N	16	19	35
Mean (SD)	0.67 (0.39)	0.93 (0.54)	0.81 (0.49)
Mean change (SD)	-1.41 (1.95)	-27.51 (20.40)	-15.58 (19.90)
95% CI	-2.45, -0.38	-37.34, -17.67	-22.41, -8.74
p-value[b]	0.0109	<0.0001	<0.0001
Visit 6 (Month 12)[a]			
N	16	20	36
Mean (SD)	0.74 (0.45)	0.96 (0.58)	0.86 (0.53)
Mean change (SD)	-1.35 (2.01)	-27.20 (19.85)	-15.71 (19.63)
95% CI	-2.42, -0.28	-36.49, -17.92	-22.35, -9.07
p-value[b]	0.0169	<0.0001	<0.0001

Source: Tables 2.1.1, 2.1.2, 2.1.3, 2.1.4, and 2.1.5; Listing 2.1

[a] All subjects (pretreated and naïve) had suppression of LH.

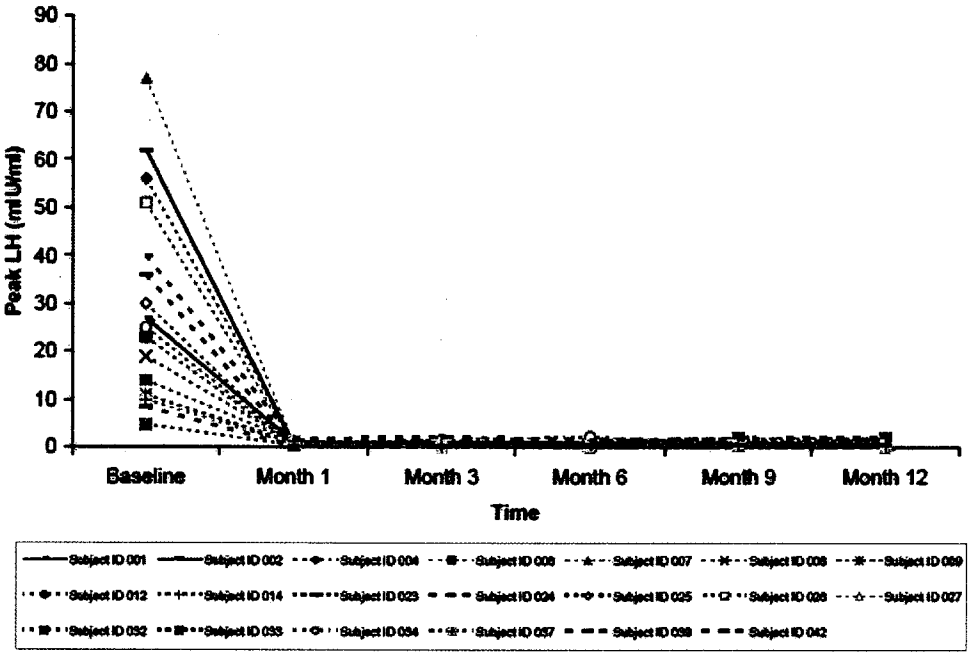
[b] P-values were calculated using a paired t-test comparing each visit assessment to the baseline assessment.

[42] Two of the 16 patients in the pre-treated cohort (patients 030 and 031) had LH concentrations of 5 mIU/mL and 5.7 mIU/mL, respectively, at screening (and LH levels of 7.1 mIU/mL and 7 mIU/mL, respectively, at Day 1).

[43] The 95% CI was 90.2 % to 100% for the whole group, 83.1% to 100% for treatment-naïve patients and 79.4% to 100% for treatment-experienced patients. The mean ± SD for the peak LH at Month 3 was 0.68 ± 0.46 (range: 0.14 to 2.20) for the whole group, 0.80 ± 0.51 (range: 0.22 to 2.2) for the treatment-naïve group and 0.53 ± 0.35 (range 0.14 to 1.3) for the pre-treated cohort.

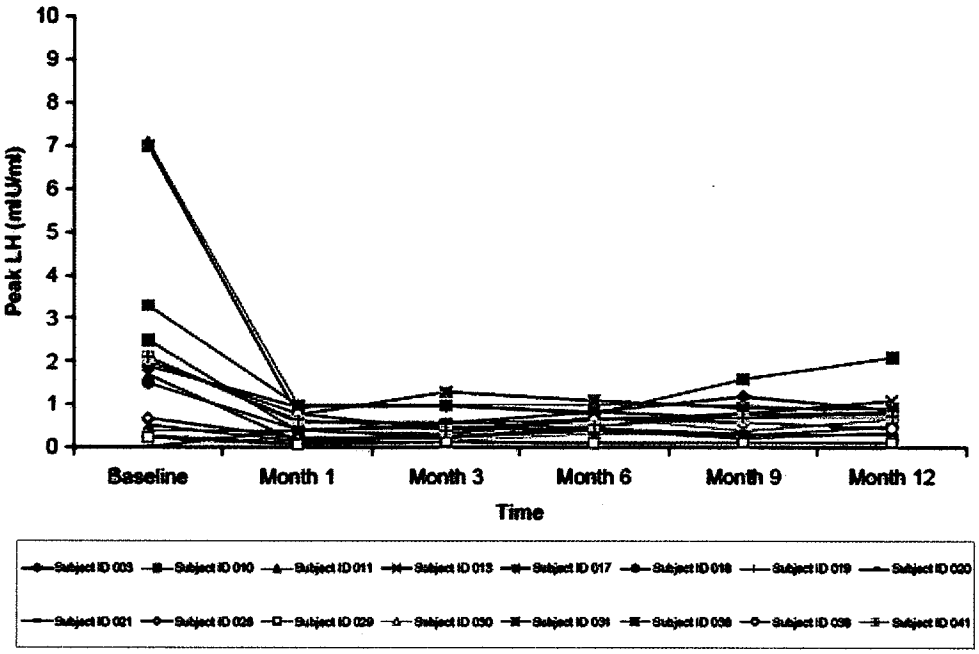
Applicant's Post-text Figure 2.9.3 graphically illustrates that all patients in the treatment-naïve group had peak LH concentrations suppressed on Histrelin treatment (this graphic display has been checked and has been found to be consistent **with the Post-text Listing 2.1 entitled "LH and FSH Assessments – Efficacy Population).**

Post-text Figure 2.9.3
Peak LH (mIU/ml) Results at Each Visit
Primary Efficacy Evaluation
Naive Population



Similarly, all patients in the pre-treated group had peak LH concentration below the pre-defined threshold of pubertal suppression during Histrelin **treatment (see applicant's Post-text Figure** 2.9.2 below; this graphic display has been found to be consistent with the Post-text Listing 2.1 **entitled "LH and FSH Assessments – Efficacy Population").**

Post-text Figure 2.9.2
Peak LH (mIU/ml) Results at Each Visit
Primary Efficacy Evaluation
Pre-Treated Population



Secondary efficacy analyses

Mean Peak Serum FSH concentrations

At baseline, the mean values for the peak serum FSH concentrations were in the pubertal range for the treatment-naïve cohort[44] and slightly above the protocol specified definition of suppression (i.e. < 2.5 mIU/ml following stimulation with leuprolide acetate) for patients in the pretreated group[45]. **As displayed in applicant's Table 7,** on histrelin treatment, the mean values for the peak FSH concentrations were suppressed throughout the trial for the treatment-naïve group ($p<0.0001$ for all time points evaluated when compared to baseline) but they remained suppressed only up to Month 6 for the pre-treated group.

[44] Mean ± SD: 14.46 ± 6.7; range: 7.10 to 30.0.
[45] Mean ± SD: 2.83± 2.12; range: 0.11 to 7.10.

Table 7 Mean Change from Baseline in Peak Serum FSH (mIU/mL) Through Month 12 of Histrelin Implant Therapy – All Subjects

	Pretreated Subjects	Naïve Subjects	All Subjects
FSH (mIU/mL)			
Baseline (Day 1/Visit 1)			
N	16	20	36
Mean (SD)	2.83 (2.12)	14.46 (6.70)	9.29 (7.79)
Median	2.20	12.50	8.05
Min, Max	0.11, 7.10	7.10, 30.00	0.11, 30.0
Visit 2 (Month 1)			
N	16	20	36
Mean (SD)	1.46 (0.88)	1.07 (0.49)	1.24 (0.70)
Mean change (SD)	-1.36 (1.69)	-13.39 (6.64)	-8.05 (7.87)
95% CI	-2.26, -0.47	-16.50, -10.29	-10.71, -5.39
p-value[a]	0.0055	<0.0001	<0.0001
N (%)[b]	14 (87.5)	20 (100)	34 (94.4)
Visit 3 (Month 3)			
N	16	20	36
Mean (SD)	1.57 (0.99)	1.49 (0.68)	1.53 (0.82)
Mean change (SD)	-1.25 (1.88)	-12.97 (6.66)	-7.76 (7.78)
95% CI	-2.25, -0.25	-16.08, -9.85	-10.39, -5.13
p-value[a]	0.0179	<0.0001	<0.0001
N (%)[b]	13 (81.3)	18 (90.0)	31 (86.1)
Visit 4 (Month 6)			
N	16	18	34
Mean (SD)	2.07 (1.25)	1.61 (0.68)	1.83 (1.00)
Mean change (SD)	-0.75 (1.97)	-13.19 (7.02)	-7.34 (8.17)
95% CI	-1.80, 0.29	-16.68, -9.70	-10.19, -4.48
p-value[a]	0.1459	<0.0001	<0.0001
N (%)[b]	11 (68.8)	16 (80.0)	27 (75.0)
Visit 5 (Month 9)			
N	16	19	35
Mean (SD)	2.56 (1.61)	2.20 (1.18)	2.36 (1.39)
Mean change (SD)	-0.26 (1.96)	-12.50 (7.05)	-6.91 (8.14)
95% CI	-1.31, 0.78	-15.90, -9.10	-9.70, -4.11
p-value[a]	0.6012	<0.0001	<0.0001
N (%)[b]	9 (56.3)	14 (70.0)	23 (63.9)
Visit 6 (Month 12)			
N	16	20	36
Mean (SD)	2.75 (2.40)	2.48 (1.38)	2.60 (1.88)
Mean change (SD)	-0.08 (2.34)	-11.98 (6.40)	-6.69 (7.78)
95% CI	-1.32, 1.17	-14.97, -8.98	-9.32, -4.06
p-value[a]	0.8962	<0.0001	<0.0001
N (%)[b]	9 (56.3)	13 (65.0)	22 (61.1)

Source: Tables 2.4.1, 2.4.2, 2.4.3, 2.4.4, and 2.4.5; Listing 2.1

[a] P-values were calculated using a paired t-test comparing each visit assessment to the baseline assessment.

[b] Proportion of subjects who achieved suppression of FSH.

Although the mean values for peak FSH were suppressed on treatment through Month 12 for the treatment-naïve group, not all patients displayed FSH suppression at all timepoints (excepting the Month 1 timepoint). Specifically, 18/20 (90%) were suppressed at Month 3, 16/20 (80%) at Month 6, 14/20 (70%) at Month 9 and 13/20 (65%) at Month 12.

For the pre-treated group the percentage of patients with peak FSH suppression on trial was as follows: 14/16 (87.5%) at Month 1; 13/16 (81.3%) at Month 3; 11/16 (68.8%) at Month 6; 9/16

(56.3%) at Months 9 and 12, respectively. Interestingly, at baseline (i.e. on non-histrelin GnRH agonist treatment) the percentage of patients with FSH suppression was 62.5%, which is only slightly higher than the histrelin suppression at Months 9 and 12 of 56.3%.

Visual inspection of the individual values above the suppression threshold for patients in both cohorts indicates that some patients were not fully suppressed at all (or most) timepoints during the trial, while others had only occasional values in the pubertal range (mostly during the later part of the trial (Post-text Listing 2.1: LH **and FSH Assessments – Efficacy Population); as a** general rule, values above the suppression threshold were not observed frequently in the first 6 months of treatment.

Mean serum estradiol concentrations

The vast majority of the patients enrolled were female (33/36 overall, 13/13 of pre-treated patients, and all 20 treatment-naïve patients). As expected, the estradiol serum level at baseline for the treatment-naïve group (mean: 24.50 ± 22.27 pg/ml; range: 5.0 to 72.0) exceeded the upper limit of normal for the prepubertal range of ≤ 20 pg/ml[46]. On Histrelin treatment the mean estrogen levels decreased fourfold at Month 1 (5.85 ± 2.37) and remained at similar (suppressed) levels through Month 12 (Table 8); changes in mean estrogen levels were statistically significant for all timepoints.

Pre-treated patients had mean estradiol levels in the suppressed range at baseline (mean ± SD: 5.92 ± 2.2; range 5.0 to 13.0); on treatment they were maintained below the protocol specified threshold of estrogen suppression through Month 12.

Estrogen suppression was maintained in 100 % of patients in the pre-treated group throughout the trial and in 100% of treatment-naïve group up and including Month 9; at Month 12 one patient (037) in the latter group had an estradiol level of 27 pg/mL (thus 95% of the treatment-naïve patients were suppressed at Month 12).

[46] Since estrogen secretion is episodic not all patients with precocious puberty have all the time above normal estrogen levels despite clinical signs of estrogen excess.

Table 8 Mean Changes from Baseline in Serum Estradiol (pg/mL) Concentrations Through Month 12 of Histrelin Implant Therapy – All Female Subjects

	Pretreated Subjects	Naive Subjects	All Subjects
Females: Estradiol (pg/mL)			
Baseline (Visit 1/Day 1)			
N	13	20	33
Mean (SD)	5.92 (2.22)	24.50 (22.27)	17.18 (19.53)
Median	5.00	17.00	6.00
Min, Max	5.00, 13.00	5.00, 72.00	5.00, 72.00
Visit 2 (Month 1)			
N	13	20	33
Mean (SD)	5.38 (0.65)	5.85 (2.37)	5.67 (1.88)
Mean change (SD)	-0.54 (2.37)	-18.65 (22.72)	-11.52 (19.73)
95% CI	-1.97, 0.89	-29.28, -8.02	-18.51, -4.52
p-value[a]	0.4281	0.0016	0.0021
n (%)[b]	13 (100)	20 (100)	33 (100)
Visit 3 (Month 3)			
N	13	20	33
Mean (SD)	5.23 (0.83)	5.55 (1.82)	5.42 (1.50)
Mean change (SD)	-0.69 (1.44)	-18.95 (22.59)	-11.76 (19.64)
95% CI	-1.56, 0.18	-29.52, -8.38	-18.72, -4.79
p-value[a]	0.1079	0.0014	0.0016
n (%)[b]	13 (100)	20 (100)	33 (100)
Visit 4 (Month 6)			
N	13	20	33
Mean (SD)	5.00 (0.0)	5.30 (0.73)	5.18 (0.58)
Mean change (SD)	-0.92 (2.22)	-19.20 (22.01)	-12.00 (19.28)
95% CI	-2.26, 0.42	-29.50, -8.90	-18.84, -5.16
p-value[a]	0.1590	0.0010	0.0011
n (%)[b]	13 (100)	20 (100)	33 (100)
Visit 5 (Month 9)			
N	13	20	33
Mean (SD)	5.85 (1.52)	5.25 (0.55)	5.48 (1.06)
Mean change (SD)	-0.08 (1.89)	-19.25 (22.34)	-11.70 (19.70)
95% CI	-1.22, 1.07	-29.71, -8.79	-18.68, -4.71
p-value[a]	0.8858	0.0011	0.0018
n (%)[b]	13 (100)	20 (100)	33 (100)
Visit 6 (Month 12)			
N	13	20	33
Mean (SD)	6.31 (2.93)	6.35 (4.91)	6.33 (4.19)
Mean change (SD)	0.38 (3.38)	-18.15 (23.56)	-10.85 (20.45)
95% CI	-1.66, 2.43	-29.17, -7.13	-18.10, -3.60
p-value[a]	0.6888	0.0027	0.0046
n (%)[b]	13 (100)	19 (95.0)	32 (97.0)

Source: Tables 2.3.1, 2.3.2, 2.3.3, 2.3.4, and 2.3.5; Listing 2.2

[a] P-values were calculated using a paired t-test comparing each visit assessment to the baseline assessment.

[b] Proportion of subjects who achieved suppression of estradiol.

Note: LOCF was used to replace missing values between two visits with non-missing results

Mean serum testosterone concentrations

There were only three male patients enrolled in the trial, all in the pre-treated group. All three had suppressed testosterone levels at baseline (testosterone suppression was defined as a serum level <30 ng/dl). Suppression of testosterone levels was maintained in all three patients through Month 12 of Histrelin implant therapy (Applicant**'s Table 9, below; confirmed from Post-text Listing 2.2 – Hormone Assessments Efficacy Population).**

Table 9 **Mean Changes Mean Changes from Baseline in Serum Testosterone (ng/dL) Concentrations Through Month 12 of Histrelin Implant Therap – All Male Subjects**

	Pretreated Subjects	All Subjects
Males: Testosterone (ng/dL)		
Baseline (Visit 1/Day 1)		
N	3	3
Mean (SD)	10.63 (1.18)	10.63 (1.18)
Median	10.00	10.00
Min, Max	9.90, 12.00	9.90, 12.00
Visit 2 (Month 1)		
N	3	3
Mean (SD)	7.27 (2.32)	7.27 (2.32)
Mean change (SD)	-3.37 (2.06)	-3.37 (2.06)
95% CI	-8.48, 1.75	-8.48, 1.75
p-value[a]	0.1054	0.1054
Visit 3 (Month 3)		
N	3	3
Mean (SD)	8.63 (1.87)	8.63 (1.87)
Mean change (SD)	-2.00 (1.40)	-2.00 (1.40)
95% CI	-5.48, 1.48	-5.48, 1.48
p-value[a]	0.1318	0.1318
Visit 4 (Month 6)		
N	3	3
Mean (SD)	12.33 (2.52)	12.33 (2.52)
Mean change (SD)	1.70 (2.94)	1.70 (2.94)
95% CI	-5.61, 9.01	-5.61, 9.01
p-value[a]	0.4226	0.4226
Visit 5 (Month 9)		
N	3	3
Mean (SD)	10.43 (4.37)	10.43 (4.37)
Mean change (SD)	-0.20 (4.57)	-0.20 (4.57)
95% CI	-11.56, 11.16	-11.56, 11.16
p-value[a]	0.9465	0.9465
Visit 6 (Month 12)		
N	3	3
Mean (SD)	9.33 (3.79)	9.33 (3.79)
Mean change (SD)	-1.30 (3.46)	-1.30 (3.46)
95% CI	-9.89, 7.29	-9.89, 7.29
p-value[a]	0.5819	0.5819

Source: Tables 2.2.1, 2.2.2, 2.2.3, 2.2.4, and 2.2.5; Listing 2.2
[a] p-values were calculated using a paired t-test comparing each visit assessment to the baseline assessment.
Note: There were no naïve male subjects. All pretreated subjects (100%) achieved suppression of testosterone at each time point.

Bone age

Bone age measurements were performed at baseline and Month 12 and were centrally read. As expected in patients with CPP (and precocious puberty in general), bone age (BA) was advanced relative to chronological age (CA) in both subgroups **(applicant's Table 10, below). Specifically,** patients in the treatment-naïve cohort had a mean ± SD baseline BA of 9.90 ± 1.8 years which was advanced by more than two years relative to the mean CA of 7.04 ± 1.34. For the pre-treated cohort the mean baseline BA of 11.68 ± 1.88 was close to 3 years ahead of the mean CA

of 8.84 ± 1.57. The mean change from baseline in **bone age at "Month 12" of Histrelin treatment** was 0.91 ± 0.5 years for treatment-naïve patients[47], 0.43 ± 0.39 years for the pre-treated patients[48] and 0.70 ± 0.51 years for the two groups combined[49].

Inspection of Post-text listing 2.4 entitled Bone Age and Chronological Age –Efficacy Population indicates that twenty eight out of the 36 patients (78%) had advances in CA that were larger than the changes in the bone age; conversely 8/36 patients (22%) had bone age advancements higher than those of chronological age (all but one were treatment-naïve). In all but one case the differences were relatively small.

Table 10 Bone Age Versus Chronological Age (Years)

Time Point	Chronological Age (yrs)			Bone Age (yrs)		
	Pre-treated Subjects N=16	Naïve Subjects N=20	All Subjects N=36	Pre-treated Subjects N=16	Naïve Subjects N=20	All Subjects N=36
Screening						
N	16	20	36	16	20	36
Mean (SD)	8.84 (1.57)	7.04 (1.34)	7.84 (1.69)	11.68 (1.88)	9.90 (1.80)	10.69 (2.02)
Median	8.93	7.40	7.81	12.05	10.63	11.33
Range	5.55, 11.61	4.44, 8.93	4.44, 11.61	5.45, 14.55	6.43, 12.60	5.45, 14.55
Visit 6[a]						
N	16	20	36	16	20	36
Mean (SD)	9.87 (1.57)	8.15 (1.40)	8.91 (1.70)	12.11 (1.65)	10.81 (1.52)	11.39 (1.69)
Median	10.09	8.45	9.02	12.36	11.49	11.92
Range	6.68, 12.61	5.43, 10.20	5.43, 12.61	6.89, 14.76	7.48, 12.89	6.89, 14.76
Change from Screening to Month 12						
N	16	20	36	16	20	36
Mean (SD)	1.02 (0.21)	1.11 (0.10)	1.07 (0.16)	0.43 (0.39)	0.91 (0.50)	0.70 (0.51)
Median	1.03	1.11	1.04	0.23	0.99	0.63
Range	0.48, 1.41	0.99, 1.33	0.48, 1.41	-0.04, 1.44	0.29, 2.26	-0.04, 2.26
95% CI	(0.91, 1.13)	(1.07, 1.16)	(1.02, 1.13)	(0.22, 0.64)	(0.68, 1.15)	(0.52, 0.87)
p-value	<0.0001	<0.0001	<0.0001	0.0006	<0.0001	<0.0001

Source: Tables 2.5 and 2.6; Listing 2.4
[a] Month 12

Descriptive statistics for the BA/CA ratios at baseline and Month 12 are presented in applicant's Post-text Table 2.7. The mean BA/CA ratios decreased during histrelin treatment. The changes in BA/CA ratio were statistically significant at Month 12 as follows: $p<0.0001$ for the pre-treated group, 0.0002 for the treatment-naïve group and $p<0.0001$ for the two groups combined.

[47] For a mean CA change of 1.11 ± 0.10 years.
[48] For a mean CA change 1.02 ± 0.21 years.
[49] For a mean CA change 1.07± 0.16 years.

Post-text Table 2.7
Summary Statistics on Bone Age/Chronological Age Ratio Results
Secondary Efficacy Evaluation
Efficacy Population

			Prior CPP Medication History[a]	
	Statistics	Efficacy N=36	Pre-treated N=16	Naïve N=20
Bone Age/Chronological Age Ratio at Screening	N	36	16	20
	Mean±S.D.	1.38±0.17	1.33±0.16	1.42±0.17
	Median	1.39	1.31	1.43
	Min, Max	0.98 , 1.91	0.98 , 1.61	1.13 , 1.91
Bone Age/Chronological Age Ratio at Month 12 (Visit 6)	N	36	16	20
	Mean±S.D.	1.29±0.14	1.24±0.13	1.34±0.13
	Median	1.30	1.21	1.35
	Min, Max	1.03 , 1.69	1.03 , 1.48	1.03 , 1.69
Change in Bone Age/Chronological Age Ratio from Screening to Month 12	N	36	16	20
	Mean±S.D.	-0.08±0.07	-0.09±0.06	-0.08±0.08
	Median	-0.09	-0.10	-0.08
	Min, Max	-0.22 , 0.14	-0.20 , 0.05	-0.22 , 0.14
	95% CI	(-0.11 , -0.06)	(-0.12 , -0.06)	(-0.11 , -0.04)
	P-value	<0.0001	<0.0001	0.0002

Transabdominal pelvic ultrasound

Transabdominal pelvic ultrasounds were measured at baseline and Month 12 and were locally read. **The applicant states that "uterine and ovarian volumes either decreased from Baseline or** remained fairly consistent throughout the 12 months of histrelin implant treatment." **Review of** the Data Listings 2.7.1.1 and 2.7.1.2 which present the individual information on ovarian and uterine volumes, including occasional comments, allows the following descriptive observations to be made:

- 22/33 patients (67%) had both baseline and Month 12 uterine ultrasounds (some patients missed one or both ultrasounds); of these, 16/22 patients (73%) had decreased uterine volume at Month 12 relative to baseline while the remainder 2/22 patients (27%) showed the opposite effect.
- 23/33 patients (70%) had data for both ovaries at baseline and Month 12. Of these, 13/23 patients (56.5%) had a decreased Month 12 ovarian volume for each ovary relative to baseline, 5/23 patients (21.7%) had increased volumes at Month 12 and 5/23 patients (21.7%) had one ovary larger and another smaller relative to the corresponding baseline ovarian volume.

Lack of standardizations of the readings and the absence of a control group limit the ability to draw firm conclusions.

Height and height velocity

Descriptive statistics for the mean height Z-score at baseline, Month 6 and Month 12 are presented in applicant's Post-text Table 2.9.3. The mean height Z-score decreased slightly from baseline (1.48 ± 1.36) to Month 12 (1.36 ± 1.20). Although this observation suggests that the height acceleration seen with puberty is slowing down, the data need to be interpreted with some caution because there is no control group and pubertal growth rates are quite variable in general. The applicant also points out that the number (%) of patients who had height Z-scores within the normal range (i.e. ± 2 SD) was higher at Month 12 (26/36 or 72.2%) relative to baseline (21/36 or 58.3%).

Post-text Table 2.9.3
Summary Statistics on Z-score and Percentile for Height for Age
Secondary Efficacy Evaluation
Efficacy Population

	Statistics	Z-Score	Percentile (%)
Height for Age at Baseline [Visit 1 (Day 1)]	N	35	35
	Mean±S.D.	1.48±1.36	84.84±25.16
	Median	1.62	94.76
	Min, Max	-3.21 , 4.08	0.07 , 100.00
Height for Age at Month 6	N	36	36
	Mean±S.D.	1.38±1.35	82.80±26.69
	Median	1.57	94.13
	Min, Max	-2.64 , 4.03	0.41 , 100.00
Height for Age at Month 12	N	36	36
	Mean±S.D.	1.36±1.20	82.53±25.13
	Median	1.46	92.68
	Min, Max	-1.91 , 3.77	2.80 , 99.99

The mean height velocity measured in 35/36 patients (one outlier patient with spina bifida who was not measured accurately was appropriately left out from this analysis) indicates rates of linear growth in the prepubertal range[50]. Similar observations are made for the mean height velocity SD score which was between the mean and – 1SD[51]. The absence of height velocity measurements at baseline makes drawing further conclusions difficult.

Investigator assessment of disease progression

Eight female subjects (4 naïve and 4 pretreated) were judged by the investigator to have shown evidence of progression of puberty during the 12 months of the study. They are listed in Table 6. Most instances of clinical progression were transient or occurred early in the trial. A review of

[50] Attachment # 3 in Amendment # 008 indicates that the mean ± SD height velocity (cm/yr) measurements were as follows: 5.76 ± 2.57 at Month 6; 5.37 ± 2.06 at Month 9 and 5.68 ± 2.29 at Month 12.
[51] Attachment # 3 in Amendment # 008 indicates that the mean ± SD height velocity SDS measurements were as follows: -0.23 ± 2.89 at Month 6, -0.74 ± 2.4 at Month 9 and -0.44 ± 2.72 at Month 12.

applicant's "Post-text Listing 2.6 –Tanner Stages –Efficacy Population" indicated that of the 33 female patients who received Histrelin, 13/33 patients (39.4%) had regression of Tanner stage for breast development at Month 12 relative to baseline, 14/33 (42.4%) were unchanged and 6/33 (18%) had progression (thus 82% had stabilization of this symptom). All cases of progression of Tanner stage of breast development were by no more than one Tanner stage and tended to occur earlier during the treatment (Months 1-3). They were inconsistently associated with advancement in pubic hair Tanner stage. For the 3 male patients the pubic Tanner stage was unchanged at Month 12 relative to baseline in 2 of them and advanced by one Tanner stage for the third patient.

Table 6: Investigator assessment of disease progression through Month 12

Patient ID (treatment status)	Observation
002 (naïve)*	Had Tanner Stage 3 for breast development at screening which advanced to Tanner Stage 4 at **Month 1**; remained as such through Month 12 and regressed to Stage 3 at Month 13.
019 (pretreated)*	Had Tanner Stage 2 for breast development at screening and through Month 6; advanced to Tanner Stage 3 for breast development at **Month 9**. Regressed again to Tanner Stage 2 at Months 12 and 13.
032 (naïve)*	Had Tanner Stage 2 for pubic hair at screening that changed to Tanner Stage 3 for pubic hair at **Month 6**; persisted as such at the Month 9 visit and regressed to Stage 2 at Months 12 and 13.
003 (pretreated)	Had Tanner Stage 3 for breast development at screening and through Month 3; changed to Tanner Stage 4 at **Month 6** and remained unchanged through Month 13. In addition, while being Tanner Stage 3 for pubic hair for the first year, progressed to Stage 4 at **Month 13.**
012 (naïve)	Had Tanner Stage 3 for breast development at screening. Had Tanner Stage 4 for breast development at **Month 1** and remained as such through Month 13.
028 (pretreated)*	Had Tanner Stage 2 for breast development at screening, which regressed to Stage 1 at month 1, progressed to Stage 2 at **Months 3** and 6, regressed again at Month 9 and returned to Stage 2 at Month 13. Similar observations were made with respect to pubic hair (oscillations on treatment were observed but remained the same as at screening at the last timepoint evaluated).
037 (naïve)	Had Tanner Stage 2 for breast development at screening which advanced to Stage 3 at **Month 9** and remained as such through Month 13. Was Tanner Stage 1 for pubic hair at screening and through Month 9 and advanced to Stage 2 at **Month 12** and 13.
021 (pretreated)*	Progression based on presence of vaginal bleeding at **Month 3**.

Source: Text and Post-text Listing 2.6 and 3.6. Bolded are the timepoints when the investigators described the disease progression.
*Asterisk indicates transient changes for the period studied.

Acute-on-chronic effect

The applicant evaluated the effect of implant replacement on serum gonadal steroids (the "acute-over-chronic effect") in 31 patients who received a new implant at the end of the first year of treatment. The applicant selected the Month 13 timepoint (one month after implant replacement) as a time to evaluate the acute-on-chronic changes. **Applicant's Table 16 indicates that the mean** LH levels at Month 13 were in the suppressed range (i.e. ≤ 4 mIU/mL). The upper value of the

range of values indicates that all patients were suppressed[52]. This occurred in the context of an increase in the mean histrelin concentration from Month 12 to Month 13 (from 0.28±0.37 ng/mL **to 0.44±0.29 ng/mL). The applicant states that "collectively, the results of the AOC analyses** show that insertion of the second implant did not result in any short-term increase in LH, FSH, estradiol, or testosterone levels and that suppression of these hormonal l**evels was maintained."** There is, however, a major limitation in drawing such a broad conclusion since the applicant did not measure an earlier timepoint (e.g. 1 or 2 weeks). More reassurance is provided by the adult data from NDA 21-732 (CSR 301) that indicates 100% testosterone suppression at 48-72 hours following implant reinsertion. It should be recognized that implant removal and insertion of a new implant are completed within the same appointment and that, reportedly, histrelin **concentrations are detectable "within 5 minutes of implantation in majority of patients".**

Table 16 Summary of Mean Serum LH at Month 13 – AOC Population

			Prior CPP Medication History	
	Statistics	Efficacy N=31	Pre-treated N=13	Naive N=18
Serum LH at Month 12 (Visit 6)[a]	N	31	13	18
	Mean±S.D.	0.84±0.55	0.74±0.50	0.92±0.58
	Median	0.71	0.73	0.70
	Min, Max	0.13 , 2.10	0.13 , 2.10	0.18 , 2.00
Serum LH at Month 13 (Visit 7)[a]	N	29	13	16
	Mean±S.D.	0.44±0.27	0.36±0.20	0.50±0.31
	Median	0.39	0.31	0.44
	Min, Max	0.10 , 1.10	0.10 , 0.71	0.15 , 1.10
Change in Serum LH from Month 12 to Month 13[a]	N	29	13	16
	Mean±S.D.	-0.43±0.38	-0.37±0.41	-0.48±0.35
	Median	-0.34	-0.24	-0.38
	Min, Max	-1.46 , 0.11	-1.46 , 0.11	-1.04 , -0.01
	95% CI	(-0.57 , -0.29)	(-0.62 , -0.13)	(-0.67 , -0.29)
	P-value	<0.0001	0.0065	<0.0001

Source: Table 2.14, Listing 2.1
[a] Subjects with histrelin concentration below the level of quantification (BLQ < 0.05 ng/ml) at these timepoints were not included.

Reversibility of gonadotropin suppression

The data on peak gonadotropin (LH) concentrations for 5 patients who did not receive a second histrelin implant at Month 12 indicate that the suppression is reversible (summarized in **applicant's Table 18). All patients with data** at Month 13 had distinct increases in peak LH measurements[53].

[52] All patients (29 or 100%) had suppressed LH levels at Month 12 and Month 13; 58.6% had suppressed FSH levels at Month 12 and 62.1% at Month 13; all male patients (2) had suppressed testosterone levels at Months 12 and 13, respectively; all but one female patient had estradiol suppression at Month 12 and all at Month 13.
[53] Four of the 5 subjects did not receive a second implant because they reached an age appropriate for puberty while the 5th one (Subject 014) did not continue the study due to weight gain.

Table 18 Subjects Who Did Not Receive a Second Implant – LH Values

Subject ID	Month 12 LH (mIU/mL)	Month 13 LH (mIU/mL)
011	0.67	8.1
028	0.79	NA
034	0.78	8.5
014	1.7	16
030	0.78	6.7

Source: Listing 2.1

Integrated efficacy data across trials.

Table 7 integrates the efficacy data across trials 03-CPP-HIS-300 and 01-02-001. In order to find a way to integrate the efficacy data and to facilitate between-trial comparisons, the data from trial 03-CPP-HIS-300 has been separated for the treatment-naïve and the pre-treated groups. The data from trial 01-02-001 are presented only up to Month 9 (at this timepoint the original implant(s) was replaced with a new implant. The data displayed in Table 7 indicates that the peak LH, peak FSH and serum estrogen levels were maintained in pre-defined suppression range for the vast majority of patients up to Month 12.

Table 7: Percentage of patients with hormonal suppression in the treatment-naïve and the pre-treated group: clinical trials 03-CPP-HIS-300 and 01-02-001.

Study 03-CPP-HIS-300 Treatment-naïve patients (N =20) through Month 12						
	Baseline	Month 1	Month 3	Month 6	Month 9	Month 12
% Patients with LH suppression	0/20 (0%)	20/20 (100%)	20/20 (100%)	18/18 (100%)	19/19 (100%)	20/20 (100%)
% Patients with FSH suppression	0/20 (0%)	20/20 (100%)	18/20 (90%)	16/20 (80%)	14/20 (70%)	13/20 (65%)
% Patients with estrogen suppression	12/20 (60%)	20/20 (100%)	20/20 (100%)	18/18 (100%)	19/19 (100%)	17/18 (95%)
Study 03-CPP-HIS-300 Pre-treated patients (N=16) through Month 12						
	Baseline	Month 1	Month 3	Month 6	Month 9	Month 12
% Patients with LH suppression	14/16 (87.5%)	16/16 (100%)	16/16 (100%)	16/16 (100%)	16/16 (100%)	100%16/16 (100%)
% Patients with FSH suppression	10/16 (62.5%)	14/16 (87.5%)	13/16 (81.3%)	11/16 (68.8%)	9/16 (56.3%)	9/16 (56.3%)
% Patients with estrogen suppression**	13/13 (100%)	13/13 (100%)	13/13 (100%)	13/13 (100%)	13/13 (100%)	13/13 (100%)
Study 01-02-001 Pretreated patients (N=11) through Month 9						
	Baseline	Month 1	Month 3	Month 6	Month 9	Month 12
n/N (%) of patients with LH suppression	4/11 (36%)	*	*	10/10 (100%)	11/11 100%	NA
n/N (%) of patients with FSH suppression	10/11 (91%)	*	*	10/10 (100%)	11/11 100%	NA
n/N (%) of patients with estrogen suppression	10/11 (91%)	11/11 (100%)	10/11 (91%)	10/11 (91%)	11/11 (100%)	NA

NA = not applicable because implants were replaced at this timepoint. On a new implant, at Month 12 all six peak LH and FSH measurements were suppressed.

*Data not included in the table because the number of patients with data measured on trial for this timepoint was very limited (one measurement at Month 1 and 5 measurements at Month 3; all measurements at these timepoints were in the suppressed range.
**Only 13/16 patients were female.
Source: For Study 01-02-001: Post-text Listing 2.2 LH and FSF Assessments –Efficacy Population and Post-text Listing 2.1 - Hormone Assessments – Efficacy Population.
Source: For Study 03-CPP-HIS-300: Post-text Listing 2.1 LH and FSF Assessments –Efficacy Population and Post-text Listing 2.2 - Hormone Assessments – Efficacy Population.
N.B. Several measurements were slightly outside the specified timepoint.
N= number of patients within each group; n = number of patients with a particular measurement.

6.1.5 Clinical Microbiology

Not applicable (histrelin acetate is not an antimicrobial).

6.1.6 Efficacy Conclusions

Analysis of the histrelin acetate clinical program indicates that a 50-mg histrelin implant was effective in suppressing the biochemical and clinical manifestations of central precocious puberty in a vast majority of patients. The efficacy conclusions for the histrelin clinical program are summarized next by study.

6.1.6.1 Study 03-CPP-HIS-300

Effects on the pituitary-gonadal axis

- All patients showed LH suppression at the Month 3 timepoint (primary efficacy analysis). In fact, such suppression was observed for all patients at the first timepoint evaluated on trial (Month 1) and at all other timepoints through Month 12, inclusively[54].
- An examination of the mean peak LH data for the treatment-naïve and pretreated groups indicates that histrelin was efficacious for both groups; it suppressed the elevation in peak LH levels observed at baseline in treatment-naïve patients and maintained LH suppression in pretreated patients throughout the trial.
- Similar observations (albeit less dramatic) were seen for FSH measurements. For the treatment-naïve group the mean values of peak FSH serum concentrations declined in the suppressed range and stayed so for up to Month 12; for the pre-treated cohort they were maintained suppressed up to Month 6. The percentage of suppressed patients in both treatment-naïve and pretreated patients declined over time. By 12 months 65% of the treatment-naïve patients and 56% of the pre-treated patients had peak FSH values in the

[54] **Although patients were not formally 'washed out" of the previous GnRH analog, a potential carry-over effect is** not of significance in this situation because the primary analysis is conducted at a time (3 months) that exceeds any potential therapeutic effect of previous GnRH agonist medications and, most importantly, the effect in the treatment-naïve group was similar to that seen in the pretreated group.

suppressed range; these percentages, however, were comparable to those observed for the pre-treated group at baseline[55]. Overall, there was a trend that showed a discrete increase in mean FSH values with time[56].

- Gonadal suppression was achieved in most patients (33/36 patients were female and only 3 patients were male). For treatment-naïve patients the mean estrogen levels were reduced four-fold on histrelin (a statistically significant finding for all timepoints assessed) and were brought in the suppressed range for the whole duration of the trial. For pretreated patients the mean estrogen levels were maintained in the suppressed range. Responder analyses indicate that the vast majority of patients had suppressed estrogen levels on histrelin (all pretreated patients through Month 12 and all treatment-naïve patients through Month 9 [57]). All three male patients had suppressed testosterone levels throughout the trial.

Other efficacy analyses

The following efficacy analyses indicate, in general, a favorable effect of histrelin therapy on bone age progression, growth rate, clinical signs of puberty, and uterine/ovarian size:

- Bone age progression slowed down during Histrelin treatment (specifically, the mean bone age advancement was less than the chronological age advancement[58] and the bone age/chronological age ratio decreased on treatment for both treatment-naïve and pretreated patients[59]). Most patients (28/36 or 78%) had advances in bone age that were smaller than the changes in chronological age[60].
- The mean height velocity on treatment was approximately 5 cm/yr, which is consisted with a prepubertal growth rate.
- Although transabdominal ultrasounds were used to evaluate the size and structure of the uterus and ovaries[61], the lack of standardizations of the readings and the absence of a control group limits the ability to draw firm conclusions; at Month 12, uterine and ovarian volumes (for each ovary) were lower than baseline in 73% and 56.5 % of the study population, respectively.
- The vast majority of patients had either arrest or reduction in the progression of clinical signs of puberty as judged by the investigators (82% of girls and two out of the three boys). All cases of progression of Tanner staging of breast development were by no

[55] 62.5% of patients in the pretreated group had suppressed LH levels at baseline; in contrast none of the treatment-naïve patients were suppressed at the beginning of treatment.
[56] It should be recognized, however that LH and gonadal steroid suppression are the most important pharmacodynamic endpoints indicative of successful suppression.
[57] At Month 12 all but one of the treatment naïve patients (95 %) had estrogen suppression. One patient (037) had an estradiol level of 27 pg/mL at Month 12 (suppression was defined as < 20 pg/mL).
[58] Specifically the mean change in bone age over one year was 0.91 ± 0.5 years for treatment-naïve patients, 0.43 ± 0.39 years for the pre-treated patients and 0.70 ± 0.51 years for the two groups combined.
[59] For pre-treated patients it decreased from 1.33 ± 0.16 to 1.24 ± 0.13 (change of -0.09 ± 0.06; p<0.0001). For treatment-naïve patients it changed from 1.42 ± 0.17 to 1.34 ± 0.13 (change of -0.08 ± 0.08; p=0.0002). For the whole group combined it changed from 1.38 ± 0.17 to 1.29 ± 0.14 (change -0.08 ± 0.07, p<0.0001).
[60] All the patients who had higher BA changes were in the treatment naïve group (8/36 patients or 22%).
[61] Both uterus and ovaries are enlarged during CPP.

more than one Tanner stage and tended to occur earlier during the treatment (i.e. at Months 1-3).

6.1.6.2 Study 01-02-001

Effects on the pituitary-gonadal axis

- The mean values for the peak LH and FSH levels were suppressed on Histrelin treatment through Month 9 regardless whether patients had one or two implants (the data at Months 1 and 3 was sparse)[62]. The mean LH and FSH levels remained in the suppressed range for 6 patients who continued through Month 18 without replacement of the implant (s) suggesting that histrelin release continues for up to this time. LH and FSH suppression was present in all (100%) of patients at Month 6 and continued through Month 18[63].
- Through Month 9, 7/7 subjects with one implant (100%) had suppressed levels of estradiol and 3/4 (75%) of the patients who received two implants had suppressed serum estradiol levels at all timepoints[64]. All 6 patients who continued the original implant(s) up to Month 18 had suppressed estrogen levels.
- Overall, there were no clinically meaningful differences in estrogen, LH and FSH levels in this small group of patients whether they received one implant or two. It is important to recognize that patients were not randomized to the two regimens (one vs. two implants).

Other efficacy analyses

As noted in the Phase III clinical trial, histrelin implant had, in general, favorable effects on several other (secondary) measures of efficacy such as bone age progression, clinical signs of puberty, growth rate and uterine/ovarian volume:

- Progression of bone age slowed down during Histrelin treatment (the mean bone age advanced by 1 year relative to a chronological age advancement of 1.6 years and the bone age to chronological age ratio declined on treatment at Month 18[65]).

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[62] For this trial the criterion for peak LH suppression was ≤ 1 mIU/mL. The criterion for peak FSH suppression was ≤ 2.5 mIU/mL. The reason for which different thresholds were selected for LH suppression in Study 01-02-001 (≤ 1 mIU/mL) and Study 03-CPP-HIS-300 (≤ 4 mIU/mL) is related to the fact that gonadotropin testing (i.e. stimulation) was performed with different products that have different potencies (Factrel in the Phase II study and Lupron in the Phase III study).

[63] At baseline 36% of patients had LH suppression and 91% had FSH suppression, respectively.

[64] One patient had elevations above the pre-defined threshold of suppression of ≤ 20 pg/ml) at baseline (24.1 pg/ml), Month 3 (21.8 pg/mL) and Month 6 (22.2, pg/mL); this patient who terminated early the clinical trial due to a wound infection, had suppressed LH basal levels at the time of estrogen elevation.

[65] Inspection of individual patient data indicates that all but three patients had advances in CA exceeding advances in BA; in those few cases when radiographical assessment in BA exceeded the changes in CA such changes were small and comparable.

- Height velocity SD scores during the trial were negative indicating below average growth rates; the mean HV at 9 months of 4.6 cm indicates a prepubertal growth rate.
- Although transabdominal ultrasounds were used to evaluate the size and structure of the uterus and ovaries, the small size of the group, the lack of standardizations of the readings and the absence of a control group, limits the ability to draw firm conclusions.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

7.1.1.1 Study 01-02-001

There were no deaths reported in this trial.

7.1.1.2 Study 03-CPP-HIS-3000

There were no deaths reported in this trial.

7.1.2 Other Serious Adverse Events

7.1.2.1 Study 01-02-001

There were no serious adverse events reported in this trial.

7.1.2.2 Study 03-CPP-HIS-300

Two patients experienced one serious adverse event (SAE) each. They were amblyopia (judged **by the investigator to be "unlikely related" to the study drug), and a benign pituitary tumor ("possibly related").**

Patient 001, a 7.4-year-old female naive to GnRH therapy, was diagnosed with moderate myopia approximately 4 months after starting Histrelin treatment. On a subsequent, routine eye examination she was noticed to have moderate bilateral iritis, high refractive error, and severe bilateral amblyopia. After a fluorescein angiogram, which revealed macular dystrophy and a dark choroid effect, she was diagnosed **with Stargardt's disease in both eyes**[66]. The patient was treated with tapering topical prednisolone drops and a prescription for eyeglasses. Study

[66] **Stargardt's disease is an inheritid condition, one of the** most common forms of juvenal macular degeneration.

participation was not discontinued and she completed 12 months of therapy with the initial implant, and subsequently received a second implant.

Patient 028 was a 9.5-year-old female who has been treated for 7 years for CPP prior to enrollment in the trial. Approximately 4 months within Histrelin treatment she had an MRI as part of the work up for headaches and vertigo, which identified a benign pituitary tumor (microadenoma). The patient continued therapy with study drug and completed 12 months of Histrelin treatment. She did not receive a second implant.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

There was only one patient who discontinued the trial (See section 7.1.3.2)

7.1.3.2 Adverse events associated with dropouts

7.1.3.2.1 Study 01-02-001

One patient discontinued trial participation due to an adverse event. She was a 10-year-old girl who developed an infection at the implant insertion site approximately 10 days after a scheduled implant replacement. This infection was initially treated with antibiotics but ten days later the implant had to be removed when it was found to be extruded from the incision site. The patient withdrew from the study. The cause of withdrawal was listed as wound infection which was rated **"mild" and "definitely related to study treatment" by the investigator.**

7.1.3.2.2 Study 03-CPP-HIS-300

The applicant does not report any subjects who discontinued due to adverse events during this 12- month trial.

7.1.3.3 Other significant adverse events

None.

7.1.4 Other Search Strategies

Due to the small size of the clinical trial no additional search strategies were employed.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were collected at Months 1, 3, 6, 9, 12, 15 and 18 in Study 01-02-001. In Study 03-CPP-HIS-300 adverse events were evaluated at Months 1, 3, 6, 9, 12 and 13 (in the extension phase they are to be evaluated at Months 15, 18, 21 and 28). They were recording in specific sections of the CRF. MedDRA Version 7.1 was used to classify all adverse events with respect to preferred term and system organ class (SOC). Adverse events collected in the study were classified by severity and relationship to the study medication. In general, the safety measurements included in the study were standard for studies of investigational drugs.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

A visual sampling of Adverse Event Post-text Listings 3.1.1 revealed consistent and appropriate concordance between verbatim and preferred terms.

7.1.5.3 Incidence of common adverse events

7.1.5.3.1 Study 01-02-001

Eight of the 11 subjects enrolled (72.7%) reported at least an adverse event during the study. All adverse events were reported as mild in intensity. Overall 4 of the 11 subjects (36.4%) reported implant insertion site AEs **(preferred terms: "application site pain", "implant site irritation", "implant site reaction" and "wound infection")**[67]**. All were judged "treatment-related" by the** investigator. The only other AEs which were deem**ed treatment-related were "disease progression" and "influenza-like illness" (one patient or 9.1% each).** There was no evidence that patients with one or two implants had different patterns of adverse events. Most other TEAEs represented common background childhood illnesses or signs/symptoms. A**pplicant's Table 17 summarizes the number** and percentage of patients with adverse events and treatment-related adverse events observed during the trial.

[67] Preferred and verbatim terms were as follows: (i.e., application site pain [pain and discomfort at implant area], implant site irritation [itching at implant insertion location], implant site reaction [implant area protruding], and wound infection).

Table 17 Adverse Events – All Treated Subjects

	Histrelin Implant(s)	
Number of treated subjects	11	
Number of subjects with ≥1 AE	8 (72.7)	
	All AEs	Treatment-Related AEs
Application site pain	2 (18.2)	2 (18.2)
Abdominal pain	1 (9.1)	0
Alopecia	1 (9.1)	0
Bronchitis	1 (9.1)	0
Disease progression	1 (9.1)	1 (9.1)
Headache	1 (9.1)	0
Implant site irritation	1 (9.1)	1 (9.1)
Implant site reaction	1 (9.1)	1 (9.1)
Influenza	1 (9.1)	0
Influenza like illness	1 (9.1)	1 (9.1)
Pain in extremity	1 (9.1)	0
Pharyngitis	1 (9.1)	0
Rash pustular	1 (9.1)	0
Streptococcal infection	1 (9.1)	0
Wound infection	1 (9.1)	1 (9.1)

[a] A subject may have reported more than 1 AE.
NOS=not otherwise specified
Source: Tables 3.1.1 and 3.1.3; Listing 3.1

The applicant provides the following narratives for several patients who experienced complications related to the implant insertion and/or removal process that were not captured as adverse events. They included the following:

Patient ID (No. of implants)	Event
101 (2)	Ultrasound was necessary in order to locate the implant prior to removal.
103 (2)	Infection and partial extrusion of the implant (patient discontinued the study).
105 (2)	Implant was unintentionally perforated during suturing at insertion time and had to be removed.
108 (1)	Implant breakage during its removal; residual implant piece required subsequent removal under sedation in the operating room; another residual piece of implant still suspected (patient being under evaluation).
111 (2)	Implants remained in place for 27 months (reason not provided).

Source: Text in Study Report for Study 01-02-001.

7.1.5.3.2 Study 03-CPP-HIS-300

Treatment-emergent adverse events

All subjects had at least one treatment-emergent adverse event. The vast majority of TEAEs were mild or moderate in intensity. The only TEAEs reported as severe the already described SAEs (amblyopia and pituitary adenoma), and migraine headache (judged as "possibly related" to the treatment by the investigator), which occurred in the same patient with pituitary adenoma. (patient 028). Three patients had episodes of vaginal bleeding: an 8.9 year-old treatment-naïve patient (026) had dysmenorrhea of moderate intensity and menorrhagia of mild intensity that each lasted one day, and two pretreated girls (021 and 031) reported intermittent spotting of mild intensity within 1-2 months after implant insertion that resolved within 2 or 3 day. Most other

TEAEs represented common background childhood illnesses or signs/symptoms. The TEAEs recorded on trial in ≥ 2 patients are summarized in applicant's **Table 22. Implant site reaction** was the most frequently reported TEAEs.

Table 22 Adverse Events That Occurred in ≥2 Subjects Overall – All Treated Subjects

	Pre-treated N=16 n (%)	Naive N=20 n (%)	All Subjects N=36 n (%)
Subjects with >1 AE	16 (100)	20 (100)	36 (100)
Implant Site Reaction	9 (56.3)	13 (65.0)	22 (61.1)
Upper Respiratory Tract Infection	3 (18.8)	8 (40.0)	11 (30.6)
Headache	5 (31.3)	4 (20.0)	9 (25.0)
Pyrexia	3 (18.8)	6 (30.0)	9 (25.0)
Vomiting	4 (25.0)	5 (25.0)	9 (25.0)
Cough	3 (18.8)	2 (10.0)	5 (13.9)
Epistaxis	3 (18.8)	1 (5.0)	4 (11.1)
Ear Infection	1 (6.3)	2 (10.0)	3 (8.3)
Keloid Scar	2 (12.5)	1 (5.0)	3 (8.3)
Nasal Congestion	1 (6.3)	2 (10.0)	3 (8.3)
Pharyngolaryngeal Pain	2 (12.5)	1 (5.0)	3 (8.3)
Scar	2 (12.5)	1 (5.0)	3 (8.3)
Sinusitis	1 (6.3)	2 (10.0)	3 (8.3)
Suture Related Complication	2 (12.5)	1 (5.0)	3 (8.3)
Urticaria	1 (6.3)	2 (10.0)	3 (8.3)
Weight Increased	2 (12.5)	1 (5.0)	3 (8.3)
Abdominal Pain Upper	1 (6.3)	1 (5.0)	2 (5.6)
Anxiety	0	2 (10.0)	2 (5.6)
Conjunctivitis	1 (6.3)	1 (5.0)	2 (5.6)
Erythema	1 (6.3)	1 (5.0)	2 (5.6)
Fatigue	0	2 (10.0)	2 (5.6)
Influenza	1 (6.3)	1 (5.0)	2 (5.6)
Injection Site Pruritus	1 (6.3)	1 (5.0)	2 (5.6)
Menorrhagia	0	2 (10.0)	2 (5.6)
Metrorrhagia	2 (12.5)	0	2 (5.6)
Migraine	2 (12.5)	0	2 (5.6)
Mood Swings	0	2 (10.0)	2 (5.6)
Multiple Allergies	0	2 (10.0)	2 (5.6)
Nasopharyngitis	0	2 (10.0)	2 (5.6)
Pharyngitis Streptococcal	1 (6.3)	1 (5.0)	2 (5.6)
Post Procedural Pain	1 (6.3)	1 (5.0)	2 (5.6)
Rash	2 (12.5)	0	2 (5.6)
Rhinitis	0	2 (10.0)	2 (5.6)
Seasonal Allergy	0	2 (10.0)	2 (5.6)
Tonsillitis	1 (6.3)	1 (5.0)	2 (5.6)
Upper Respiratory Tract Congestion	0	2 (10.0)	2 (5.6)
Wrist Fracture	2 (12.5)	0	2 (5.6)

Source: Table 3.1.1; Listing 3.1.1

Drug-related adverse events

The incidence of adverse events that were deemed treatment-related by the investigator is **summarized in applicant's Table 23. Overall, twen**ty-two (61.1%) of patients experienced one or more adverse events with injection-site reactions (18 patients or 50%) being the most frequent ones (preferred terms: discomfort, bruising, soreness, pain, tingling, or swelling). TEAEs reported in two patients (5.6 %) were metrorrhagia, suture related complication, and scar. Others TEAEs reported in only one patient (2.8%) were: breast tenderness, dysmenorrhea, epistaxis,

erythema, feeling cold, gynecomastia, headache, keloid scar, menorrhagia, migraine, mood swings, benign pituitary tumor, pruritus, and increased weight.

Table 2.7.4.2.1.1.2 – 2 Summary of Treatment-related Adverse Events in the Phase III Study

	Pre-treated Subjects N=16 n (%)	Naive Subjects N=20 n (%)	TOTAL Subjects N=36 n (%)
Subjects With At Least 1 Treatment-Related AE	9 (56.3)	13 (65.0)	22 (61.1)
Implant Site Reaction	6 (37.5)	12 (60.0)	18 (50.0)
Metrorrhagia	2 (12.5)	0 (0.0)	2 (5.6)
Scar	1 (6.3)	1 (5.0)	2 (5.6)
Suture Related Complication	2 (12.5)	0 (0.0)	2 (5.6)
Breast Tenderness	0 (0.0)	1 (5.0)	1 (2.8)
Dysmenorrhoea	0 (0.0)	1 (5.0)	1 (2.8)
Epistaxis	1 (6.3)	0 (0.0)	1 (2.8)
Erythema	0 (0.0)	1 (5.0)	1 (2.8)
Feeling Cold	1 (6.3)	0 (0.0)	1 (2.8)
Gynaecomastia	1 (6.3)	0 (0.0)	1 (2.8)
Headache	1 (6.3)	0 (0.0)	1 (2.8)
Keloid Scar	1 (6.3)	0 (0.0)	1 (2.8)
Menorrhagia	0 (0.0)	1 (5.0)	1 (2.8)
Migraine	1 (6.3)	0 (0.0)	1 (2.8)
Mood Swings	0 (0.0)	1 (5.0)	1 (2.8)
Pituitary Tumour Benign	1 (6.3)	0 (0.0)	1 (2.8)
Pruritus	0 (0.0)	1 (5.0)	1 (2.8)
Weight Increased	0 (0.0)	1 (5.0)	1 (2.8)

Source: Section 5.3.5.2 Study 03-CPP-HIS-300, Table 3.1.2, Listing 3.1.1
Note: A treatment-related AE was defined as *possibly*, *probably*, or *definitely* related according to the investigator.

The applicant provides narratives for 11 subjects who had events related to the implant insertion or removal process that were either unexpected or were considered to be an adverse event. They included the following:

Patient ID	Event
001	Insertion was not successful with a trocar and the implant had to be manually inserted. Local bruising and soreness with the second implant.
009	The implant was partially broken during removal.
018	The capsule of the implant was fractured during the removal procedure.
003	The implant had to be manually inserted (patient was obese with a BMI of 26.6 mg/kg.). Implant removal required ultrasound in order to locate it and general anesthesia for actual removal.
012	Implant was noted to have a crack upon removal.
028	Implant had to be located by ultrasound at time of removal. Implant was found to be fractured.
027	Insertion was not successful with a trocar and the implant had to be manually inserted. Upon removal only a segment of the implant was actually removed. A decision was made to leave the first implant in and to remove it completely at the time of the second implant removal.
014	Difficulty fitting the implant in the trocar; prolonged insertion time. Implant was removed with some difficulty in two pieces.

023	Difficulty releasing the implant from the trocar during insertion and the implant had to be manually inserted. Keloid scar around the implant; the implant was removed in multiple pieces. One piece may not be accounted for.
037	Implant was removed in several pieces.
021	Implant was removed in several pieces.

Source: Text in Study Report for Study 03-CPP-HIS-300.

7.1.5.4 Common adverse event tables

Refer to Section 7.1.5.4.

7.1.5.5 Identifying common and drug-related adverse events

Adverse events related to the implant site, placement or removal of the implant were clearly the most common drug-related adverse events (see Section 7.1.5.3 for details).

7.1.5.6 Additional analyses and explorations

Due to the small size of the datasets no additional analyses and explorations were conducted.

7.1.6 Less Common Adverse Events

There was no specific pattern of "less common" adverse events. For the Study 01-02-001 refer to Section 7.1.5.3 for a list of adverse events that occurred in only one patient. Adverse events that occurred in only one patient in Study 03-CPP-HIS-300 were collected under the following terms: abdominal pain, acne, adenoidal disorder, affect lability, amblyopia, arthralgia, attention deficit/hypperactivity disorder, breast tenderness, bronchitis, cardiac murmur, constipation, cranioplasty, cystitis,depression, dermatitis allergic, diarrhea, dizziness, dry skin, dysmenorrhea, erythema multiforme, eye redness, feeling cold, fungal infection, growing pains, gynecomastia, hematoma, hypertrophy breast, induration, infectious mononucleosis, injection site reaction, iritis, kudney infection, liver function test abnormal, lower respiratory tract infection, myalgia, myopia, nausea, nodule, otitis externa, pituitary tumor benign, pruritus, rash popular, respiratory tract congestion, rhinorrhea, sinus congestion, skin odor abnormal, skin papilloma, swelling, trichorrhexis, upper limb fracture, urinary tract infection, vaginal discharge, vertigo, and viral infection.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory evaluations included standard analytes (standard hematology[68] and chemistry[69] analytes, urinalysis) as well as the following hormonal assessments: TSH, prolactin, T4, IGF-I, and IGFBP-3. Laboratory testing was done centrally.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

None of the Phase II and Phase III studies had a control group.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

7.1.7.3.1.1 Study 01-02-001

Hematology

Descriptive statistics for the main hematology analytes are presented in Table 8. There were no clinically meaningful changes in any of the hematology analytes analyzed.

Table 8: Mean hematology values in the Phase II study

Variable	Baseline	Month 9	Change from baseline to Month 9	Month 18	Change from baseline to Month 18
WBC (k/uL)					
N	11	11	11	10	10
Mean ±SD	6.68±1.81	6.57±1.76	-0.11±1.55	6.52±1.25	0.01±1.40
RBC (M/uL)					
N	11	11	11	10	10
Mean ±SD	4.74±0.37	4.71±0.34	-0.03±0.28	4.69±0.26	0.02±0.31
Hb (g/dL)					
N	11	11	11	10	10
Mean ±SD	12.86±0.89	12.60±0.67	-0.26±0.61	12.82±0.70	0.04±0.83
HTC (%)					
N	11	11	11	10	10
Mean ±SD	36.98±2.80	36.75±2.27	-0.24±2.18	37.10±2.09	0.42±2.97
Platelets (K/uL)					
N	11	11	11	10	10
Mean ±SD	267.73±68.16	279.36±87.50	11.64±48.86	268.70±56.48	10.40±26.84

[68] Hemoglobin, hematocrit, red blood cell count, total white blood cell count, differential count, and platelet count.
69 Albumin, blood urea nitrogen, creatinine, AST, alkaline phosphatase, globulin, total bilirubin, total protein, uric acid, lactic dehydrogenase, glucose, calcium, phosphorus, and total cholesterol.

Neutrophils (%)					
N	11	11	11	10	10
Mean ±SD	44.52±8.98	42.54±9.97	-1.98±8.14	42.91±10.90	-0.89±7.85
Lymphocytes (%)					
N	11	11	11	10	10
Mean ±SD	43.67±8.39	44.75±10.13	1.07±6.87	44.88±9.12	0.70±6.04
Monocytes (%)					
N	11	11	11	10	10
Mean ±SD	7.01±1.22	7.66±1.26	0.65±1.41	7.29±1.67	0.28±2.26
Eosinophils (%)					
N	11	11	11	10	10
Mean ±SD	4.45±2.73	4.45±2.55	0.01±1.95	4.54±3.33	-0.16±2.18
Basophils (%)					
N	11	11	11	10	10
Mean ±SD	0.35±0.22	0.60±0.44	0.25±0.58	0.38±0.19	0.07±0.25

Source: Table 2.7.4.3.1.1-1

Clinical chemistry

The mean clinical chemistry values at Months 9 and 18 and the mean changes to these timepoints **are presented in applicant's Table 2.7.4.3.1.1-2.** There were no clinically meaningful changes for the timepoints analyzed.

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Table 2.7.4.3.1.1 - 2 Mean Clinical Chemistry Values in the Phase II Study

Lab Parameter	Baseline Visit 1 (Day 1)	Visit 5 (Month 9)	Change from Baseline to Visit 5	Visit 8 (Month 18)	Change from Baseline to Visit 8
Statistic	n				
	mean±S.D.				
Glucose (mg/dL)	11	11	11	10	10
	87.67±12.65	81.89±16.52	-5.78±19.28	83.46±8.43	-4.03±15.07
Calcium (mg/dL)	11	11	11	10	10
	9.94±0.31	10.15±0.39	0.22±0.41	9.86±0.22	-0.09±0.32
Phosphorus (mg/dL)	11	11	11	10	10
	4.89±0.85	4.78±0.42	-0.11±0.62	4.81±0.66	-0.13±0.74
Urea (mg/dL)	11	11	11	10	10
	23.55±5.48	24.07±4.35	0.53±5.47	26.03±5.44	3.46±7.02
Creatinine (mg/dL)	11	11	11	10	10
	0.45±0.10	0.52±0.11	0.06±0.07	0.56±0.10	0.11±0.06
Uric Acid (mg/dL)	11	11	11	10	10
	3.82±0.98	3.91±1.24	0.09±0.65	3.73±0.50	0.12±0.56
LDH (U/L)	10	11	10	10	9
	406.20±77.43	418.09±83.86	22.30±90.16	424.10±98.52	29.22±69.11
AST (GOT) (U/L)	10	11	10	10	9
	25.10±7.28	23.82±7.73	-0.60±5.08	21.50±5.42	-1.89±4.31
Alkaline Phosph (U/L)	11	11	11	10	10
	233.00±16.37	221.82±52.13	-11.18±54.70	230.40±57.95	-1.00±57.07
T. Bilirubin (mg/dL)	11	11	11	10	10
	0.43±0.15	0.40±0.12	-0.03±0.15	0.42±0.10	0.00±0.11
T. Protein (g/dL)	11	11	11	10	10
	7.35±0.55	7.42±0.54	0.07±0.45	7.18±0.43	-0.13±0.19
Albumin (g/dL)	11	11	11	10	10
	4.15±0.24	4.31±0.29	0.16±0.28	4.42±0.17	0.28±0.29
Globulin (g/dL)	11	11	11	10	10
	3.21±0.48	3.12±0.38	-0.09±0.40	2.76±0.35	-0.41±0.36
T. Cholesterol (mg/dL)	11	11	11	10	10
	157.15±24.74	162.23±30.61	5.07±25.48	162.02±22.54	3.68±21.05
ALT (GPT) (U/L)	1	4	0	3	0
	13.00	32.75±35.54		16.67±2.89	
Triglycerides (mg/dL)	0	4	0	3	0
		89.88±46.71		65.43±7.21	

Source: Section 5.3.5.2 Study 01-02-001, Table 3.2.2.1

Hormone evaluations (T4, TSH, prolactin)

The mean levels of free T4, TSH and prolactin at baseline, Month 9 and Month 18, as well as the **mean changes from baseline to these timepoints, are summarized in applicant's Table** 2.7.4.4.3.1-1. All subjects were reported to have TSH, free T_4 levels in the normal range on treatment. There were minimal changes in mean T_4 and TSH values. This change is unlikely to be clinically significant[70].

7.1.7.3.1.2 Study 03-CPP-HIS-300

Hematology

[70] Isolated prolactin deficiency is associated with puerperal alactogenesis. Although it has been suggested that prolactin is also an immunoregulatory hormone (prolactin receptors have been found on T lymphocytes and B lymphocytes, there is no evidence to support that prolactin deficiency is associated with an immunodeficient state.

Descriptive statistics for hematology analytes (hematocrit, hemoglobin, red blood cell and white blood cell counts) at baseline through Months 12 are **presented in applicant's Table 2.7.4.3.2.1-1.** There were no clinically meaningful changes in mean values for any of the analytes.

Table 2.7.4.3.2.1 - 1 Mean Hematology Values in the Phase III Study

	Baseline at Screening	Visit 6 (Month 12)	Change from Baseline To Visit 6
Statistic	n		
Lab Parameter	mean±S.D		
Hematocrit (%)	35	31	30
	37.63±2.89	37.01±2.95	-0.45±2.45
Hemoglobin (g/dL)	35	31	30
	12.95±0.99	12.59±1.13	-0.31±0.79
Platelet Count (10^3/µL)	35	31	30
	315.06±71.07	315.94±62.88	4.40±49.81
Red Blood Cells (10^6/µL)	35	31	30
	4.47±0.41	4.40±0.33	-0.03±0.26
White Blood Cells (10^3/µL)	35	31	30
	6.79±1.79	6.29±2.11	-0.60±2.18

Source: Section 5.3.5.2 Study 03-CPP-HIS-300, Table 3.2.1.1

Clinical chemistry

Descriptive statistics for clinical chemistry analytes (albumin, alkaline phosphatase, ALT, AST, BUN, Ca, creatinine, serum glucose, LDH, phosphorus, total bilirubin, total protein, and uric acid) at baseline through Months 12 are presented **in applicant's Table 2.7.4.3.2.1. There were** no clinically meaningful changes in mean values for any of the analytes.

Table 2.7.4.3.2.1 - 2 Mean Clinical Chemistry Values in the Phase III Study

	Baseline at Screening	Visit 6 (Month 12)	Change from Baseline To Visit 6
Statistic	n		
Lab Parameter	mean±S.D.		
Albumin (g/dL)	36	31	31
	4.16±0.29	4.17±0.30	0.01±0.29
Alkaline Phosphatase (IU/L)	36	31	31
	255.14±87.92	212.94±63.51	-29.42±53.94
ALT (SGPT) (IU/L)	33	31	28
	17.67±4.32	18.97±7.68	0.93±7.50
AST (SGOT) (IU/L)	33	31	28
	26.42±5.49	24.74±4.99	-1.46±5.59
Blood Urea Nitrogen (mg/dL)	36	31	31
	10.14±3.03	10.03±2.02	0.29±3.93
Calcium (ISE) (mg/dL)	36	31	31
	9.79±0.34	9.69±0.36	-0.10±0.28
Creatinine (mg/dL)	36	31	31
	0.46±0.10	0.52±0.10	0.05±0.07
Glucose, Serum (mg/dL)	36	31	31
	92.36±11.23	85.77±11.08	-6.97±17.86
LDH (IU/L)	33	29	26
	177.15±35.72	175.55±35.51	-3.92±31.09
Phosphorous (mg/dL)	36	31	31
	4.98±0.51	5.02±0.56	0.09±0.55
Total Bilirubin (mg/dL)	36	31	31
	0.63±0.22	0.68±0.31	0.05±0.28
Total Protein (g/dL)	36	31	31
	6.89±0.44	6.88±0.47	-0.04±0.24
Uric Acid (mg/dL)	36	31	31
	4.01±1.02	4.21±0.82	0.20±0.80

Source: Section 5.3.5.2 03-CPP-HIS-300, Table 3.2.2.1

Hormone evaluations (T_4, TSH, DHEA)

As seen in the Phase II trial 01-02-001 there were only minimal changes from baseline to Month 12 in mean values for T^4 and TSH. There were, however elevations in mean DHEA levels, which increased by about 1/3. The applicant comments **that "high values are not unexpected in this** population, as DHEA is a precursor of the sex steroids." **The significance, if any, of this finding** is not clear.

Table 2.7.4.4.3.2 - 1 Mean DHEA Sulphate, FreeT4, and TSH Values in the Phase III Study

Lab Parameter	Baseline at Screening	Visit 6 (Month 12)	Change from Baseline To Visit 6
Statistic	n mean±S.D.		
DHEA Sulfate (µg/dL)	35	36	35
	52.66±38.22	72.58±48.74	20.97±26.32
Free T4 (ng/dL)	36	10	10
	1.32±0.29	1.40±0.38	0.08±0.39
TSH (µU/mL)	36	36	36
	1.44±0.70	1.74±0.75	0.30±0.85

Source: Section 5.3.5.2 Study 03-CPP-HIS-300, Table 3.2.4.1

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.7.3.2.1 Study 01-02-001

There were few out of range hematology and clinical chemistry analytes. Most were borderline elevations or reductions. A few patients had occasional elevations in LDH (all were < 2X ULN).

7.1.7.3.2.2 Study 03-CPP-HIS-3000

Hematology

There were several out of range values for standard hematology analytes:

- eleven WBC measurements in 9 patients were below the lower limit of normal. Most were relatively minor deviations (i.e. above 3,500/µL). One measurement (patient 037) was 2,800/µL at Month 12 but 3,900/µL at subsequent measurement at Month 13.
- there were no abnormally low platelet counts; 11 elevated measurements of platelet count of no clinical significance were noted in 7 patients.
- several hemoglobin measurements were minimally below the lower limit of the normal range (the lowest one was 10.8 mg/dL); for two patients the low Hb values were reported at about the time of adverse events of metrorrhagia (Patient 031) and menorrhagia (Patient 037).

Clinical chemistry

There were several out of range values for standard clinical chemistry analytes:

- all three abnormal LDH values were mild out of range deviations
- all above normal serum glucose measurements were mild elevations; there were only three elevations ≥ 120 mg/dL (120 mg/dL, 123 mg/dL and 121 mg/dL, respectively) in individual patients; there were no instances of hypoglycemia
- there were 20 out of range phosphorus measurements in 17 patients, representing mostly minimal deviations from normal; the three lowest one swere 3.9 mg/dl, 3.5 mg/dl and 3.9 mg/dl, each in a different patient; the highest ones were 6 mg/dl in two different patients
- total bilirubin was minimally elevated in two patients: 1.4 mg/dl (patient 024) and 1.5 (patient 014)
- one patient (019) had an ALT elevation of 55 IU (< 2X ULN) at Month 12 followed by an elevation of 167 IU/L (approximately 3 X ULN) one month later; there were accompanying but less pronounced elevations in AST at these timepoints (39 IU/L at Month 12 and 100 IU/L at Month 13, respectively); the patient was on both on Depakote and Tegretol treatment for a seizure disorder; the investigator identified this change as an **AE and deemed it elevation "unlikely to be related to the study drug";**
- there were two borderline elevations in AST in two different patients
- five patients had small elevations in alkaline phosphatase (four of them at screening)
- there were three mild, above normal uric acid elevations and a few occasional borderline reductions in albumin or total protein
- there were no cases of increased serum creatinine concentrations

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

There were no marked outlier measurements and no dropouts for abnormalities in hematology and clinical chemistry analytes in either study.

7.1.7.4 Additional analyses and explorations

7.1.7.5 Special assessments

Due to the small size of the datasets no additional analyses were conducted.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Standard measurements of vital signs were completed at each study visit (see schedule of events in Section 6.1.3)

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

None of the two clinical studies included in this submission included a control group.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

7.1.8.3.1.1 Study 01-02-001

As illustrated by applicant's Table 2.7.4.4.1.1-1 there were no clinically meaningful changes in mean values for blood pressure and heart rate.

Table 2.7.4.4.1.1 - 1 Mean Blood Pressure and Heart Rate Values in the Phase II Study

Parameter / Visit	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)
Statistic	n mean±S.D.		
Baseline [Day 1 (Visit 1)]	11	11	11
	112.27±9.03	62.27±11.14	90.55±17.69
Month 9 (Visit 5)	11	11	11
	107.91±12.49	64.45±10.50	86.36±10.20
Month 18 (Visit 8)	10	10	10
	105.70±11.12	59.30±11.69	72.70±11.15

Source: Section 5.3.5.2 Study 01-02-001, Table 3.3

7.1.8.3.1.2 Study 03-CPP-HIS-3000

Descriptive statistics for vital signs (systolic and diastolic blood pressure, heart rate, height and **weight) are presented in applicant's Table 3.3. There were no clinically meaningful changes in** mean vital signs measurements and no outliers on-treatment for up to 12 months. As expected height and weight increased as children grew.

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Post-text Table 3.3
Summary Statistics On Vital Signs
Safety Population

	Statistics	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)	Height (cm)	Weight (kg)
Day 1 (Visit 1)	N	36	36	36	36	36
	Mean±S.D.	108.50±10.54	64.08±8.82	88.97±13.82	135.74±14.87	39.10±13.28
	Median	109.00	65.00	88.00	137.25	38.30
	Min, Max	87.00 , 130.00	43.00 , 84.00	62.00 , 131.00	105.90 , 178.30	18.80 , 78.20
Month 1 (Visit 2)	N	36	36	36	35	35
	Mean±S.D.	108.03±10.70	62.50±6.88	92.53±14.49	136.55±14.75	39.92±13.64
	Median	106.50	60.00	91.50	137.50	38.80
	Min, Max	85.00 , 128.00	49.00 , 78.00	57.00 , 129.00	105.90 , 178.50	19.40 , 78.80
Month 3 (Visit 3)	N	36	36	36	36	36
	Mean±S.D.	108.72±9.08	63.92±7.26	90.33±16.59	137.01±14.83	40.94±13.54
	Median	109.00	65.00	89.00	137.30	39.75
	Min, Max	86.00 , 137.00	46.00 , 76.00	52.00 , 115.00	106.40 , 178.50	20.50 , 79.00
Month 6 (Visit 4)	N	36	36	36	36	36
	Mean±S.D.	108.06±8.81	63.72±7.76	91.64±17.80	138.41±14.64	42.44±13.57
	Median	108.50	61.00	91.00	138.90	40.00
	Min, Max	91.00 , 129.00	45.00 , 84.00	56.00 , 140.00	107.70 , 181.50	20.70 , 76.10
Month 9 (Visit 5)	N	36	36	36	36	36
	Mean±S.D.	110.06±10.77	63.36±7.74	86.28±15.73	139.64±14.45	44.21±13.87
	Median	110.00	63.50	84.00	140.10	42.15
	Min, Max	87.00 , 132.00	46.00 , 85.00	54.00 , 123.00	108.70 , 182.10	21.90 , 79.80
Month 12 (Visit 6)	N	36	36	36	36	36
	Mean±S.D.	108.64±11.52	65.14±9.39	87.53±13.47	141.38±13.82	45.34±13.88
	Median	110.50	66.00	86.00	141.30	43.15
	Min, Max	83.00 , 133.00	48.00 , 81.00	55.00 , 112.00	111.70 , 183.40	23.50 , 82.00

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Refer to Section 7.1.8.3.2. There were no outlier measurements in either study.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Refer to Section 7.1.8.3.2. There were no marked outlier measurements and no dropouts for vital signs in either study.

7.1.8.4 Additional analyses and explorations

None done.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECGs were not evaluated in either of the clinical trials

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

See section 7.1.9.1.

7.1.9.3 Standard analyses and explorations of ECG data

See section 7.1.9.1.

7.1.9.3.1 Analyses focused on measures of central tendency

See section 7.1.9.1.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

See section 7.1.9.1.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

See section 7.1.9.1.

7.1.9.4 Additional analyses and explorations

See section 7.1.9.1.

7.1.10 Immunogenicity

Immunogenicity was not evaluated in either trials. The active moiety of the implant (histrelin acetate) is an approved drug product. The medical literature on the immunogenicity of GnRH agonists is extremely limited; to date the immunogenicity of GnRH agonists has not been reported as a safety concern[71].

7.1.11 Human Carcinogenicity

The active moiety of the implant (histrelin acetate) is an approved drug product.

[71] Hager S et al: Gonadotropin-releasing hormone analogue treatment for precocious puberty. Twenty years of experience. Endocr Dev 8, 94-125, 2005.

7.1.12 Special Safety Studies

None.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Given the known mechanism of action of histrelin and the experience accumulated with GnRH agonists over the last 20 years, there is no concern of dependence or withdrawal symptoms with this drug product.

7.1.14 Human Reproduction and Pregnancy Data

There were no pregnancies reported during either clinical trial.

7.1.15 Assessment of Effect on Growth

Effects on growth were secondary analyses of efficacy (refer to Section 6.1.4). Histrelin acetate is expected to slow down growth rates through suppression of gonadal steroids.

7.1.16 Overdose Experience

There were no cases of overdose described in either clinical trial.

7.1.17 Postmarketing Experience

The histrelin implant has not been marketed to date in children with CPP. A very similar, once-yearly histrelin implant is approved for the palliative treatment of advanced prostate cancer in adults. The two patient populations (children with CPP and aged men with prostate cancer) are so different that attempts to extrapolate the adverse event profile from adults to children would be speculative. The only exception is represented by adverse events related to the implant insertion, removal and the implant site. This issue has been discussed at the December 7, 2005 pre-NDA meeting. The sponsor indicated at that time that the incidence of extruded implants in adults decreased in the postmarketed phase to approximately 0.5% from 4% in the original studies; the reduction was ascribed to improved insertion technique.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Refer to Section 6.1.3 for clinical study design description.

7.2.1.2 Demographics

Refer to Section 6.1.3

7.2.1.3 Extent of exposure (dose/duration)

In clinical trial 01-02-001 eleven patients were treated between 11.4 and 20.7 months; some patients received a single 50 mg implant; others had two 50-mg implants. In Study 03-CPP-HIS-300 thirty-six patients were treated for approximately 12 months (mean: 362.90±10.04 days; range: 336.00 to 381.00 days).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

There were no secondary sources of clinical information for this NDA regarding the CPP indication.

7.2.2.2 Postmarketing experience

Histrelin implant has not been marketed in children.

7.2.2.3 Literature

There is only one clinical trial published to date regarding the use of the histrelin implant in children. Hirsch HJ et al (Pediatrics, Vol. 116, No.6, 2005) described the clinical experience accumulated with 11 girls treated with histrelin implant; this publication summarizes data from the trial 01-02-001 described in this NDA.

7.2.3 Adequacy of Overall Clinical Experience

Taking into consideration that the active pharmaceutical ingredient in the histrelin implant is an already approved drug substance, the clinical experience provided in studies 03-CPP-HIS-300 and 01-02-001 was adequate to evaluate the efficacy and safety of this new drug product. Since the active moiety from the histrelin implant is already approved, the major focus of this clinical program has been to prove that this new way of delivery (i.e. via an implant) is also safe and effective. The duration of the clinical trials (18 months in the Phase II trial and 12 months in the Phase III trial) was adequate to establish efficacy and a reasonable benefit vs. risk profile. The efficacy assessments selected were appropriate for the proposed indication. The number of patients treated (47 patients *in toto* divided almost evenly between naïve and pre-treated patients) is also acceptable in view of the fact that central precocious puberty is a rare condition. The safety measures included (adverse events, standard analytes and a variety of hormonal changes, bone X-rays, etc.) were also adequate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

See pharmacology and toxicity review.

7.2.5 Adequacy of Routine Clinical Testing

The efficacy assessments selected were appropriate for the purpose of the NDA and included endpoints and analyses that evaluated the effects of histrelin suppression on the pituitary (LH, FSH), gonadal hormones (estrogen and testosterone) and on clinical signs and symptoms of precocious puberty (e.g. Tanner staging, accelerated growth, gonadal and uterine enlargement). The safety measures included (standard analytes and a variety of hormonal changes, bone X-rays, etc.) were also adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The active moiety for the histrelin implant is an approved drug product. See also the clinical pharmacology review.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The active moiety in the histrelin implant is an approved drug. No further studies are recommended at this point.

7.2.8 Assessment of Quality and Completeness of Data

The quality of the data was acceptable.

7.2.9 Additional Submissions, Including Safety Update

The applicant submitted a safety update on March 25, 2007 (Amendment # 6). It includes adverse event data collected over a 6-month duration from 31 patients (out of the original 36 patients) who enrolled in the extension phase of Study 03-CPP-HIS-300. There were no deaths, no SAEs, no patient discontinuations due to adverse events and no new unexpected adverse events reported. An update on the treatment-related adverse events that occurred in > 2 patients **is reproduced in applicant's Table 6, below.** Treatment-related adverse events that occurred in only one patient (2.1%) were: breast tenderness, disease progression, dysmenorrhea, epistaxis, erythema, feeling cold, gynecomastia, headache, implant site irritation, implant site reaction, influenza-like illness, insomnia, keloid scar, menorrhagia, migraine, mood swings, pain exacerbated, pituitary tumor benign, pruritus, skin irritation, wound infection.

	Phase III Subjects N=36 n (%)	Phase II Subjects N=11 n (%)	Combined Subjects N=47 n (%)
Subjects With At Least One Treatment-Related AE	25 (69.4)	6 (54.5)	31 (65.9)
Implant Site Reaction	18 (50.0)		18 (38.3)
Weight Increased	4 (11.1)		4 (8.5)
Metrorrhagia	3 (8.3)		3 (6.4)
Application site pain		2 (18.1)	2 (4.3)
Scar	2 (5.6)		2 (4.3)
Suture Related Complication	2 (5.6)		2 (4.3)

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The only adverse events that could be attributed to the study drug were those related to the insertion/removal of the implant or to the implant site, as well as adverse events related to the mechanism of action of the drug (i.e. suppression of gonadal steroids) were.

There were some limitations of the clinical program. Because the data on uterine and ovarian volume were not standardized it was difficult to interpret and only general assessments could be made. The height velocity data was also interpreted with some difficulty in absence of baseline height velocity information. These limitations, however, applied mostly to assessments which mechanistically are secondary to the action of the pituitary and gonadal hormones and importantly, the suppressive effect of the histrelin implant on stimulated LH and sex steroids was clearly demonstrated in other analyses. Another limitation was the absence of a control group. It is, however, unethical to withhold GnRH treatment from children with central precocious puberty.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The data from the Phase II and Phase III clinical studies have been pooled only for the analysis of treatment-emergent adverse events (see Table 9 in section 7.4.1.2.

7.4.1.1 Pooled data vs. individual study data

There were no differences in patterns of adverse events between the Phase II and Phase III clinical trials.

7.4.1.2 Combining data

Table 9 summarizes the adverse events from both trials that occurred at least in two patients (4.3%) in the combined dataset.

Table 9: Adverse events occurring in more than 2 patients in the combined Phase II and Phase III trials

Preferred term for AE	Number (%) of adverse events N=47
Implant Site Reaction	23 (48.9%)
Upper Respiratory Tract Infection	11 (23.4%)
Headache	10 (21.3%)
Pyrexia	9 (19.1%)
Vomiting	9 (19.1%)
Cough	5 (10.6%)
Epistaxis	4 (8.5%)
Ear Infection	3 (6.4%)
Influenza	3 (6.4%)
Keloid Scar	3 (6.4%)
Nasal Congestion	3 (6.4%)
Pharyngolaryngeal Pain	3 (6.4%)
Scar	3 (6.4%)
Sinusitis	3 (6.4%)
Suture Related Complication	3 (6.4%)
Urticaria	3 (6.4%)
Weight Increased	3 (6.4%)
Abdominal Pain	2 (4.3%)
Abdominal Pain Upper	2 (4.3%)
Anxiety	2 (4.3%)
Application Site Pain	2 (4.3%)
Bronchitis	2 (4.3%)
Conjunctivitis	2 (4.3%)
Erythema	2 (4.3%)
Fatigue	2 (4.3%)
Injection Site Pruritus	2 (4.3%)
Menorrhagia	2 (4.3%)
Metrorrhagia	2 (4.3%)

Migraine	2 (4.3%)
Mood Swings	2 (4.3%)
Multiple Allergies	2 (4.3%)
Nasopharyngitis	2 (4.3%)
Pharyngitis Streptococcal	2 (4.3%)
Post Procedural Pain	2 (4.3%)
Rash	2 (4.3%)
Rhinitis	2 (4.3%)
Seasonal Allergy	2 (4.3%)
Tonsillitis	2 (4.3%)
Upper Respiratory Tract Congestion	2 (4.3%)
Wrist Fracture	2 (4.3%)

Source: Table 2.7.4.7. Summary of Clinical Safety.

7.4.2 Explorations for Predictive Factors

The small size of the studies did not allow exploratory analyses of predictive factors.

7.4.2.1 Explorations for dose dependency for adverse findings

The Phase III study 03-CPP-HIS-300 used a single dose (i.e. a single histrelin implant of 50 mg). This dose was established as effective in providing hormonal suppression during the Phase II study 01-02-001, which explored and compared a 50-mg implant with two 50-mg implants in a very small dataset. Therefore, no further dose dependency explorations were done.

7.4.2.2 Explorations for time dependency for adverse findings

A post hoc analysis of timing of adverse events by system organ class (SOC) indicates that **"general disorders and administration site conditions" was the only SOC that showed a time-**dependent incidence in trial 03-CPP-HIS-300 with 2/3 of such events occurring in the first day of the trial (25 out of 28 AEs were under the p**referred term of "implant site reaction").**

7.4.2.3 Explorations for drug-demographic interactions

Due to the small size of the datasets, no drug-demographics analyses were conducted.

7.4.2.4 Explorations for drug-disease interactions

Due to the small size of the datasets, no drug-disease analyses were conducted.

7.4.2.5 Explorations for drug-drug interactions

Due to the small size of the datasets, no drug-drug analyses were conducted.

7.4.3 Causality Determination

Due to the lack of a control group and the small size of the dataset, causality is difficult to establish with the exception of adverse events related to the insertion and removal of the implant itself or those adverse events that can be plausibly related to the mechanism of action of the study drug (e.g. withdrawal bleeding). Not surprisingly implant site reactions were viewed as treatment related by the investigators. Most other adverse events were background childhood illnesses.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dose effect was explored in trial 01-02-001 wherein some patients received either one 50-mg implant or two 50-mg implants (based loosely **on patients' weights** and ease of implant insertion). Although the lack of randomization and the small size of the dataset limit seriously the ability to draw firm conclusions, descriptive comparisons of efficacy between patients treated with one vs. two-implants do not suggest an efficacy benefit from higher histrelin doses. Despite variability in baseline body weight, the 50-mg implant was efficacious across the whole range of **patients' weights**[72]. It is theoretically possible that a lower histrelin dose may be as effective as the 50-mg implant over 12 months of treatment. However, the presence of a discrete time-dependent upward trend for the mean serum concentrations of LH, FSH, and estradiol observed in trial 03-CPP-HIS-300 argue against such an argument.

8.2 Drug-Drug Interactions

No drug-drug interaction studies were conducted.

8.3 Special Populations

The applicant did not conduct formal studies that evaluated the effect of age, gender, or race on the efficacy of the histrelin implant. Some of the efficacy analyses were presented by gender but there were only 3 boys enrolled in the clinical program (this is consistent with the known prevalence of CPP[73]). Despite this limitation, the different efficacy parameters evaluated in both

[72] There was a four-fold difference between the smallest patient weight of approximately 20 kg and the largest weight of approximately 80 kg.
[73] The prevalence of central precocious puberty has a striking female preference (3-23 s to 1).

clinical studies allow for a reasonable conclusion that histrelin implant is efficacious in both boys and girls.

8.4 Pediatrics

Treatment of central precocious puberty is a pediatric indication. A pediatric waiver should be granted for children less then 4 years of age (the youngest children treated were 3.7 years for Study 01-02-001 and 4.5 years in Study 03-CPP-HIS-300, respectively) and over 12 years (age when puberty should be allowed to proceed naturally). Although some children may require CPP treatment before age 4 (some CPP clinical trials enrolled patients as young as 1-2 years of **age) these children's arms may be too small relative the length of the current implant and, more** importantly, would be exposed to a higher dose per kg of body weight than school-age children (implant comes in a single strength of 50 mg and dose titration is not feasible).

8.5 Advisory Committee Meeting

There were no Advisory Committee meetings regarding this application.

8.6 Literature Review

GnRH analogues have been marketed for approximately 20 years. Their safety profile has been recently reviewed[74]. Adverse events described in published literature are local reactions **(including sterile abscesses; some may interfere with the drug's absorption and result in loss of** efficacy), allergic reactions, weight gain, expected effects of estrogen suppression (transient delay in mineralization, reduction of height velocity, withdrawal bleeding, moodiness, hot flashes, headaches, nausea). Hyperandrogenism has been described during GnRH treatment for CPP in girls; it is not clear if a causal relation exists or if it is just coincidental with the treatment.

8.7 Postmarketing Risk Management Plan

The applicant has not presented a formal risk management plan. A need for a risk management measure beyond the physician label does not appear necessary at this time (the adverse event profile of gonadotropin releasing-hormone agonists is relatively well understood).

8.8 Other Relevant Materials

None.

[74] Tonini G and Lazzerini M: Side effects of GnRH analogue treatment in childhood. Journal of Pediatric Endocrinology and Metabolism 13, 795-803 (2000).
Heger et al: Gonadotropin- realising hormone analogue treatment for precocious puberty. Twenty years of experience. Endocr. Dev. Basel, Karger, 8, 94-125 (2005).
Antoniazzi F and Zamboni G: Central Precocious Puberty. Pediatr. Drugs, 4, 211-231 (2004).

9 OVERALL ASSESSMENT

9.1 Conclusions

Overall, the histrelin acetate clinical program indicates that a 50-mg histrelin implant was effective in suppressing the biochemical and clinical manifestations of central precocious puberty in a vast majority of patients. The 50-mg histrelin acetate implant had an acceptable safety profile and an acceptable benefit to risk ratio. The safety profile of the histrelin implant was comparable to that described for GnRH analogs in general. Despite the limitations imposed by the occurrence of adverse events related to the implant insertion/removal and the reactions at the implant site (which should be appropriately labeled) this extended formulation will clearly benefit some patients eliminating the need for multiple injections.

9.2 Recommendation on Regulatory Action

Given that one 50-mg histrelin acetate implant is effective in suppressing the pituitary-gonadal axis and stabilizing clinical signs of precocious puberty, and it has an acceptable safety profile, it should be approved from a clinical perspective for the indication of central precocious puberty.

A pediatric waiver should be granted for children less then 4 years of age (the youngest children were 3.7 years for Study 01-02-001 and 4.5 years in Study 03-CPP-HIS-300, respectively) and over 12 years (age when puberty should be allowed to proceed naturally).

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The applicant has not presented a formal risk management plan. A need for risk management actions beyond the physician label does not appear necessary at this time (the adverse event profile of gonadotropin releasing-hormone agonists is, in general, well understood).

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

Adverse events related to the implant site should be collected in the postmarketing phase and presented in periodic safety reports. They should be characterized by the following categories: adverse events related to the procedure itself (i.e. implant insertion and implant removal) and to the implant site (i.e. implant site reactions).

9.4 Labeling Review

The proposed label is, in general, acceptable. Relatively minor changes have been made in the proposed label with the purpose of enhancing clarity and eliminating redundant statements (see Appendix 10.2 for line by line review; due to electronic formatting problems the line-by-line labeling review does not contain graphics).

9.5 Comments to Applicant

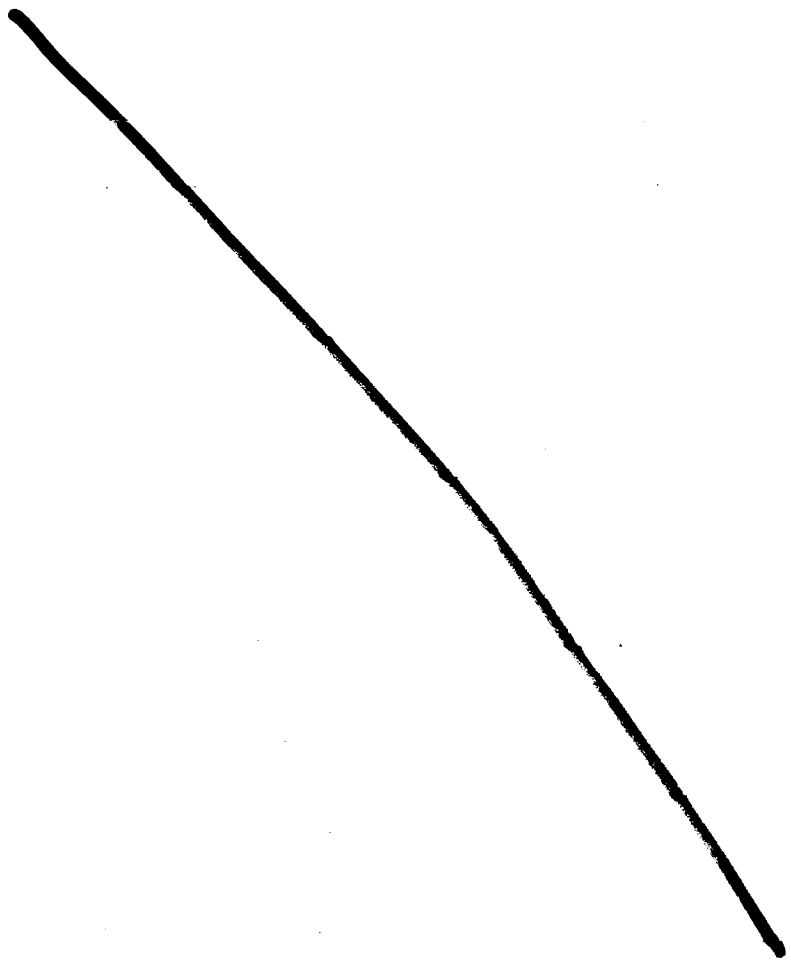
See labeling changes and recommendations.

10 APPENDICES

10.1 Review of Individual Study Reports

The two studies of this NDA are reviewed individually in the body of this review. Refer to the appropriate sections of the clinical review.

10.2 Line-by-Line Labeling Review



12 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical-__1____

REFERENCES

1. Antoniaxxi F and Zamboni G: Central precocious puberty. Current treatment options. Pediatr Drugs 694): 211-231, 2004.
2. Barradell LB and McTavish D: Histrelin. A review of its therapeutic properties and therapeutic role in central precocious puberty. Drugs 45 (4): 570-588, 1993.
3. Carel JC at al: Precocious puberty and statural growth. Human reproduction Update, 10 (2), 135-147, 2004.
4. Conn PL and Crawley WF: Gonadotropin-releasing hormones and its analogues. N Engl J Med 324 (2) 93-103, 1991.
5. Eckert KL et al: A single-sample, subcutaneous gonadotropin-releasing hormone test for central precocious puberty. Pediatrics 97 (4) 517-519, 1996.
6. Feuillan PF et al: Reproductive axis after discontinuation of gonadotropin-releasing hormone analog treatment of girls with precocious puberty: long term follow-up comparing girls with hypothalamic hamartoma to those with idiopathic precocious puberty. J Clin Endocrinol and Metab84: 44-49.
7. Feuillan PF et al:Follow-up of children and young adults after GnRH-agonist therapy for central precocious puberty. J Endocrinol Invest 24: 734-736, 2001.
8. Garibaldi LR et al: The relationship between luteinizing hormone and estradiol secretion in female precocious puberty: evaluation by sensitive gonadotropin assays and the leuprolide stimulation test. J Clin Endocrinol and Metab 76: 851-856, 1993.
9. Ghai K and Rosenfield RL: Maturation of the normal pituitary-testicular axis, as assessed by gonadotropin-releasing hormone agonist challenge. J Clin Endocrinol and Metab 78: 1336-1340, 1994.
10. Heger S et al: Long-term GnRH agonist treatment for female central precocious puberty does not impair reproductive function. Molecular and Cellular Endocrinology (article in press).
11. Hager S et al: Gonadotropin-releasing hormone analogue treatment for precocious puberty. Twenty years of experience. Endocr Dev 8, 94-125, 2005.
12. Hirsh HJ et al; The histrelin implant: a novel treatment for central precocious puberty. Pediatrics, 116 (6), e798-3802, 2005.
13. Ibanez L et al: Use of leuprolide acetate response patterns in the early diagnosis of pubertal disorders: comparison with the gonadotropin-releasing hormone test. J Clin Endocrinol and Metab 78: 30-35, 1994
14. Jensen AMB et al: Central precocious puberty in girls: internal genitalia before, during, and after treatment with long-acting gonadotropin-releasing hormone analogues. J Pediatrics 132; 105-108, 1998.
15. Juul A et al: Serum insulin-like growth factor-1 (IGF-1) and IGF-binding protein 3 levels are increased in cnetral precocious puberty: efffects of two different treatment regimens with gonadotropin-releasing hormone agonists, without or in combination with an antiandrogen (cyproterone acetate). J Clin Endocrinol and Metab 80, 3059-67.
16. Juul Anders: The effects of estrogens on linear growth. Human reproduction Update, 7 (3) 301-313, 2001.
17. Kaplowitz P: Precocious puberty in girls and the risk of a central nervous system abnormality: the elusive search for diagnostic certainty. Pediatrics, 109 91) 139-141, 2002.

18. Kaplowitz P: Precocious puberty in girls and the risk of a central nervous system abnormality: the elusive search for diagnostic certainty. Pediatrics, 109 91) 139-141, 2002.
19. Klein KO: Precocious Puberty: Who has it? Who should be treated? J Clin Endocrinol and Metab 84; 211-13, 1999.
20. Klein KO: Increased final height in precocious puberty after long-term treatment with LHRH agonists: the National Institutes of Health experience. J Clin Endocrinol and Metab 86: 4711-4716, 2001.
21. Klein KO et al: Use of an ultrasensitive recombinant cell bioassay to determine estrogen levels in girls with precocious puberty treated with luteinizing hormone-releasing hormone agonist. J Clin Endocrinol and Metab 83; 2387-9, 1998.
22. Lampit M et al: Estrogen mini-dose replacement during GnRH agonist therapy in central precocious puberty: A pilot study. J Clin Endocrinol and Metab 87: 687-690, 2002.
23. Lee PA: Central precocious puberty. An overview of diagnosis, treatment, and outcome. Endocrinology and Metabolism Clinics of North America, 28(4) 901-917, 1999.
24. Muller J et al: Hormonal changes during GnRH analogue therapy in children with central precocious puberty. Journal of Pediatric Endocrinology and Metabolism, 13, 739-746 (2000).
25. Neely EK et al: Normal ranges for immunochemilunometric gonadotropin assays. J Pediatrics 127(1) 40-46, 1995.
26. Neely EK et al: Spontaneous serum gonadatropin concentrations in evaluation of precocious puberty. J Pediatrics 127(1) 47-52, 1995.
27. Raivio T et al: Treatment of gonadotropin-defieient boys with recombinant human FSH: long-term observation and outcome. European Journal of Endocrinology 156, 105-111 (2007).
28. Salerno M et al: Central precocious puberty: a single blood sample after gonadotropin-releasing hormone agonist administration in monitoring tretment. Horm Res, 50: 205-211, 1998.
29. Tonini G and Lazzerini M: Side Effects of GnRH Analog treatment in childhood. Journal of Pediatric Endocrinology and Metabolism, 13, 795-803 (2000).
30. Weise et al: Determinants of growth durng gonadotropin-releasing hormone analog therapy for precocious puberty. J Clin Endocrinol and Metab 89: 103-7, 2004.

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