Study Number: 03-CPP-HIS-300

STUDY TITLE: Phase III, Open-Label Study to Evaluate the Efficacy and Safety of the Histrelin Implant in Children With Central Precocious Puberty – Clinical Study Report

INVESTIGATOR AND STUDY CENTER: Multicenter

STUDY PERIOD:
First subject dosed: 03 Sep 04
Last visit date (V 7): 31 Mar 06

CLINICAL PHASE: III

OBJECTIVES: The objective of this study was to evaluate the efficacy and safety of the 50 mg histrelin implant in male and female children with central precocious puberty (CPP).

METHODOLOGY: This is an open-label, Phase III study that is being conducted at 9 investigative sites in the United States. This report includes results for the first 12 months of treatment. Boys and girls with CPP were screened for participation in the study within 30 days before insertion of the histrelin implant. Medical history; physical examination including height, body weight, vital signs, and Tanner Staging; and informed consent were completed during this time. GnRH analog stimulation testing, an x-ray of the left hand and wrist, computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain, and a transabdominal ultrasound (girls only) were also performed. At intervals throughout the trial, blood samples were collected for the determination of serum testosterone (boys) or estradiol (girls), thyroid stimulating hormone (TSH), thyroxine (T4), dehydroepiandrosterone (DHEA)-sulfate, and histrelin levels, as well as routine safety laboratory testing.

A total of 36 eligible children were enrolled. Sixteen children were currently receiving GnRH analog therapy for ≥6 months (ie, Pretreated Group) while the remaining 20 were naïve to treatment (Naïve Group). All children were required to visit the study unit 1, 3, 6, 9, 12, and 13 months after implantation. At the 12-month visit, all subjects had their initial implant from Day 1 removed and those subjects who continued to meet all efficacy (ie, prepubertal response to GnRH analog stimulation and no other signs of disease progression as determined by the investigator) and safety requirements were eligible to receive a new histrelin implant. After completing assessments at the Month 13 visit, subjects who received a new implant at Month 12 were allowed to continue treatment in the extension phase as shown in the following table.

Screening	**Initial Phase**							**Extension Phase[a]**			
Within 30 days	**V 1**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**	**V 9**	**V 10**	**V 11**
	Day 1	**1 mo**	**3 mo**	**6 mo**	**9 mo**	**12 mo**	**13 mo[b]**	**15 mo**	**18 mo**	**21 mo**	**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.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Male or female children, 2 to 11 years of age, with CPP and pre-treatment bone age advanced for their chronological age. Approximately one-half of the children enrolled were receiving GnRH analog treatment for the treatment of CPP, and the remaining one-half were naïve to treatment.

NUMBER OF SUBJECTS (PLANNED, ENROLLED, ANALYZED): The planned enrollment was 32 subjects (16 pretreated and 16 naïve). Forty (40) subjects were enrolled; 36 (16 pretreated and 20 naïve) were treated and analyzed for efficacy, safety, and pharmacokinetics. Four subjects were screening failures.

DURATION OF TREATMENT: The duration of the treatment in the Initial Phase was 12 months; the 12-month data are presented in this report. At Month 12, subjects who showed continued efficacy and had no safety concerns, as determined by the investigator, were eligible to receive a new implant and continue treatment in the 12-month extension phase of the study (through Month 24).

STUDY DRUG, DOSE AND MODE OF ADMINISTRATION, LOT NUMBERS: The histrelin implant is a sterile, nonbiodegradable, diffusion-controlled reservoir drug delivery system designed to deliver histrelin continuously for 12 months after subcutaneous implantation. The sterile histrelin implant contains 50 mg histrelin acetate. The implant was surgically inserted into the inner surface of the upper arm between the bicep and tricep. The lot number for the histrelin implants was 404.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, LOT NUMBERS: None

EFFICACY ASSESSMENTS: Efficacy was evaluated through GnRH analog stimulation testing, assessment of hormone concentrations (eg, testosterone [boys] or estradiol [girls], TSH, free T4, and DHEA-sulfate), Tanner Staging, hand and wrist x-rays to determine bone age, height and body weight (ie, growth velocity), transabdominal pelvic ultrasound (girls only), and investigator assessment of disease progression.

PHARMACOKINETIC ASSESSMENTS: Blood samples were collected before implantation and at each visit through Month 12 of the Initial Phase, and will be collected at Month 13, Month 18, and Month 24 visits of the Extension Phase for the determination of histrelin serum concentrations. Additional blood samples were collected at predetermined time points on Day 1 through Day 4 in a subgroup of subjects who volunteered for the procedure.

SAFETY ASSESSMENTS: Safety was monitored at each visit through the reporting of adverse events (AEs), vital sign measurements, and physical examinations. Clinical laboratory testing was performed at screening and at Month 12 of the Initial Phase, Month 13, and Month 24 of the Extension Phase.

STATISTICAL METHODS: This study report presents analyses of data through Month 12 of histrelin implant treatment. Continuous variables were summarized using descriptive statistics (sample size, mean, standard deviation, median, minimum and maximum). Discrete variables were summarized by frequency and percentages. Ninety-five percent confidence intervals were provided whenever possible. When applicable, all statistical tests were conducted against a 2-sided alternative hypothesis, employing an overall significance level (α) of 0.05.

Efficacy Endpoints:

Primary efficacy endpoint

- Percentage of children with suppression of LH to prepubertal levels 3 months after histrelin implantation (Visit 3). For this report, suppression of LH was analyzed at intermediate time points through 12 months of treatment in the same manner as the primary efficacy analysis at Month 3. Suppression was defined as a peak serum LH concentration <4 mIU/mL after GnRH analog stimulation, where peak LH was determined to be the maximum value among the results at 0, 30, and 60 minutes after implantation.

Secondary efficacy endpoints:

- Suppression of FSH (peak <2.5 mIU/mL)
- Maintenance of serum testosterone (boys) or estradiol (girls) suppression

- Thyroid stimulating hormone (TSH), dehydroepiandrosterone (DHEA)-sulfate, and free thyroxine (T4) concentrations
- Growth velocity standard deviation score <2.5
- Bone age advancement of ≤18 months
- No progression of disease as determined by the investigator's assessment of disease progression

Observational endpoints after 12 months of histrelin implant therapy included:

- No progression in signs of puberty as measured by Tanner Staging
- Absence of menses after 4 to 6 weeks of histrelin implant therapy (girls only)

Safety Endpoints:

- Adverse events
- Clinical laboratory testing
- Vital signs
- Physical examinations

STUDY POPULATION: Male and female children with CPP who were previously treated with standard GnRH analogs or who were naïve to treatment.

EFFICACY RESULTS: The results from the initial 12 months of this study indicated that the histrelin implant delivered steady concentrations of histrelin, which induced suppression in all of those naïve to treatment and maintained suppression of gonadotropins for 12 months in all children who had previously received standard GnRH analog therapy for the treatment of CPP. Secondary and observational measures of efficacy (ie, suppression of estradiol or testosterone; TSH, DHEA-sulfate, and free T4; Tanner staging; bone age; and transabdominal pelvic ultrasound findings; Z-scores; growth velocity standard deviation (SD) scores; and investigator assessment of disease) also appeared to indicate stabilization of disease.

PHARMACOKINETIC RESULTS: All 36 treated subjects were included in the pharmacokinetic analysis. Mean serum histrelin concentration began to increase as early as approximately 6 to 8 hours after implantation. Mean histrelin concentration was highest at Month 1 and decreased through Month 12, remaining above the limit of quantification at most time points. Continuous subcutaneous release was evident, as histrelin plasma levels were sustained throughout the study period for all subjects.

SAFETY RESULTS: All 36 subjects reported at least one AE during the first 12 months of the study. The most commonly reported AE was implant site reaction. The majority of AEs were mild or moderate in intensity. Two subjects experienced an SAE: 1 subject experienced amblyopia (unlikely related) and 1 subject had a benign pituitary tumor (possibly related). No subject was discontinued from the study due to an AE. There were no clinically significant findings in hematology, clinical laboratory, or urinalysis parameters, or in vital signs or physical examination findings.