CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-058

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-058 / 0
Drug Name:	Supprelin LA (histrelin acetate subcutaneous implant 50 mg
Indication(s):	Treatment of central precocious puberty (CPP) in children
Applicant:	Valera Pharmaceuticals
Dates:	Letter date: June 30, 2006
	PDUFA Goal date: April 30, 2007
Review Priority:	Standard
Biometrics Division:	Metabolism and Endocrine Team
Statistical Reviewer:	Janice Derr, Ph.D.
Concurring Reviewers:	Jon T. Sahlroot, Statistics Team Leader
	Thomas Permutt, Division Director
Medical Division:	Division of Metabolism and Endocrine Products
Clinical Team:	Dragos Roman, M.D., Medical Reviewer
	Theresa Kehoe, M.D., Medical Team Leader
	Mary H. Parks, M.D., Division Director
Project Manager:	Jennifer Johnson

Keywords: clinical studies, NDA review

Introduction

Submission NDA 22058/0 is a new drug application for Supprelin® LA (histrelin acetate subcutaneous implant) 50 mg. The applicant, Valera Pharmaceuticals, is seeking approval of Supprelin LA for the treatment of central precocious puberty (CPP) in children. This submission includes the final study report for Study 03-CPP-HIS-300, an open-label study evaluating the histrelin implant in children with CPP.

Central precocious puberty is the early onset of hypothalamic-pituitary-gonadal activity, where the early onset takes place before the age of 8 in girls and 9 in boys. If left untreated, CPP can result in short stature and psychosocial problems for children undergoing sexual maturation years before their peers. The incidence of CPP is 10 times greater in girls than in boys. In most girls 4 years of age or older, a specific cause for the early activation of the pubertal axis cannot usually be identified, while in younger girls, the early activation can often be attributed to a lesion in the nervous system. Most boys with CPP (around 60%) have an identifiable underlying disease. The objective of treatment is to stop or reverse sexual development so as to prevent the accompanying rapid growth that ultimately limits **a child's height. Current medical therapy** involves intramuscular injections of gonadotropin-releasing hormone (GnRH) analogs such as leuprolide, with treatments every four weeks[1].

This NDA submission is based on a diffusion-controlled reservoir system that is implanted subcutaneously. This drug delivery system delivers histrelin acetate continuously for 12 months. Histrelin acetate is a GnRH analog. In 2004, an implant based on this design was approved for the palliative treatment of metastatic prostate cancer (Vantas®; see NDA 021732). The approved histrelin implant was subsequently redesigned to allow greater daily release of histrelin to treat children with CPP. The clinical program for the CPP indication consists of two clinical studies. The first study (Phase 2) enrolled 11 girls who had previously received standard GnRH analogs for the treatment of CPP. Patients received either one or two implants and were observed for 18 months. The second clinical study (Phase 3) included 36 children; 33 girls and 3 boys. All patients received one implant and were observed for 12 months[2]. In a pre-NDA meeting on 12/7/05, the Agency agreed that Valera had sufficient information, including the data from these two clinical studies, to submit the NDA (see IND 067582/011).

Overall Summary

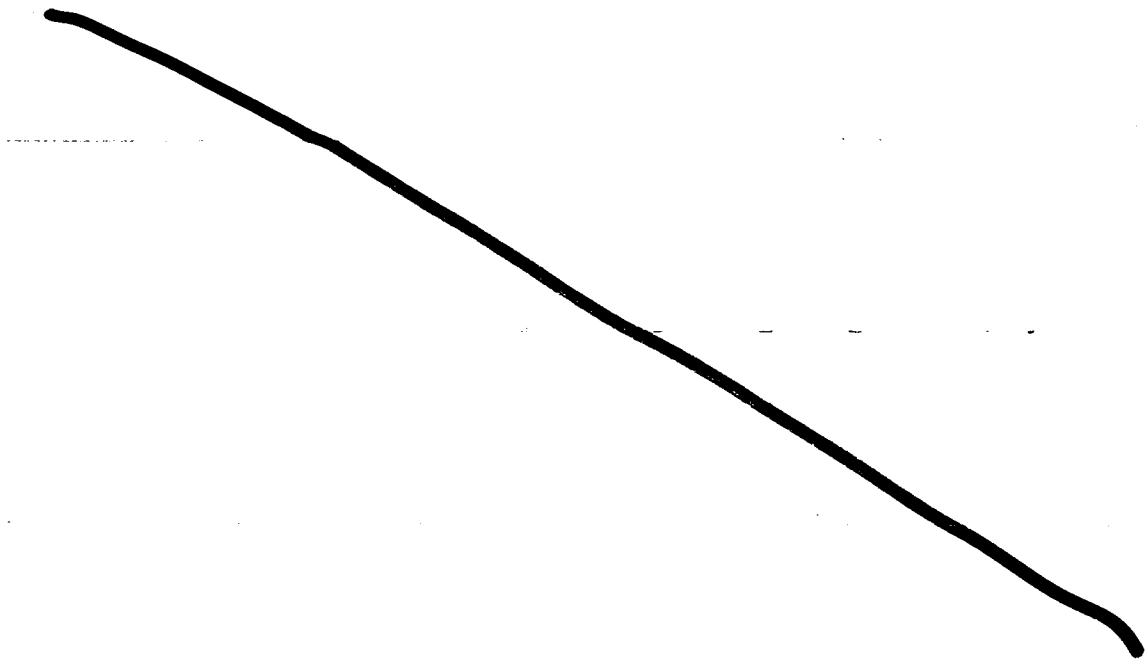
In my opinion, the summary statistics for LH and FSH in the Phase 3 clinical study are consistent **with the sponsor's conclusion that histrelin implants** induced and maintained suppression of LH within 1 month in those naïve to treatment, and maintained suppression of basal LH concentrations for 12 months in both boys and girls previously treated with standard GnRH analogs. I confirmed the key summary statistics for LH and FSH at baseline, month 3 and month

[1] Source of this paragraph: Section 2.5, clinical overview (paraphrased)
[2] Source of this paragraph: Section 2.5, clinical overview (paraphrased)

12. Before insertion of the histrelin implant, 2 of the 16 subjects who had received prior GnRH analog therapy (pretreated) and all 20 subjects with no prior therapy (naïve) had peak serum LH concentrations ≥ the pre-defined critical level of 4 mIU/mL after leuprolide acetate stimulation. By one month after implantation, all naïve subjects had peak LH concentrations < 4 mIU/mL, and peak LH levels stayed below this level at each measurement period through month 12. All pretreated subjects had peak LH levels < 4 mIU/mL at each measurement period through month 12. The pattern of peak FSH levels through the first 12 months was similar to the pattern for peak LH, although peak FSH levels were not below the pre-defined critical level of 2.5 mIU/mL in all subjects. The clinical assessments of growth and maturation, such as the shift in Tanner Staging and the shift in bone age/chronological age from baseline to month 12, were generally consistent with the effects of the histrelin implant on LH and FSH. However, the statistical interpretation of time trends in the data is limited due to the open-label, single arm design. In addition, the inclusion of only 3 males in the Phase 3 study, all of whom were pretreated, may limit the extension of the study conclusions to males with CPP. This is an issue for further evaluation from the medical perspective.

Labelling

I evaluated the draft labeling text that referred to Study HIS-300. My recommendations are summarized in TABLE 1.



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1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Statistical- 1

Study Reviewed

Study 03-CPP-HIS-300: "Phase III, open-label study to evaluate the efficacy and safety of the **histrelin implant in children with central precocious puberty."**

Objective: The objective of study HIS-300 was to evaluate the efficacy and safety of the 50 mg histrelin implant in male and female children with central precocious puberty (CPP).

Design: This was an open-label, Phase III study that was conducted at 9 investigative sites in the U.S. Boys and girls with CPP were screened for participation in the study within 30 days before insertion of the histrelin implant. Eligibility included a diagnosis of CPP and pre-treatment bone age advanced for their chronological age. A total of 36 eligible children were enrolled. Of these, 16 children had received prior GnRH analog therapy for at least 6 months (the pretreated group) and the remaining 20 were naïve to treatment (the naïve group). All children received the 50 mg histrelin implant. Post-treatment study visits took place at 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. Those subjects who continued to meet all efficacy 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. The extension phase included visits at months 15, 18, 21 and 24.

The study was conducted at 9 clinical sites in the U.S. The period of the trial was 12 months; the first patient started on September 3, 2004 and the last patient completed month 12 on March 31, 2006.

Patient disposition: A total of 40 subjects were initially enrolled in the study; four of these subjects were screening failures (Subjects 005, 022, 035 and 040) and did not receive a histrelin implant. Of the 36 eligible subjects who received a histrelin implant, 16 had a history of previous GnRH analog therapy for the treatment of CPP and 20 were naïve to treatment. All 36 subjects were analyzed for efficacy and safety. One subject (subject 042) was lost to follow-up, but this loss took place after the second implant was inserted at month 12. This subject did not return for the month 13 visit. Two subjects missed clinic visits in the first year of the study: Subject 012 missed the clinic visits at month 6 and month 9, and Subject 014 missed the clinic visit at month 6. All subjects attended the key clinic visits at month 3 and month 12.

Patient demographic and baseline characteristics: A summary of the demographic characteristics of the 36 subjects is given in TABLE 2. There were three male subjects in the study, and they were all in the pretreated group. The remaining 33 subjects were female. The majority of pretreated and naïve subjects were Tanner Stage 2 or 3 for breast development or testicular size and pubic hair development at baseline TABLE 3. The summary statistics for LH and FSH at baseline are different between the two subgroups, reflecting the hormonal response to prior treatment in the pre-treatment subgroup but not in the naïve subgroup (
TABLE 4 and TABLE 5).

TABLE 2 Summary of demographic and baseline characteristics for all randomized patients

	Pretreated Subjects N=16	Naïve Subjects N=20	All Subjects N=36
Age (yrs)			
N	16	20	36
Mean (SD)	8.9 (1.47)	7.1 (1.37)	7.9 (1.66)
Median	9.1	7.5	8.1
Min, Max	5.6, 11.6	4.5, 9.1	4.5, 11.6
Gender, N (%)			
Male	3 (18.8)	0	3 (8.3)
Female	13 (81.3)	20 (100)	33 (91.7)
Weight (kg)			
N	16	20	36
Mean (SD)	46.2 (13.51)	33.4 (10.25)	39.1 (13.28)
Median	43.7	33.3	38.3
Min, Max	22.3, 78.2	18.8, 59.3	18.8, 78.2
Height (cm)			
N	16	20	36
Mean (SD)	143.4 (13.89)	129.6 (12.90)	135.7 (14.87)
Median	144.3	133.3	137.3
Min, Max	117.3, 178.3	105.9, 153.4	105.9, 178.3
Body mass index (kg/m2)			
N	16	20	36
Mean (SD)	22.0 (3.31)	19.5 (3.38)	20.6 (3.54)
Median	21.2	19.1	20.3
Min, Max	16.2, 27.0	13.3, 25.2	13.3, 27.0

Source: Study HIS-300 Clinical Report, Table 4

TABLE 3 Tanner staging at baseline

	Pretreated Subjects N=16	Naïve Subjects N=20	All Subjects N=36
Breast Development/Testicular Size			
1	0	0	0
2	6 (37.5)	2 (10.0)	8 (22.2)
3	8 (50.0)	11 (55.0)	19 (52.8)
4	1 (6.3)	7 (35.0)	8 (22.2)
5	1 (6.3)	0	1 (2.8)
Pubic Hair Development			
1	1 (6.3)	4 (20.0)	5 (13.9)
2	3 (18.8)	10 (50.0)	13 (36.1)
3	10 (62.5)	3 (15.0)	13 (36.1)
4	2 (12.5)	3 (15.0)	5 (13.9)
5	0	0	0

Source: Study HIS-300 Clinical Report, Table 5

Analysis populations: **The sponsor defined the "efficacy population" as the 36 subjects who** received the implant. All 36 subjects had complete data for the primary and secondary efficacy endpoints at month 3 and month 12. Because of the complete data at these key time points there was no imputation used in the efficacy database.

Efficacy endpoints: Efficacy was evaluated through GnRH analog stimulation testing, assessment of hormone concentrations (e.g., testosterone for boys and estradiol for girls, TSH,

free T4, and DHEA-sulfate), Tanner Staging, hand and wrist x-rays to determine bone age, height and body weight (i.e., growth velocity), transabdominal pelvic ultrasound (girls only) and investigator assessment of disease progression.

The primary efficacy endpoint was the percentage of children with suppression of LH to prepubertal levels 3 months after histrelin implantation. 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 included the following:

- Suppression of FSH (peak < 2.5 mIU/mL)
- Maintenance of serum testosterone in boys or suppression of estradiol in girls
- Concentrations of TSH, DHEA-sulfate and 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

Additional descriptive 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)

Statistical summaries of efficacy: The results from the study, presented in the original NDA submission through month 12, were summarized with descriptive statistics. The applicant also reported 95% confidence intervals for certain outcomes, such as the percentage of patients with suppression of LH at month 3, and reported p-values for within-subject changes with respect to baseline. In my opinion, a confidence interval can be a useful descriptive measure of the extent of variability in an estimate. However, because this is an open-label study with a single treatment arm, I believe that a p-value from a statistical test of a within-subject change from baseline does not have a clear interpretation. For this reason, the focus of my review is on the descriptive summaries of the study results. An exception to this approach is with the ratio of bone age to chronological age, where the observed mean is compared with the expected ratio of 1, based on the use of historical information to construct the level **of "bone age" from** radiographic records (see p. 13).

LH and FSH: I confirmed the key summary statistics for LH and FSH that are presented in TABLE 4 and TABLE 5. Before insertion of the histrelin implant, 2 of the 16 pretreated and all 20 naïve subjects had peak serum LH concentrations ≥ 4 mIU/mL after leuprolide acetate stimulation. By one month after implantation, all naïve subjects had peak LH concentrations < 4 mIU/mL, and peak LH levels stayed below this level at each measurement period through month 12. All pretreated subjects had peak LH levels < 4 mIU/mL at each measurement period through month 12. The profile plots of LH vs. time depict these results for individual subjects (FIGURE 1 and FIGURE 2). While the suppression of LH was observed in each subject at each time period,

the suppression of FSH to a level below 2.5 mIU/mL occurred in a majority of patients, but not all, and the suppression did not last through month 12 in every subject. Before insertion of the histrelin implant, 6 of the 16 pretreated subjects and all 20 naïve subjects had peak serum FSH concentration ≥ 2.5 mIU/mL after leuprolinde acetate stimulation. At month 3, 18 of the naïve subjects (90%) and 13 of the pretreated subjects (81%) had peak FSH levels < 2.5 mIU/mL. At month 12, 13 of the naïve subjects (65%) and 9 of the pretreated subjects (56%) had peak FSH concentrations below this level. The profile plots of LH vs. time depict these results for individual subjects (FIGURE 3 and FIGURE 4).

TABLE 4 Peak LH results

			Prior CPP Medication History	
		Total N=36	Pretreated N=16	Naïve N=20
Peak LH at Baseline (mIU/ml)	Mean ± sd	16.6 ± 19.8	2.1 ± 2.2	28.2 ± 20.0
	min, max	0.02, 77.0	0.02, 7.1	4.8, 77.0
	median	9.2	1.8	24.0
Peak LH at Month 3	Mean ± sd	0.7 ± 0.5	0.5 ± 0.4	0.8 ± 0.5
	min, max	0.1, 2.2	0.1, 1.3	0.2, 2.2
	median	0.5	0.4	0.7
Change in Peak LH from Baseline to Month 3	Mean ± sd	-15.9 ± 19.6	-1.6 ± 1.9	-27.4 ± 19.9
	min, max	-76.1, 0.2	-6.1, 0.2	-76.1, -4.0
	median	-8.9	-1.2	-23.1
LH suppression at Month 3	% of cases	100%	100%	100%
Peak LH at Month 12	Mean ± sd	0.9 ± 0.5	0.7 ± 0.5	1. 0 ± 0.6
	min, max	0.1, 2.1	0.1, 2.1	0.2, 2.0
	median	0.8	0.8	0.8
Change in Peak LH from Baseline to Month 12	Mean ± sd	-15.7 ± 19.6	-1.4 ± 2.0	-27.2 ± 19.9
	min, max	-75.7, 0.3	-6.3, 0.3	-75.7, -3.6
	median	-8.6	-1.0	-23.1
LH suppression at Month 12	% of cases	100%	100%	100%

Source: Study HIS-300 Clinical Report, Post-text Tables 2.1.2 and 2.1.5

TABLE 5 Peak FSH results

		Total N=36	Prior CPP Medication History: Pretreated N=16	Prior CPP Medication History: Naïve N=20
Peak FSH at Baseline (mIU/ml)	Mean ± sd	9.3 ± 7.8	2.8 ± 2.1	14.5 ± 6.7
	min, max	0.1, 30.0	0.1, 7.1	7.1, 30.0
	median	8.1	2.2	12.5
Peak FSH at Month 3	Mean ± sd	1.5 ± 0.8	1.6 ± 1.0	1.5 ± 0.7
	min, max	0.5, 3.8	0.5, 3.8	0.6, 3.1
	median	1.4	1.3	1.4
Change in Peak FSH from Baseline to Month 3	Mean ± sd	-7.8 ± 7.8	-1.3 ± 1.9	-13.0 ± 6.7
	min, max	-27.8, 0.4	-6.3, 0.4	-27.8, -5.1
	median	-6.4	-0.7	-11.1
FSH suppression at Month 3	% of cases	86.1%	81.3%	90.0%
Peak FSH at Month 12	Mean ± sd	2.6 ± 1.9	2.8 ± 2.4	2.5 ± 1.4
	min, max	0.6, 10.0	0.6, 10.0	0.7, 5.5
	median	2.2	2.1	2.2
Change in Peak FSH from Baseline to Month 12	Mean ± sd	-6.7 ± 7.8	-0.1 ± 2.3	-12.0 ± 6.4
	min, max	-27.1, 4.6	-5.8, 4.6	-27.1, -3.9
	median	-5.6	0.1	-10.7
FSH suppression at Month 12	% of cases	61.1%	56.3%	65.0%

Source: Study HIS-300 Clinical Report, Post-text Tables 2.4.2 and 2.4.5

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FIGURE 1 Peak LH (mIU/ml) results at each visit; Pretreated group; Individual subject profiles (note difference in scale on LH axis between Figure 1 and Figure 2)

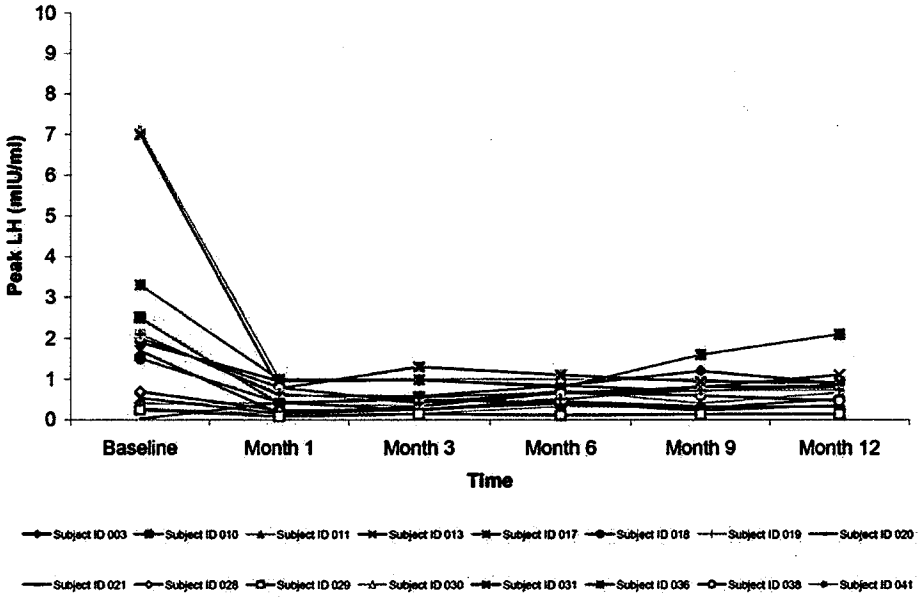
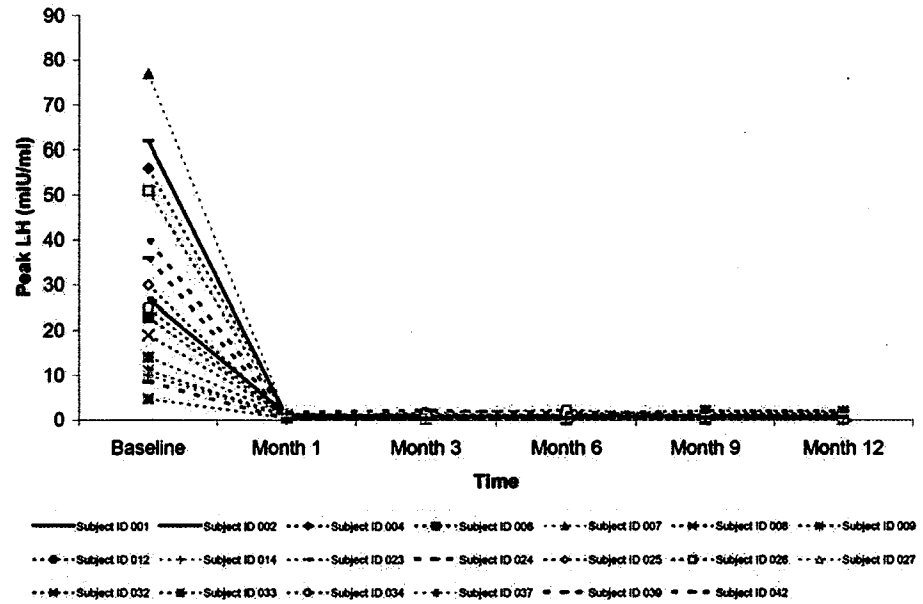


FIGURE 2 Peak LH (mIU/ml) results at each visit; Naïve group; Individual subject profiles



Source: HIS-300 Clinical Report, Post-text Figures 2.9.2 and 2.9.3

FIGURE 3 Peak FSH (mIU/ml) results at each visit; Pretreated group; Individual subject profiles (note difference in scale on LH axis between Figure 3 and Figure 4)

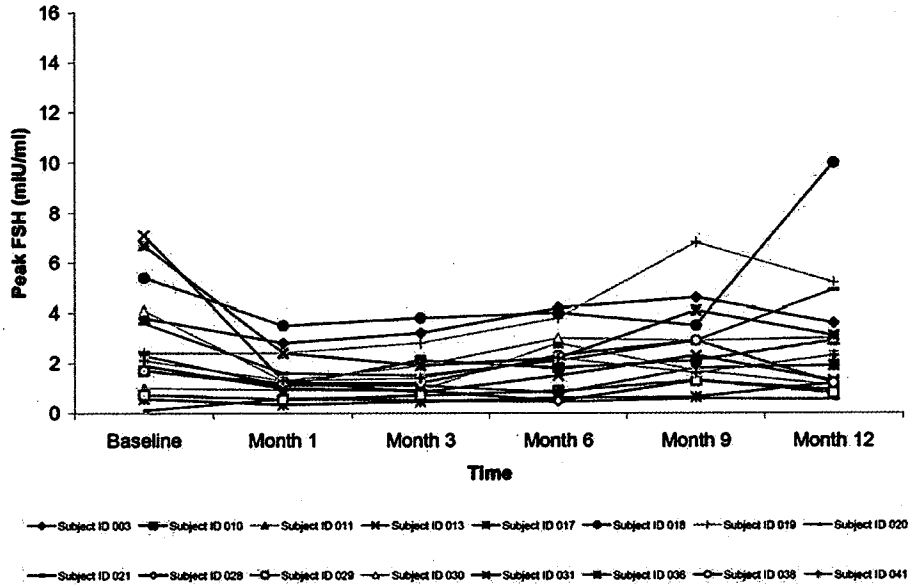
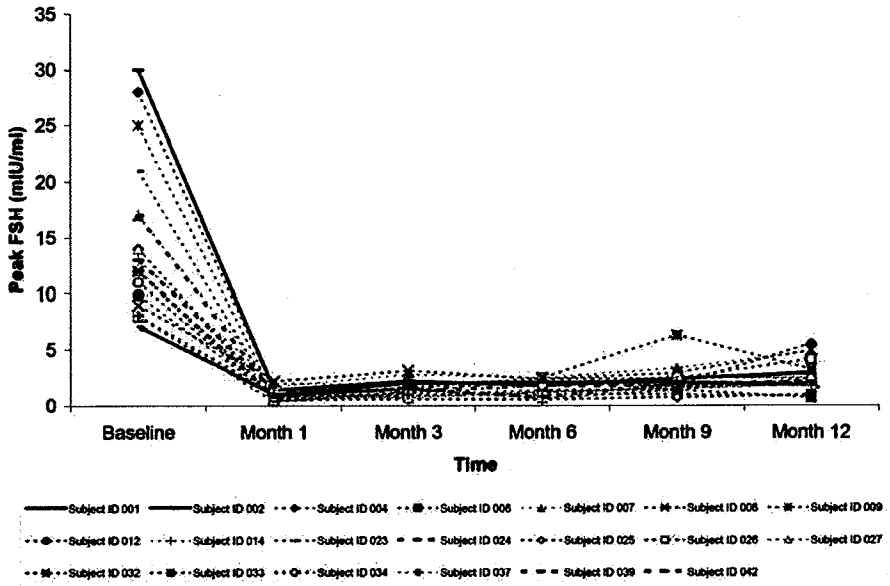


FIGURE 4 Peak FSH (mIU/ml) results at each visit; Naïve population; Individual subject profiles



Source: Study HIS-300 Clinical Report, post-text Figure 2.11.2 and 2.11.3

Tanner Staging: The majority of subjects showed either no change (42%) or a reduction (42%) in Tanner Staging for breast development / testicular size, and either no change (61%) or a reduction (14%) in Tanner Staging for pubic hair development. This finding is consistent with the clinical efficacy of histrelin (TABLE 6). However, this finding should be interpreted with caution because of the open-label design of the study and the lack of a placebo group. The evaluation of Tanner Staging may have been **influenced by the raters' knowledge of the** treatment assignment of the patients.

TABLE 6 Shift table showing Tanner Staging at baseline and month 12

		Month 12				
		Stage 1 N(%)	Stage 2 N(%)	Stage 3 N(%)	Stage 4 N(%)	Stage 5 N(%)
Breast Development / Testicular Size						
Baseline	Stage 1	0	0	0	0	0
	Stage 2	4 (11.1%)	2 (5.6%)	2 (5.6%)	0	0
	Stage 3	2 (5.6%)	4 (11.1%)	10 (27.8%)	3 (8.3%)	0
	Stage 4	0	0	5 (13.9%)	2 (5.6%)	1 (2.8%)
	Stage 5	0	0	0	0	1 (2.8%)
Pubic Hair Development						
Baseline	Stage 1	4 (11.1%)	1 (2.8%)	0	0	0
	Stage 2	2 (5.6%)	5 (13.9%)	6 (16.7%)	0	0
	Stage 3	0	1 (2.8%)	10 (27.8%)	2 (5.6%)	0
	Stage 4	0	0	2 (5.6%)	3 (8.3%)	0
	Stage 5	0	0	0	0	0

Note: The boxes shaded in gray on the diagonal represent no change in Tanner Staging between baseline and month 12. The boxes in the upper diagonal shaded in light blue represent a progression of Tanner Staging. The boxes in the lower diagonal shaded in light yellow represent a reduction in Tanner Staging between baseline and month 12.

Source: Study HIS-300 Clinical Report, Table 15

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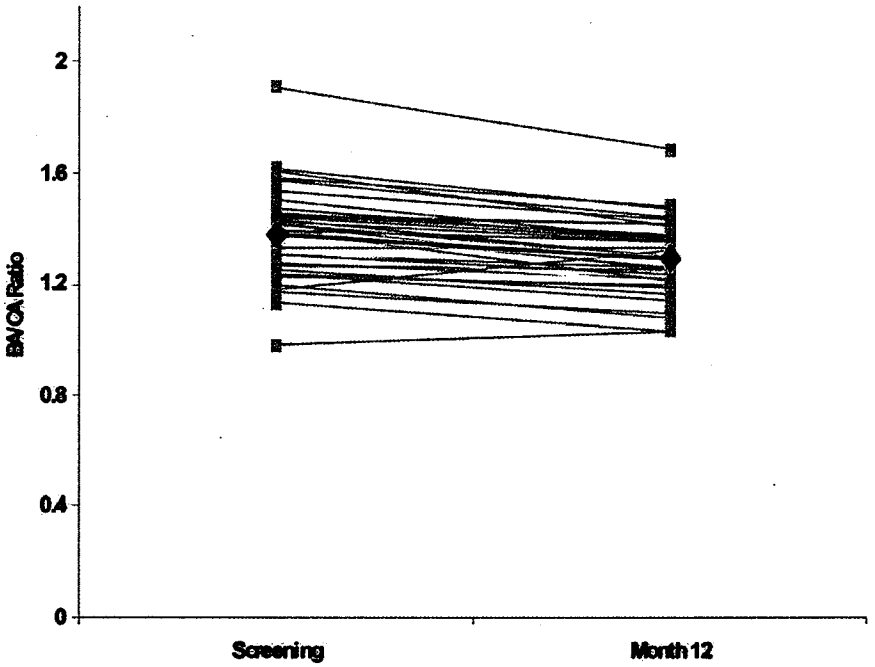
Bone age/chronological age: At baseline, the mean ratio of bone age to chronological age was 1.38 ± s.d. 0.17. This ratio is consistent with the expectation that children with CPP will tend to have a greater bone age than expected based on their chronological age, i.e., a ratio greater than 1. At month 12, the mean ratio of bone age to chronological age was 1.29 ± 0.14. While this mean ratio is also greater than 1, it represents a numerical decrease from baseline to month 12. Most subjects (33 of 36 subjects) had a numerical decrease in bone age/chronological age between baseline and month 12 (FIGURE 5). Based on the expectation that the ratio of bone age to chronological age is 1 at baseline and also at month 12, we can construct a statistical hypothesis test of the expected difference of 0. On this basis, the average change between baseline and month 12, with mean -0.08 and 95% CI of (-0.11, -0.06), has a p-value < 0.0001. This result supports the conclusion that histrelin has a therapeutic effect in children with CPP.

FIGURE 5 Bone age to chronological age ratio from screening to month 12; Profile plots of individual subjects (filled squares and gray lines), and profile plot of the average (filled diamond and black line).



Source: Study HIS-300 Clinical Report, Figure 5

Measurements of growth: The sponsor noted that the varied rate of growth in children 4 to 11 years over a 12-month period makes it difficult to interpret the mean values for height and body weight for subjects in Study HIS-300. For this reason, height, weight and BMI data for each subject at baseline and month 12 were transformed to Z-scores and percentiles based on the

subjects' age in months and gender. I selected the Z-scores for "height for age" for further evaluation. The mean "height for age" Z score was 1.45 ± 1.35 (s.d.) at screening and 1.36 ± 1.20 at month 12, with an average change between screening and month 12 of -0.09 ± 0.39. This average change represents a slight decrease in the extent to which this group had a greater height for their age compared to the norms used to calculate the Z scores. Although the direction of the change supports the interpretation of clinical benefit associated with histrelin, the magnitude of the change is not very great. In general, subjects remained relatively constant with respect to **their "height for age" between screening and month 12.** TABLE 7 shows that 21 subjects stayed **within ± 2 standard deviations of their "height for age," and a further 10 subjects stayed above 2** standard deviations at both screening and month 12.

TABLE 7 **"Height for age" Z scores, showing the shift from screening to month 12**

	Month 12 < -2	-2 ≤ Month 12 ≤ +2	Month 12 > +2	Total
Screening < -2	0	2 (5.6%)	0	2
-2 ≤ Screening ≤ +2	0	21 (58.3%)	0	21
Screening > +2	0	3 (8.3%)	10 (27.8%)	13
Total	0	26	10	36

Source: Reviewer calculations from database ZS.xtp

Safety: An evaluation of safety is primarily covered in the DA clinical review by Dr. Dragos Roman.

Conclusions

In my opinion, the summary statistics for LH and FSH in the Phase 3 clinical study are consistent **with the sponsor's conclusion that histrelin implants** induced and maintained suppression of LH within 1 month in those naïve to treatment, and maintained suppression of basal LH concentrations for 12 months in both boys and girls previously treated with standard GnRH analogs. I confirmed the key summary statistics for LH and FSH at baseline, month 3 and month 12. The clinical assessments of growth and maturation, such as the shift in Tanner Staging and the shift in bone age/chronological age from baseline to month 12, were generally consistent with the effects of the histrelin implant on LH and FSH. However, the statistical interpretation of time trends in the data is limited due to the open-label, single arm design. In addition, the inclusion of only 3 males in the Phase 3 study, all of whom were pretreated, may limit the extension of the study conclusions to males with CPP.

Signatures/Distribution list

Janice Derr, Ph.D.
Mathematical Statistician

Concur:

J. Todd Sahlroot, Ph.D.

T. Permutt, Ph.D.

cc:
NDA 022058/ 0
DMEP/JJohnson,DRoman, TKehoe, MParks
OB/TSahlroot, TPermutt, ENevius, LPatrician

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/s/

Janice Derr
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Todd Sahlroot
4/24/2007 07:20:21 AM
BIOMETRICS

Thomas Permutt
4/24/2007 09:35:56 AM
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