



2.0 Synopsis

| Abbott Laboratories | Individual Study Table Referring to Part of Dossier: | (For National Authority Use Only) |
|--|--|-----------------------------------|
| Name of Study Drug: Abbott-43818 (ABT-818) leuprolide acetate for depot suspension (Lupron Depot®) | Volume: | |
| Name of Active Ingredient: leuprolide acetate | Page: | |
| Title of Study: A Phase 3, Randomized, Multi-Center, Open-Label Study to Evaluate the Efficacy and Safety of Leuprolide Acetate 11.25 and 30 mg Formulations in Children with Central Precocious Puberty | | |
| Coordinating Investigator: Peter A. Lee, MD, PhD, [REDACTED] | | |
| Study Sites: 18 sites in the US and 4 in Puerto Rico redacted information 03Jul2014 | | |
| Publications: One | | |
| Studied Period (Years): First Subject First Visit: 10 June 2008 Last Subject Last Visit: 12 March 2010 | Phase of Development: 3 | |
| Objectives: The objectives of this study were to assess the efficacy and safety of the 11.25 and 30 mg formulations of leuprolide acetate, each with a 3-month treatment interval, for 6 months in the treatment of central precocious puberty (CPP) in children who were either naïve to previous treatment with a gonadotropin-releasing hormone agonist (GnRHa) or who had previously been treated with GnRHa for at least the prior 6 months to Day 1. | | |
| Methodology: <p>This Phase 3, randomized, multicenter, open-label study evaluated the efficacy and safety of leuprolide acetate depot 11.25 mg and leuprolide acetate depot 30 mg, each with a 3-month treatment interval, in children with CPP. Both of these formulations have been previously approved for other indications: Lupron Depot-3 Month 11.25 mg formulation for endometriosis and anemia caused by uterine leiomyomata in March 1997 and Lupron Depot-4 Month 30 mg formulation for advanced prostate cancer in May 1997.</p> <p>This study included a Screening Period (up to 4 weeks) two 3-month treatment cycles, and a posttreatment follow-up period (12 weeks following the Month 6 visit). Study visits occurred at Screening, Day 1 (first leuprolide acetate depot injection), Week 2 (only for subjects in a pharmacokinetic subset), Months 1, 2, 3 (second leuprolide acetate depot injection), 6, and 12 weeks later for a posttreatment follow-up visit. Additionally, telephone calls were made to the parent to assess the injection site following both injections and potential acute hormonal flare response.</p> | | |



Methodology (Continued):

Screening evaluations included medical/family history; complete physical exam with vital signs; height and weight; pubertal staging (breasts in female subjects, genitals in male subjects, pubic hair in both male and female subjects) and testicular volume in male subjects; GnRHa stimulation testing with blood draws for luteinizing hormone (LH), follicle-stimulating hormone (FSH) (both measured using an immunochemiluminometric assay [ICMA 3rd generation]), and sex steroids (testosterone or estradiol, both measured using high-performance liquid chromatography [HPLC]); adrenal steroid testing to rule out congenital adrenal hyperplasia; transabdominal pelvic ultrasound for determination of uterine and ovarian volumes in female subjects and ultrasound in male subjects to rule out steroid-secreting tumor, to measure testicular volume and presence or absence of abnormality and characterization (location, size) of the abnormality, if present; hand/wrist radiographs for bone age (to be read by a central reader); safety laboratory assessments, collection of adverse events and concomitant medications; and menstrual bleeding calendar (female subjects). A pregnancy test in female subjects was performed at the discretion of the investigator and/or based on Institutional Review Board (IRB) requirements.

Periodic procedures and evaluations during the study included: GnRHa stimulation testing with blood draws for LH, FSH, and sex steroid levels; leuprolide pharmacokinetic sampling (subset of subjects); transabdominal ultrasound for determination of uterine and ovarian volumes in female subjects; bone age radiographs; pubertal staging (breast in female subjects, genitals in male subjects, pubic hair in both male and female subjects); testicular volume in male subjects; physical examination including height in triplicate (for calculation of growth rate) and weight measurements; menstrual bleeding calendar in female subjects; and safety laboratory and vital signs evaluations. Pregnancy testing in female subjects may have been performed at the discretion of the investigator and/or based on IRB requirements. Adverse events and concomitant medication use were assessed throughout the study, as were clinical responses to an increase in gonadotropins and sex steroids (hormonal flare and acute-on-chronic reaction). Information on injection site reactions was captured by the site on the day of each injection and by a telephone call to the parent who assessed the injection site the day following each injection.

After completing the 6-month treatment period, subjects either entered follow-up and received standard-of-care treatment, as deemed appropriate by the treating endocrinologist, or eligible subjects participated in a separate open-label, extension study (Study L-CP07-177). Subjects not participating in the open-label extension study were asked to return for a 12-week post-treatment follow-up visit for a brief physical examination with vital signs and assessment of adverse events and concomitant medications. A pregnancy test in female subjects might have been performed at the discretion of the investigator and/or based on IRB requirements.

Number of Subjects (Planned and Analyzed):

Efficacy and Safety: Approximately 20 subjects naïve to previous GnRHa treatment (minimum of 15) and a minimum of 20 subjects previously treated with a GnRHa were planned for each of the leuprolide acetate depot dose groups; 84 subjects were randomized and analyzed, including 21 subjects to each of the previous GnRHa treatment status subgroups of each leuprolide acetate depot dose group.

Pharmacokinetics: 48 subjects planned (first 24 subjects randomized to each of the dose groups); 48 subjects included in the analyses (47 subjects for first dose and 38 for second dose).



Diagnosis and Main Criteria for Inclusion:

Children with CPP, chronological age at onset of pubertal symptoms < 8 years in female subjects and < 9 years in male subjects at Day 1, and bone age advanced at least 1 year beyond the chronological age at time of diagnosis or first GnRHa therapy. Subjects naïve to GnRHa treatment had additional eligibility criteria, including: female subjects 2 to 8 years inclusive and male subjects 2 to 9 years, inclusive, at Day 1; pretreatment pubertal response to leuprolide acetate stimulation (LH ≥ 8 mIU/mL) at Screening; breast pubertal staging (according to modified Tanner scoring system) of at least 2 in female subjects at Screening; and, testicular volume of at least 4 cc or testicular length greater than 2.5 cm in male subjects at Screening. Subjects who were previously treated with GnRHa must have been 2 to 10 years, inclusive, for female subjects and 2 to 11 years, inclusive, for male subjects at Day 1, received standard GnRHa therapy for at least 6 months prior to Day 1, and had documented maintenance of LH suppression as evidenced by peak stimulated LH < 4 mIU/mL at Screening.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

In this study, study drug supplies included investigational product (leuprolide acetate 11.25 mg and 30 mg depot formulations), stimulation test medication (Leuprolide Acetate Injection), and Lupron Depot-PED (7.5 mg, 11.25 mg, and 15 mg) administered monthly for standard of care treatment during the follow-up period. Leuprolide acetate depot 11.25 mg and 30 mg were administered intramuscularly (IM) every 3 months. A dose of 20 mcg/kg of daily leuprolide acetate daily injection was administered subcutaneously for the stimulation test. The lot numbers for study drug and other medications supplied to the sites are listed as follows.

| | Formulation | Dosage | Mode of Administration | Lot Number | Manufacturer and Location |
|--|---|---------------------------------|------------------------|----------------------------|---------------------------|
| Investigational Product: | | | | | |
| Leuprolide acetate depot 11.25 mg | 11.25 mg syringe | 11.25 mg q 3 months | IM | 612202E21 | [REDACTED] |
| Leuprolide acetate depot 30 mg | 30 mg syringe | 30 mg q 3 months | IM | 52561AP21 | [REDACTED] |
| Other Medications: | | | | | |
| Lupron Injection (For Pediatric Use) | 5 mg/mL (1 mg/0.2 mL) supplied in a 2.8 mL multiple dose vial | 20 mcg/kg | SC | 43859Z722, 58958Z723 | [REDACTED] |
| Leuprolide Acetate Injection | 5 mg/mL (1 mg/0.2 mL) supplied in a 2.8 mL multiple dose vial | 20 mcg/kg | SC | 31305745B | [REDACTED] |
| Lupron Depot-PED (leuprolide acetate for depot suspension) | 7.5 mg, 11.25 mg, and 15 mg syringe | 7.5 mg, 11.25 mg, 15 mg q month | IM | Not Available ^a | [REDACTED] |

a. Commercial Lupron Depot-PED was provided by [REDACTED]



Duration of Treatment:

Subjects were to receive a total of 2 injections of either leuprolide acetate depot 11.25 mg or leuprolide acetate depot 30 mg, each injection administered IM 3 months apart (6 months of treatment). The first injection was administered at Day 1, and the second injection was administered at Month 3 (Day 84). Subjects who were not adequately suppressed on therapy, as evidenced by peak-stimulated LH level of ≥ 4 mIU/mL, or had accelerated progression of pubertal symptoms at Month 2 or beyond were not to receive the second leuprolide acetate depot injection.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

None.

Criteria for Evaluation

Efficacy Population (N = 84): Subjects who received at least 1 dose of study drug and had at least 1 postbaseline measurement of peak-stimulated LH at Month 2 or later were included in the intent-to-treat (ITT) population for the primary efficacy analysis. For all other efficacy analyses, subjects must have received at least 1 dose of study drug and had at least 1 postbaseline measurement of the appropriate variable to be included in the ITT population for the analyses.

Safety Population (N = 84): All subjects who received at least 1 dose of study drug were included in all safety summaries and analyses.

Pharmacokinetic (PK) Population (N = 48 for either dose): 47 subjects evaluated for first dose and 38 for second dose. The data from all subjects with samples collected for plasma leuprolide determinations were included in the PK analyses.

Exposure-Response Population (N = 48): Subjects with samples collected for plasma leuprolide determinations and who had at least 1 post baseline measurement of peak-stimulated LH were included in the analyses.

Statistical Methods

Efficacy: All efficacy analyses were summarized for all subjects within each leuprolide acetate depot dose group, and for treatment-naïve and previously-treated subgroups within each dose group. The primary efficacy endpoint was suppression of LH from Month 2 through Month 6 as determined by peak stimulated LH < 4 mIU/mL at Months 2, 3, and 6. The analysis was performed using a life table method adapted from Koch et al. (Am J Med. 1984;77(5B):43-50). The percentage of subjects suppressed and the 2-sided 95% confidence intervals (CI) were calculated for each treatment group using the life table method, and subjects who withdrew from efficacy assessments, successfully completed, or prematurely discontinued the trial without peak stimulated LH ≥ 4 mIU/mL were censored at their last measurement of peak-stimulated LH. In addition, analyses of the primary efficacy endpoint were conducted for each of the subgroups of subjects naïve to GnRHa treatment and previously treated within each leuprolide acetate depot dose group. The difference of percent of subjects who had peak-stimulated LH suppressed from Month 2 through Month 6 between 11.25 mg and 30 mg dose groups and a 95% CI on the difference among all, treatment-naïve, and previously-treated subjects for the primary endpoint was calculated. Six sensitivity analyses for LH suppression rate were conducted – by exact method among completers, by Kaplan-Meier method, and by 4 life table method analyses (counting discontinued subjects as either failures or successes, with a 7-day window for the Month 6 visit, and excluding the LH measurement by electrochemiluminescent assay). Subgroup analyses were also performed for the primary efficacy endpoint.



Statistical Methods

Efficacy (Continued):

Secondary endpoints included: suppression of sex steroids (estradiol < 20 pg/mL in girls and testosterone < 30 ng/dL in boys) measured at Months 1, 2, 3 and 6; peak-stimulated LH concentrations at Months 1, 2, 3 and 6; suppression of the physical signs of puberty (i.e., breast development in girls and genital development in boys according to pubertal staging and testicular volume in boys by Prader beads) at Month 6; change from baseline in growth rate after 6 months of treatment; and, ratio of change from baseline in bone age/change from baseline in chronological age after 6 months of treatment.

Other efficacy endpoints included: number and percent of subjects who failed suppression of peak-stimulated LH per primary endpoint analysis by visit; number and percent of female subjects with bleeding or spotting among all subjects and by baseline menarche status (yes/no); the simple percentage of subjects with suppressed LH as determined by peak-stimulated LH < 4 mIU/mL at Months 1, 2, 3, 6, and Final Visit; change from baseline in basal and peak-stimulated LH, FSH, as well as basal and stimulated estradiol (for females) and testosterone (for males), to Week 2 (only basal LH obtained), Months 1, 2, 3, 6 and Final Visit; the ratio and change from baseline in the ratio of bone age to chronological age at Month 6 and the Final Visit; regression or no progression in pubic hair in both females and males; change from baseline in uterine length, uterine volume, and ovarian volume to Month 6 and Final Visit in females; number and percent of female subjects with endometrial stripe present at Month 6 summarized by baseline endometrial stripe presence status (yes/no); change from baseline in endometrial stripe thickness (double layer) to Month 6 and the Final Visit in female subjects; change from baseline in testicular length (cm), penile length (cm), and penile width (cm) by physical examination, and in testicular volume by Prader beads to Month 6 and the Final Visit in male subjects; change from baseline in BMI standardized score to Month 6 and the Final Visit; change from baseline in height standardized score to Month 6 and the Final Visit; and, the difference between basal and peak-stimulated LH, basal and stimulated estradiol, and basal and stimulated testosterone concentrations to examine hormonal flare effects after the first injection and acute-on-chronic response after the second injection.

For each binary variable, the percentage of subjects with the characteristic of interest at each visit was calculated. For each continuous variable, the sample size, mean, median, standard deviation, minimum and maximum were calculated.

For suppression in LH by visit, suppression in sex steroids by visit and suppression in physical signs of puberty at Month 6 and at Final Visit, 95% binomial exact CIs were calculated along with the percentages. For the change from baseline in growth rate, change from baseline in the ratio of bone age to chronological age, and change from baseline in endometrial thickness, paired t-test was performed to test if the change was different than 0. For ratio of change from baseline in bone age/change from baseline in chronological age, Wilcoxon signed rank test was performed to test if the ratio was less than 1.

Subgroup analyses were conducted for the primary endpoint of peak-stimulated LH suppression from Month 2 through Month 6, change from baseline in growth rate, and change from baseline in bone age versus change from baseline in chronological age. The subgroups assessed in these analyses were based on sex, race, baseline peak-stimulated LH value, time to treatment from onset of puberty, age at onset of puberty, predicted adult stature at baseline, and baseline BMI standardized score.



Statistical Methods

Pharmacokinetics: Statistical analyses were conducted to explore attainment of steady state, investigate dose-proportionality and linear kinetics, and assess accumulation of leuprolide. Leuprolide concentration values below the lower limit of quantitation (LLOQ) were assumed to be equal to LLOQ for all statistical pharmacokinetic/pharmacodynamic analyses.

A statistical analysis was conducted on leuprolide concentrations for the 11.25 and 30 mg doses at 4, 8, and 12 weeks (Months 1, 2, and 3) after the first leuprolide acetate depot injection and at 12 weeks after the second injection (Month 6) within subjects, as repeated measures for each subject. A linear mixed effects model was used. For the fixed effects part, the model included leuprolide acetate dose and time as main effects and a dose-by-time interaction term. For the random effects part, a general covariance structure (unstructured) was chosen, and it gave the largest value under the Akaike's Information Criterion. To explore attainment of steady state, a trend analysis was performed from 4 to 12 weeks within each dose level. To assess the accumulation of leuprolide, 12-week concentration values were compared after the first and second injections. To investigate dose proportionality and linear kinetics, a one-way analysis of covariance (ANCOVA) was performed for the log-transformed, dose normalized leuprolide concentration at each of the following time points: 4, 8, and 12 weeks after the first injection and at 12 weeks after the second injection. Values below the LLOQ were set equal to LLOQ. The model for one way ANCOVA included classification by dose level, with either age or weight as a covariate. The hypothesis of no difference between the 2 dose levels was tested within the framework of the ANCOVA.

Exposure-Response Analysis: An exposure-response analysis was conducted to explore the relationship between leuprolide concentration and the probability of LH suppression (defined as peak-stimulated LH levels < 4 mIU/mL). The exposure-response analysis was conducted for leuprolide concentrations and probability of LH suppression at 4, 8, 12, and 24 weeks (Months 1, 2, 4, and 6) in the pharmacokinetic subset subjects. Repeated binary data were used for modeling the probability of LH suppression with the following explanatory variables: baseline LH level, log-transformed leuprolide plasma concentration, time (4, 8, 12, and 24 weeks), age, sex, BMI, body surface area (BSA), weight, and race (black, white, and others).

Safety: All adverse events during the treatment period were summarized. Safety laboratory vital signs, injection site reactions, and signs and symptoms consistent with a hormonal response were also summarized.

Summary/Conclusions

Demographic and Other Baseline Characteristic Results: The leuprolide acetate depot dose groups were generally similar to one another at baseline – both overall and for the subgroups of subjects according to previous GnRH α treatment status – based on demographic characteristics and CPP characteristics. The majority of the 84 randomized and treated subjects (the safety and ITT datasets) were female (90.5%) and either white (58.3%) or black (22.6%), with 29.8% of all subjects of Hispanic ethnicity. The mean age was 7.8 years (range 1 to 11 years). Mean BMI standardized score was 1.1 across all study subjects, indicating that the study population had a higher BMI compared to standard populations of similar age and sex.



Summary/Conclusions

Demographic and Other Baseline Characteristic Results (Continued):

Treatment-naïve subjects were numerically older at onset of CPP than were those who were previously treated with a GnRHa prior to study enrollment (mean age was 6.7 versus 5.9 years in the 11.25 mg group and 6.0 versus 4.8 years in the 30 mg group) and, in a similar pattern, the time between their first visit to a physician for CPP and initiation of CPP treatment occurred, on average, 3 months more recently than that of the previously-treated subjects. Of the 76 female subjects, 7 (9.2%) had reached menarche at the time of enrollment into this study. Most female subjects (96%) were pubertal stage 2 or higher based on breast stage and most male subjects (88%) were pubertal stage 3 or higher based on genitalia development at study entry.

Mean bone age at baseline was 11.0 years. Bone age was advanced over chronological age by an average of 2.9 and 2.6 years for the leuprolide acetate depot 11.25 mg and 30 mg groups, respectively. As expected, the mean difference between bone age and chronological age was greater for subjects naïve to treatment compared with previously-treated subjects in both dose groups (3.3 versus 2.4 years, respectively, in the 11.25 mg group and 2.9 versus 2.3 years, respectively, in the 30 mg group). Mean growth rate at baseline, defined as the growth rate during the year prior to the start of study drug, was 6.9 cm/yr. Growth rate for subjects naïve to treatment was higher in both the leuprolide acetate depot 11.25 mg and 30 mg dose groups compared to previously-treated subjects (7.3 and 7.8 versus 6.6 and 6.1 cm/yr, respectively).

At baseline, mean peak-stimulated LH level was 45.9 mIU/mL in the treatment naïve subgroup and 1.8 mIU/mL in the previously-treated subgroup of the leuprolide acetate depot 11.25 mg group and 23.5 and 1.7 mIU/mL in the respective subgroups of the leuprolide acetate depot 30 mg group. Mean basal estradiol levels in female subjects were 24.6 and 1.8 pg/mL in the treatment naïve and previously-treated subgroups, respectively, of the leuprolide acetate depot 11.25 mg group and 34.2 and 1.8 pg/mL in the respective subgroups of the leuprolide acetate depot 30 mg group. Mean basal testosterone levels in male subjects were 194 and 12 ng/dL in the treatment-naïve and previously-treated subgroups, respectively, of the leuprolide acetate depot 11.25 mg group and 134 and 7 ng/dL in the respective subgroups of the leuprolide acetate depot 30 mg group.



Summary/Conclusions (Continued):

Efficacy Results: The primary endpoint of the study, suppression of peak-stimulated LH to < 4.0 mIU/mL from Month 2 through Month 6 analyzed by a life table method was achieved in 95.2% of subjects in the leuprolide acetate depot 30 mg group, including 100% of subjects who were previously treated with a GnRH α prior to study enrollment and 90.5% of subjects who were naïve to GnRH α treatment. In the leuprolide acetate depot 11.25 mg group, 78.4% of subjects had suppression of peak-stimulated LH from Month 2 to Month 6, including 80.7% and 76.2% suppression in previously-treated and treatment naïve subjects, respectively. The difference between dose groups for percent of subjects with LH suppression, as defined above, was 16.9% [95% CI 2.8%, 31.0%] across all subjects, 14.3% [95% CI -7.8%, 36.4%] among treatment-naïve subjects, and 19.3% [95% CI 2.3%, 36.4%] among previously-treated subjects. These analyses indicate that the LH suppression rate was higher in the 30 mg dose group than it was in the 11.25 mg dose group in all 3 comparisons, with the between-dose difference reaching the level of statistical significance (at α level of 0.05) for the comparison in all subjects and in the previously-treated subgroup.

Two subjects in the leuprolide acetate depot 30 mg group were treatment failures for the primary endpoint; both subjects were treatment naïve at study enrollment and failed to suppress to peak-stimulated LH < 4.0 mIU/mL by Month 2. One of these subjects was a 1 year 10 month old girl. Nine subjects in the leuprolide acetate depot 11.25 mg group were treatment failures for the primary endpoint, including 5 treatment-naïve subjects who failed to suppress peak stimulated LH to < 4 mIU/mL by Month 2 and 4 previously-treated subjects who escaped LH suppression at Months 2, 3, or 6. Sex steroids were suppressed to prepubertal levels in 7 of 9 treatment failures in the 11.25 mg dose group and in both treatment failures in the 30 mg dose group. Both subjects with lack of suppression for LH and estradiol/testosterone on the 11.25 mg dose were naïve to previous GnRH α treatment. There was no progression in pubertal stage (breast in female subjects; genitalia in male subjects) for any of the 11 subjects who failed peak-stimulated LH suppression.

The results of 6 sensitivity analyses for LH suppression rate were consistent with those from the primary analysis by the life table method, indicating that the results are robust to different methods of accounting for premature termination and different statistical methods of analysis. With the Kaplan-Meier (product limit) method, the rates of LH suppression for the 2 doses were very similar to the results by the primary life table for the primary endpoint.

A consistent trend, similar to the overall findings, was observed across all subgroup analyses of the primary endpoint, with higher LH suppression rate in the leuprolide acetate depot 30 mg group than that in the leuprolide acetate depot 11.25 mg group and higher or similar LH suppression rate in the previously-treated subgroup than in the treatment-naïve subgroup in both dose groups with sufficient sample size. LH suppression with leuprolide acetate depot 11.25 mg seemed more difficult in the children who were younger at onset of puberty (68.9% suppression in those who were ≤ 6.4 years at onset of puberty versus 86.4% suppression in those who were older), both in the treatment-naïve and previously-treated subgroups. In the 11.25 mg dose group, treatment-naïve subjects with predicted adult stature \geq lower bound of target height appeared more difficult to suppress than those with predicted adult stature $<$ lower bound of target height (61.5% versus 100%, respectively), although this finding is limited by small sample size ($n = 4$) of the subgroup of predicted adult stature $<$ lower bound of target height.



Summary/Conclusions

Efficacy Results (Continued):

Peak-stimulated LH concentrations were suppressed to numerically lower mean levels in the leuprolide acetate depot 30 mg group than in the leuprolide acetate depot 11.25 mg group, beginning early in the course of treatment. By Month 1, mean peak-stimulated LH was 1.7 mIU/mL and remained ≤ 1.8 mIU/mL at all following visits in the 30 mg group. In the 11.25 mg group, mean peak-stimulated LH was 3.1 mIU/mL at Month 1 and remained between 2.0 and 3.3 mIU/mL at subsequent visits through Month 6.

Suppression of basal sex steroids to prepubertal levels was achieved in all female and male subjects treated with leuprolide acetate depot 30 mg at all visits from Month 1 to Month 6 and all but 3 subjects in the leuprolide acetate depot 11.25 mg group, 2 of whom also escaped LH suppression.

Although bleeding or spotting due to hormonal flare associated with leuprolide acetate administration and subsequent withdrawal of estrogen was observed during the first 4 weeks of the study in some treatment-naïve subjects, only 3 female subjects (1 in 11.25 mg group and 2 in 30 mg group) experienced uterine bleeding or spotting thereafter. Uterine volume was reduced after 6 months of treatment with leuprolide acetate depot in both 30 mg subgroups and in treatment naïve subjects in the 11.25 mg group. Mean ovarian volume was also reduced among treatment-naïve subjects in both dose groups and previously treated subjects in the 30 mg group.

Six of 36 female subjects in the 30 mg group and 3 of 37 female subjects in the 11.25 mg group had progression of breast development by Month 6, with all having a 1 stage progression in breast development with the exception of 1 subject in the 30 mg dose group (from stage 3 to stage 5). Suppression of peak-stimulated LH (to < 4 mIU/mL) was observed in all 9 female subjects at the time progression was noted by the investigator and basal estradiol was in the prepubertal range for all but 1 of these subjects. Four male subjects had progression in genitalia pubertal stage or testicular volume at some time during the study (1 and 3 subjects in the 11.25 mg and 30 mg groups, respectively). Progression of clinical sexual characteristics of puberty also did not correspond with lack of hormonal suppression (i.e., peak-stimulated LH, basal testosterone) for any of the 4 male subjects.

Clinical suppression of puberty based on regression or no progression in pubic hair distribution was observed in the majority of female subjects (91%) and male subjects (86%) across both dose groups.



Summary/Conclusions

Efficacy Results (Continued):

Overall, both leuprolide acetate depot dose groups showed a similar decrease from baseline in mean incremental growth rate, with a decrease for treatment-naïve subjects twice that of previously-treated subjects at Month 6. There was no continued advancement of bone age compared to chronological age during the treatment period. The median ratio of change from baseline in bone age to change from baseline chronological age was less than 1 in both dose groups, and was statistically significantly < 1 in the 11.25 mg group. Within both dose groups, the median ratio was smaller in the previously-treated subgroup than it was in the treatment-naïve subgroup at Month 6 and Final Visit. A small mean decrease from baseline (< 0.1) in ratio of bone age to chronological age after the onset of treatment in each dose group is consistent with the degree of inhibition in bone age maturation that can be expected after a short (6 month) treatment period.

Mean BMI standardized score (1.1 across all subjects) and mean height standardized score (1.4 across all subjects) were similar at baseline between the 2 dose groups. There was little change in mean BMI standardized score or mean height standardized score in either dose group in this study, expected findings given the relatively short, 6-month treatment period.

Pharmacokinetic/Pharmacodynamic Results: Leuprolide acetate depot 11.25 mg and 30 mg injections provided sustained release of leuprolide acetate in children where mean leuprolide plasma concentrations remained constant from Week 4 to Week 12. Mean leuprolide concentrations from Week 4 to Week 12 were dose proportional across 11.25 mg and 30 mg doses. Mean leuprolide 12 week concentration after the second injection was similar to 12-week concentration after the first injection for both treatments (11.25 mg and 30 mg formulations), indicating no accumulation of leuprolide from repeated administration. Body weight and age were not found to be significant covariates on leuprolide pharmacokinetics. Exposure response analysis showed that higher leuprolide concentrations are associated with higher probability of peak-stimulated LH suppression at all study visits evaluated.

Safety Results: The safety profiles of leuprolide acetate depot 30 mg and leuprolide acetate depot 11.25 mg, each administered IM every 3 months, were generally similar based on type and incidence of treatment-emergent adverse events, laboratory test results, and measurements of vital signs.

Treatment-emergent adverse events, regardless of relationship to study drug, were reported for 38 of 42 subjects (90.5%) in the leuprolide acetate depot 11.25 mg group and 35 of 42 subjects (83.3%) in the leuprolide acetate depot 30 mg group. The commonly reported adverse events ($> 10\%$ of all subjects) were injection site pain (22.6%), headache (20.2%), pyrexia (14.3%), cough (14.3%), upper respiratory tract infection (11.9%), and nasal congestion (10.7%). The majority of treatment-emergent adverse events were of mild or moderate intensity. Only 1 adverse event – injection site pain reported on Day 1 and lasting 1 hour (30 mg group) – was rated as severe by the investigator.



Summary/Conclusions

Safety Results (Continued):

The adverse events for which the incidence was at least 5% higher (reported for at least 3 more subjects) in the leuprolide acetate depot 11.25 mg group than in the 30 mg group were nasopharyngitis (11.9% versus 4.8%) and respiratory disorder (7.1% versus 0%), with all classified as not related to study drug by the investigator. Adverse events that occurred with an incidence at least 5% higher in the 30 mg group than in the 11.25 mg group were injection site pain (26.2% versus 19.0%), headache (28.6% versus 11.9%), pyrexia (19.0% versus 9.5%), vomiting (14.3% versus 2.4%), and nausea (7.1% versus 0%). More than half of injection site pain adverse events were mild (1 transient event was characterized as severe in the leuprolide acetate depot 30 mg group), and none resulted in premature discontinuation of study drug. Nearly all (17 of 19) adverse events of injection site pain were considered by the investigator to be related to study drug. Most headache events were mild (none severe), and the majority (80% and 67% in the 11.25 mg and 30 mg groups) were not considered related to study drug (e.g., alternatives etiologies of tension/stress, viral illness, sinus inflammation, prior history of migraines). All events of pyrexia were not considered related to study drug and considered more likely caused by a viral illness (11 of 12 events) or bacterial otitis media (1 of 12 events). And, all events of nausea and vomiting in both leuprolide acetate depot dose groups were mild in intensity and all but 1 event (of nausea) were not considered related to study drug.

Adverse events consistent with clinical symptoms of hormonal flare response that occurred within 14 days after the first injection of study drug were relatively uncommon and were reported in a similar proportion of subjects in each leuprolide acetate depot dose group (14.3% and 19.0% of subjects in the 11.25 mg and 30 mg groups, respectively). These included mild constipation (2.4% and 0% in the 11.25 mg and 30 mg groups, respectively), mild dizziness (0% and 2.4%), headache of mild or moderate intensity (4.8% and 9.5%), mild musculoskeletal pain (2.4% and 0%), mild migraine (2.4% and 0%), mild alteration of mood (0% and 2.4%), mild nausea (0% and 2.4%), mild tearfulness (0% and 2.4%), and mild vomiting (2.4% in both dose groups).

To better understand the scope and clinical importance of injection site adverse events, injection site reactions were identified by Company MedDRA Query (CMQ). Injection site reactions were reported for 9 (21.4%) and 12 (28.6%) subjects in the leuprolide acetate depot 11.25 mg and 30 mg groups, respectively. In this analysis, injection site pain was also the most common event (affecting 19 of the 21 subjects with an injection site reaction). Sterile abscess at the injection site was reported for only 1 subject (in the 11.25 mg group). More than half of the injection site reaction events were mild (13 of 21 affected subjects had mild events), and none of the events were serious or resulted in premature discontinuation of study drug. There were no clinically concerning differences between dose groups for the number and type of injection site reactions.



Safety Results (Continued):

In an assessment of the injection site separate from adverse event reporting (performed by the site just after each leuprolide acetate depot injection and by phone call with parents the day following each injection using a study-specific, non-validated symptom questionnaire), 57.1% of subjects in the leuprolide acetate depot 11.25 mg group and 69.0% of subjects in the leuprolide acetate depot 30 mg group experienced at least 1 symptom at the injection site following either the first or second injection of study drug. A substantial portion (~40%) of the subjects with symptoms based on injection site assessment also had a treatment emergent adverse event(s) of injection site reaction per CMQ reported at the same time. Of note, all 21 subjects who had at least 1 treatment emergent adverse event of injection site reaction per CMQ also had their symptoms reported based on the injection site assessment. The most common symptoms following either injection (> 10%) were tender or painful at injection site of mild or moderate intensity (55.9% of all subjects), less than dime-sized redness (11.9%), and mild limitation of limb movement (11.9%). Evaluation of injection site symptom information obtained by questionnaire did not reveal any unexpected findings

No subject in either leuprolide acetate group died or had a serious adverse event that was deemed to be treatment-related by the investigator. One subject (11.25 mg group) prematurely discontinued due to an adverse event of moderate growth hormone deficiency.

Hormonal flare of LH and acute-on-chronic increase in LH were assessed following the LH stimulation test. At Day 1, mean increases from basal to peak-stimulated LH for the treatment-naïve subjects in the 11.25 and 30 mg dose groups showed evidence of hormonal flare effect; the previously-treated subjects showed no evidence of hormonal flare effect. An overall decrease in basal LH results at Month 1 indicates an absence of hormonal flare, however, an increase of 3.4 IU/mL between basal and peak-stimulated LH in the treatment-naïve subjects treated with leuprolide acetate depot 11.25 mg suggests that the pituitary – gonadal axis may not be completely suppressed in all these subjects at Month 1. Negligible mean increases in LH at Month 3, which were not associated with an increase in estradiol/testosterone, indirectly suggest the absence of hormonal acute-on-chronic reaction in both treatment-naïve and previously-treated subjects in both the 11.25 mg and 30 mg dose groups at the second injection.

No unexpected symptoms were reported in assessments separate from adverse event reporting conducted during the first 14 days following the first (clinical symptoms of hormonal flare) and second study drug injections (clinical symptoms of acute-on-chronic reaction) to evaluate behavioral and physical symptoms that may potentially be associated with an increase in gonadotropins or sex steroids. Site staff or parents reported such symptoms in 31.0% and 45.2% of the 42 subjects each in 11.25 mg and 30 mg dose groups after the first injection of study drug and for a similar proportion of subjects in the 11.25 mg dose group and fewer subjects in the 30 mg dose group after the second injection. Some of the symptoms reported by site staff or parents in the 14 days following the first injection of study drug (mood swings; headache; vaginal bleeding; discharge; crying/tearful) may have been related to a hormonal flare effect. Since there was little hormonal response following the second injection, it is unclear whether the symptoms reported after the second injection reflect an acute on chronic response or are due to other factors.



Safety Results (Continued):

No new or unexpected safety concerns were identified based on laboratory testing and measurements of vital signs. Most study subjects had normal hematology, chemistry, and urinalysis values at baseline and all postbaseline assessments. No consistent trends or clinically significant mean changes from baseline in routine laboratory values (chemistry, hematology, urinalysis) were observed in this study. In analyses of shift from baseline to final laboratory values, there was no hematology parameter for which more than 10% of subjects in 1 of the leuprolide acetate depot dose groups had a value that shifted from the low/normal range at baseline to above normal, or from the high/normal range at baseline to below normal. For chemistry indices, more than 10% of subjects in 1 of the leuprolide acetate depot dose groups had a baseline value in the low/normal range and a final value above normal for inorganic phosphorus (13.5% and 7.7% subjects in the leuprolide acetate depot 11.25 and 30 mg groups, respectively), LDH (10.7% and 12.5%, respectively), and glucose (5.6% and 15.8% respectively), although the clinical importance of this latter finding is mitigated by the fact that fasting samples were not required. Few potentially clinically significant (PCS) laboratory findings were reported, and none were of clinical concern. Small changes from baseline in vital signs and no trend with regard to direction of change from baseline over time were observed in either leuprolide acetate depot dose group.

Conclusions:

Both the 11.25 mg dose and 30 mg dose of leuprolide acetate depot, each administered IM once every 3 months, are effective in hormonal suppression.

The suppression of peak-stimulated LH suppression was observed in more subjects treated with the 30 mg dose (i.e., fewer escapes). In addition, this dose showed no escapes from suppression of sex steroids and in treatment-naïve subjects had a more rapid onset of peak-stimulated LH suppression. Both doses showed similar effects on growth rate and bone age maturation, and similar safety profiles. The availability of a 3-month depot formulation has the potential to improve treatment of CPP in children, by reducing the burden of both the number of injections and frequent number of clinic visits needed with the Lupron Depot-PED 1-month formulations.