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:

Study of Lupron Depot in the Treatment of Central Precocious Puberty

Coordinating Investigator: Peter A. Lee, MD, PhD [redacted] redacted information 03Jul2014

Study Sites: 9 sites in the US

Publications: 4 abstracts

Studied Period (Years): First Subject First Visit: 31 January 1991 Last Subject Last Visit: 22 April 2009	**Phase of Development:** 3 and 4

Objectives:

The objective of the Phase 3 treatment period was to evaluate the safety and efficacy of leuprolide acetate for depot suspension in the treatment of central precocious puberty (CPP). Efficacy was evaluated based on Tanner staging and decrease of gonadotropins and sex steroids to prepubertal levels.

The objective of the Phase 4 follow-up period was to determine, by means of long-term observation, whether there was any influence on final adult height and eventual sexual maturation, including evidence of reproductive potential, of children treated with leuprolide acetate for CPP.

Methodology:

The Phase 3, open-label, multicenter study utilized hormonal and physical measurements to evaluate the effect of leuprolide acetate for depot suspension in children with CPP.

Pretreatment procedures and evaluations included a medical history, a physical examination that included Tanner staging, clinical laboratory tests that included radiograph for bone age, gonadotropin-releasing hormone (GnRH) stimulation test (leutenizing hormone [LH], follicle stimulating hormone [FSH]), sex steroid levels (testosterone or estradiol), hematology, and chemistry), and bone age assessment for prediction of adult height using the Bayley-Pinneau method. Procedures and evaluations included physical exam, Tanner staging, height, weight, bone age, GnRH stimulation tests, sex steroid measurements, clinical labs, bone density (selected sites only), pelvic ultrasound (selected sites for girls only), and menstrual history. Study visits for safety and efficacy assessments during the treatment period were to be scheduled for Weeks 4, 8, 12, 24, 36, 48, and then every 6 months thereafter until the study drug was discontinued.

During the Phase 4 follow-up period, study visits were scheduled every 6 months until pubertal hormone levels were observed (males: peak LH > 10 U/L, peak FSH ≥ 2.5 U/L, testosterone ≥ 75 mg/dL; females: peak LH ≥ 6 U/L, peak FSH ≥ 5 U/L, estradiol ≥ 15 pg/mL). In addition to assessment of basal and stimulated hormone levels, study visits included physical exam, Tanner staging, height, weight, bone age, pelvic ultrasound (selected sites for girls only) menstrual history, and sexual history. Once pubertal development resumed and hormone values reached pubertal levels, study visits were scheduled every 12 months for 5 years. Subsequently, subjects were to be contacted annually until the age of 21 to complete a questionnaire on physical assessment, menstrual history, and sexual history.

Number of Subjects (Planned and Analyzed):

Planned: 50 or more subjects

Phase 3 Treatment Period: 55 subjects enrolled; all 55 subjects were in the intent-to-treat (ITT) population for efficacy analysis and in the safety analysis set.

Phase 4 Post-Treatment Follow-up Period: 40 subjects in the ITT population analyzed for efficacy; all 55 subjects who received at least 1 dose of study drug were included in safety analyses.

Diagnosis and Main Criteria for Inclusion:

Children with CPP, onset of Tanner stage II or greater for breast or pubic hair earlier than age 8.0 years in girls or stage 2 pubic hair or genitalia earlier than 9.0 years in boys; a pubertal response to GnRH stimulation (LH ≥ 10 U/L); chronological age < 9.0 (girls) and < 10.0 (boys) at study entry; bone age advanced at least 1 year beyond chronological age by Fels Method; if CPP was secondary to another lesion, therapy of the primary condition had been undertaken and stabilized; no evidence of abnormal pituitary, adrenal, thyroid, and gonadal function except for premature secretion of gonadotropins; eligible for therapy for at least 1 year; no irradiation to the central nervous system; no prior therapy with medroxyprogesterone acetate and/or with any GnRH analog (including prior treatment with daily subcutaneous and depot formulations of leuprolide acetate).

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

All 55 subjects were started on 7.5 mg, 11.25 mg, or 15 mg leuprolide acetate based on their weight, as it was recommended to investigators to start subjects at 300 mcg/kg. Study drug was administered intramuscularly (IM) every 28 days, with incremental adjustments of 3.75 mg at each clinic visit, if necessary, based on clinical and laboratory results. Factrel (100 mcg vials) was administered using standard method (100 mcg IV bolus) as part of the hormone stimulation test at Baseline and on Weeks 4, 8, 12, 24, 36, 48, and every 6 months thereafter during the treatment period. During the follow-up period, the hormone stimulation test was performed using Factrel every 6 months until a pubertal response was observed. The study drug lot numbers are listed as follows:

Product	**Lot Numbers**			
Leuprolide Acetate Dual-Chamber Syringe 7.5 mg Commercial Kit	55265AP21			
Leuprolide Acetate Dual-Chamber Syringe 15 mg Commercial Kit	64583AP21	58389AP21	58389AP22	53203AP21
Leuprolide Acetate 3.75 mg Vial	14-126-AP 14-126-S2 14-216-S2 46-164-AR 50-579-AR	51-644-AR 52-644-AR 52-827-AR 56-184-AR 56-185-AR	69-741-AR 69-757-AR 69-765-AR 69-767-AR 69-770-AR	87-193-S2 87-196-S2
Leuprolide Acetate 7.5 mg Vial	05-152-AP 05-267-S2 05-367-S2 22-657-S2	44-842-AR 50-579-AR 52-827-AR 56-184-AR	69-738-AR 69-764-AR 69-767-AR 69-770-AR 69-773-AR 69-776-AR	73-052-S2 73-053-S2 75-215-S2 75-216-S2
Diluent 1.5 mL Ampule	09-327-AP 21-318-AP 44-843-AR 46-165-AR 50-580-AR 51-645-AR	52-645-AR 52-827-AR 52-828-AR 56-185-AR 69-739-AR 69-742-AR	69-763-AR 69-765-AR 69-767-AR 69-768-AR 69-771-AR 69-774-AR 69-777-AR	73-053-S2 75-216-S2 87-194-S2 87-197-S2 96-152-AP 96-452-AP
Diluent 2.0 mL Ampule	21-316-AP 21-318-AP			
Factrel 100 mcg Vial	390651 3900195 3900196	3920238 3920551 3920651	3940528 3940628 3960389	3970454 3970755

Duration of Treatment:

Subjects were to continue study drug administration until the appropriate age. It was suggested that study drug treatment be discontinued at age 12 years (± 6 months) for males and 11 years (± 6 months) for females.

Criteria for Evaluation

Efficacy: The efficacy assessments were Tanner staging (pubic hair and genital development in males and pubic hair and breast development in females), basal and stimulated FSH and LH levels, basal and stimulated testosterone and estradiol levels, bone age using Fels Method, height, and record of menses.

The intent-to-treat (ITT) population for the treatment period included all 55 subjects who received at least 1 dose of study drug, regardless of the dose(s) received. Demographic data were summarized for all 55 subjects where data were available.

The ITT population for efficacy analysis for the post-treatment follow-up period consisted of all 40 subjects who had at least 1 injection of study drug in the treatment period and who had appropriate follow-up data. Demographic data were summarized for the ITT follow-up subjects with Tanner staging data during follow-up.

Safety: The safety analysis set for both the treatment period and the post-treatment follow-up period included all 55 subjects who received at least 1 dose of study drug, regardless of the dose(s) received. Safety was assessed by evaluating study drug exposure, adverse events, serious adverse events, changes in clinical laboratory determinations, vital signs, and bone mineral density.

Statistical Methods

Efficacy: The percentages of subjects with suppression (i.e., regression or no progression) during the treatment period or development during the follow-up period in Tanner staging (breast and pubic hair in females and genital and pubic hair in males) with 95% binomial exact confidence intervals were calculated. Means and mean changes from baseline or the end of treatment in basal and stimulated LH and FSH levels, basal and stimulated estradiol and testosterone levels, bone age related variables, and height related variables were summarized at each applicable time point during the treatment and follow-up periods. Height related variables were also summarized at final or near final adult height. Paired t-tests were used to test the change from baseline or end of the treatment. The percentage of subjects with high LH value (> 1.75, 3 or 4 IU/L), and the percentage of subjects with menses, spotting and any bleeding during the treatment period were summarized. Time to and age at first menses during the follow-up period were summarized.

Safety: Adverse events during treatment and follow-up periods were summarized. Safety laboratory, vital sign and bone mineral density data during the treatment period were summarized.

Summary/Conclusions

Efficacy Results:

Treatment Period

Suppression of the clinical/physical signs of puberty, assessed as regression or no change in breast Tanner staging in girls, genitalia Tanner staging in boys, and pubic hair Tanner staging in both girls and boys was rapidly achieved and sustained after initiation of treatment. Suppression of breast development in girls was 81.8% (36/44) at Week 4, and then ranged from 66.7% to 90.6% through Week 240 (5 years). In boys, suppression of genitalia development was 80% (4/5) at Week 4, and then ranged from 60% to 100% through Week 240. Pubic hair development was suppressed in 88.6% (39/44) of girls and 80% (4/5) of boys at Week 4, and suppression through Week 240 ranged from 56.3% to 91.5% in girls and from 50% to 100% in boys.

Treatment with leuprolide acetate for depot suspension was effective in rapidly suppressing bleeding and spotting in subjects who had menarche at baseline and in subjects who experienced a transient bleeding

Efficacy Results (Continued):

or spotting episode during the first 4 weeks of treatment.

As anticipated, rapid suppression of gondadotropins and sex steroids to prepubertal levels was attained. Within 1 month of starting treatment, more than 95% of subjects (53/55) had suppression of peak stimulated LH concentrations to < 1.75 mIU/mL. Mean peak stimulated LH concentrations were suppressed to 0.8 mIU/mL at Week 4 and further decreases were observed for the remainder of the treatment period with mean peak stimulated LH concentrations suppressed to ≤ 0.5 mIU/mL at all but 1 visit at Week 168. All subjects eventually suppressed, with five subjects requiring increased doses of study drug to achieve LH suppression. Mean basal and stimulated estradiol levels were decreased to the lower limit of quantitation (5 pg/mL) by Week 4 and nearly all subsequent visits. Mean stimulated and basal testosterone concentrations for males were suppressed to 18 ng/dL by Week 4 and were maintained at concentrations ≤ 25.3 ng/dL throughout the treatment period.

The mean ratio of bone age to chronological age decreased slowly during treatment from 1.5 at baseline and Week 24 to 1.2 at Week 144 and thereafter, showing that on average the subjects' chronological age was getting closer to their bone age.

The mean cumulative growth rate (calculated from baseline to each visit) decreased from 10.6 cm/yr at baseline to 6.5 cm/yr by Week 8, showing a rapid response to leuprolide acetate treatment. Thereafter, through Week 240 (5 years), the mean cumulative growth rate ranged between 5.1 cm/yr and 7.3 cm/yr, indicating that subjects maintained a fairly constant growth rate while on treatment.

Post-Treatment Period

Following discontinuation of leuprolide acetate treatment, the majority of subjects showed clinical signs of development (increase in Tanner staging score since the end of treatment) at the first 6-month follow-up visit. Breast development over that present at the end of treatment was reported in 66.7% (16/24) of girls at Follow-up Week 24 (6 months post-treatment) and in 100% (16/16) of female subjects at Follow-up Week 192 (4 years post-treatment). In boys, further genitalia development over that present at the end of treatment was reported for 80% (4/5) of male subjects at Follow-up Week 24 and in 100% (2/2) at Follow-up Week 144 (3 years post-treatment).

After stopping treatment, regular menses were reported for 27 of the 32 female subjects with available data. The mean time to regular menses was 561.3 days (approximately 1.5 years) after the end of treatment and the mean age at onset of menarche or remenarche was 12.9 years.

Peak stimulated LH values increased from an end of treatment mean of 0.4 mIU/mL to 20.6 mIU/mL at the first post-treatment follow-up visit (Follow-up Week 24). Both mean stimulated and mean basal sex steroid levels (estradiol and testosterone) reached pubertal levels at the first 6 month follow-up visit (Follow-up Week 24). These data indicate that suppression of gonadotropins and sex steroids induced during treatment with leuprolide acetate is reversible after stopping treatment.

The mean ratio of bone age to chronological age was 1.1 at the end of treatment and ranged between 1.08 and 1.12 during the first 5 years of post-treatment follow-up, indicating that bone age remained slightly advanced compared to chronological age.

Efficacy Results (Continued):

A small but clinically significant increase in growth rate, indicating a "growth spurt," was observed during the first year post-treatment, with an increase from 3.47 cm/yr at end of treatment to 4.36 cm/yr at 24 weeks post-treatment and 4.85 cm/yr at the end of the first year post-treatment. The mean growth rate subsequently decreased to 3.66 cm/yr by the end of the second year post-treatment, 1.86 cm/yr by the end of the third year, and 0.41 cm/yr by the end of the fifth year post-treatment.

At the end of treatment, the mean standardized height score was 0.7, which is clinically significantly taller than the standard population. The mean standardized height score decreased to –0.1 by the end of the fifth year post-treatment. At final or near final adult height, the 33 subjects with available height data had a mean standardized height score of –0.2, and the 19 subjects who had height collected at adulthood had a mean standardized height score of 0.0, indicating that the mean final adult height was equivalent to that of the standard population. Eighty-one percent (26/32) of subjects with final or near final adult height were within their target height range based on their parents' height, and 88.9% (17/18) with height measured at adulthood and a target height had a final adult height that was within this range.

The mean height gain (height minus predicted mature height at baseline calculated from bone age) was –5.5 cm at the end of treatment and slowly increased to + 4.1 cm by the end of the 5th year post-treatment. On average, the 29 subjects with final or near final data and predicted mature height at baseline had a height gain of 3.2 cm and the 17 subjects with available data at adulthood had a height gain of 3.9 cm.

Data to assess reproductive function were collected for 20 girls with CPP treated with leuprolide acetate who reached adulthood. This consisted of questionnaire data on all 20 subjects and ultrasound data for 11 subjects. Menstrual cycles were reported to be normal for 16 of the 20 subjects. Ovarian cysts were reported in 3 of the 20 subjects: 1 subject had cysts observed on final ultrasound and 2 subjects had prior history of ovarian cysts and diagnosis of polycystic ovarian syndrome (PCOS), including 1 with a final ultrasound that revealed no ovarian cysts. Twelve pregnancies were reported for 7 of the 20 subjects, including multiple pregnancies for 4 subjects. The outcomes of the pregnancies included 6 live births, 5 miscarriages/elective terminations of pregnancy, and 1 ongoing pregnancy.

Safety Results:

Forty-seven of the 55 subjects received study drug for longer than 2 years, including 26 subjects who received study drug for longer than 4 years. The mean duration of exposure was approximately 4 years (1418.3 ± 744.3 days). Throughout the study, 6 subjects received a maximum dose of 7.5 mg, 17 subjects received a maximum dose of 11.25 mg, and 30 subjects received a maximum dose of 15 mg.

Safety Results (Continued):

Treatment-emergent adverse events were reported for 94.5% of subjects (52/55). The most common adverse events were pharyngitis (53%), headache (45%), flu syndrome (35%), rash (33%), and cough increased (31%). Adverse events that were treatment-related (i.e., considered possibly or probably related to study drug by the investigator) were reported for 62% of subjects (34/55). The most common treatment-related adverse events were emotional lability (18%), injection site pain (13%), and headache (11%). The most common adverse events associated the route of study drug administration or hormonal changes were rash (33%), acne (27%), emotional lability (27%), injection site pain (15%), and vasodilatation (11%). The adverse events of interest were mostly mild to moderate in severity and none resulted in discontinuation of study drug. A total of 11 subjects had injection site adverse events, and the majority of these events were mild and lasted no more than 2 to 4 days. None of the injection site adverse events were serious or resulted in discontinuation of study drug.

One treatment-emergent death was reported that was considered not related to study drug by the investigator. Subject 701 died from a respiratory infection and heart arrest after more than 600 days of treatment. This subject was the only subject who prematurely discontinued treatment due to an adverse event (heart arrest). Other serious adverse events were reported for 7 subjects, but only the serious adverse events in 2 of these subjects (increase in size of pre-existing optic glioma and deteriorating vision and severe asthma exacerbation) were assessed by the investigator as possibly related to study drug.

The laboratory values over time showed no abnormal consistent trends or clinically significant mean changes from baseline. In general, there were few subjects with shifts for most variables, and there were no apparent trends. None of the very high or very low values were reported as adverse events.

Conclusions:

Leuprolide acetate for depot suspension administered at doses up to 15 mg every 28 days was generally well tolerated in this population of 55 female and male subjects with CPP who ranged from 1 to 9 years of age at the beginning of treatment and were treated for an average of 1418.3 days. During the treatment period, monthly leuprolide acetate for depot suspension rapidly and consistently suppressed clinical and hormonal parameters of puberty to prepubertal levels and maintained suppression. All patients studied had resumption of a pubertal hypothalamic-pituitary-gonadal axis within 12 months after therapy was discontinued as evidenced by clinical characteristics and hormonal concentrations. The long-term follow-up observation period revealed that leuprolide acetate treatment was associated with gains in adult height. The subjects who had height collected at adulthood had a mean standardized height score of 0.0, indicating that the mean final adult height was equivalent to that of the standard population. Girls with CPP treated with leuprolide acetate appeared to have normal reproductive function in adulthood, including menstrual cyclicity and pregnancy rates.

Overall, long-term treatment with leuprolide acetate is safe, rapidly reduces hormone production to prepubertal levels, suppresses the clinical signs of puberty, preserves adult height potential and does not appear to have any negative effects on reproductive function.