2.0 Synopsis

<table>
<tr><td>AbbVie Endocrine Inc.</td><td rowspan="3">Individual Study Table Referring to Part of Dossier:
Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug: A-43818 (ABT-818) leuprolide acetate for depot suspension (Lupron Depot)
Although the United States Adopted Names (USAN) name of leuprolide acetate is used for this study, the international nonproprietary name (INN) for this compound is leuprorelin acetate.</td></tr>
<tr><td>Name of Active Ingredient: Leuprolide acetate</td></tr>
<tr><td colspan="3">Title of Study: A 36 Month, Multi-Center, Open-Label Extension Study to Evaluate the Safety of Leuprolide Acetate 11.25 mg and 30 mg Formulations in Children with Central Precocious Puberty</td></tr>
<tr><td colspan="3">Investigator: Peter A. Lee, MD, PhD, [redacted] redacted information 10Jun2014</td></tr>
<tr><td colspan="3">Study Sites: Twenty (20) sites in the United States and Puerto Rico</td></tr>
<tr><td colspan="3">Publications: Lee PA, Klein K, Mauras N, et al. 24 months treatment experience of two leuprolide acetate 3 month depot formulations for children with central precocious puberty. Horm Res. 2012:78(supp1).</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject First Visit: 02 December 2008
Last Subject Last Visit: 08 January 2013</td><td>Phase of Development: 3</td></tr>
<tr><td colspan="3">Objectives:
The objective of this study was to assess the long-term safety of continued treatment with 11.25 mg and 30 mg 3 month (3M) depot formulations of leuprolide acetate over 36 months of treatment in children with central precocious puberty (CPP). This included the maintenance of luteinizing hormone (LH) suppression and the effects on pubertal symptoms, sex steroid levels, and bone age.</td></tr>
</table>

Methodology:

The L-CP07-177 study was a Phase 3, open-label, multicenter clinical study designed to evaluate the safety of leuprolide acetate 3M depot 11.25 mg and 30 mg (also referred to hereinafter as investigational product) in approximately 70 children with confirmed CPP who successfully completed and showed maintenance of LH suppression through the 6-month treatment period of the pivotal lead-in Study L-CP07-167 (referred to hereinafter as the pivotal study). Eligible subjects for this extension study were to receive a total of 12 IM injections of the same treatment they were previously assigned in the pivotal study (i.e., either leuprolide acetate 3M depot 11.25 mg or 30 mg). Each injection was to be administered 3 months apart for up to 36 months of treatment. The first injection was to be administered at Study Day 1; subsequent injections were to be administered at Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33. Dose adjustments were not permitted during the Treatment Period.

This study did not have a screening period; instead, subjects were assessed for eligibility during the Month 6 study visit of the pivotal study. For eligible subjects, the Day 1 visit for this study began the same day and subjects received their first injection. If a subject failed to qualify for this study, the subject entered the Follow-Up Period of the pivotal study and continued to be assessed as stated by its respective protocol.

For subjects enrolled in this extension study, the Month 6 study assessments of the pivotal study were considered as predose Day 1 for this extension study and had to be completed prior to their study drug injection on Day 1.

In addition to the Month 6 study assessments of the pivotal study and administering the informed consent for this extension study, the Day 1 procedures included updating the medical history, administering the leuprolide acetate 3M depot 11.25 mg or 30 mg injection, injection site assessment, hormonal flare response assessments, dispensing the menstrual bleeding calendar (for girls), and collection of adverse events and concomitant medications.

Subjects were assessed for safety and continued maintenance of suppression throughout the Treatment Period. Study visits occurred at Day 1, Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30 and 33 (1^{st} through the 12^{th} leuprolide acetate 3M depot injections, respectively), Month 36, and at the Safety Follow-up Visit. The study assessments at prespecified times included physical examination with vital signs; height and weight; adverse event and concomitant medication assessments, safety laboratory assessments, hormonal flare response assessments, injection site reaction assessments, pubertal staging (breasts in girls, genitals in boys, pubic hair in both boys and girls) and testicular volume in boys; Gonadotropin-releasing hormone (GnRHa) stimulation testing with blood draws for basal and peak-stimulated LH levels, and sex steroid estradiol (girls) and testosterone (boys) levels; transabdominal pelvic ultrasound for determination of uterine and ovarian volumes in girls, assessment of menstrual bleeding calendar in girls, and hand/wrist bone age radiographs for determination of bone age and predicted adult height. Pregnancy testing in girls was performed at the discretion of the investigator and/or based on Institutional Review Board (IRB) requirements.

Methodology (Continued):

Enrollment continued until all eligible subjects who participated in the pivotal study and consented to participate in this extension study, approximately 70 subjects, had been enrolled.

At the end of the Treatment Period, subjects who completed the study, or prior to resuming treatment at Month 15, or prematurely discontinued from the study entered the Safety Follow-up Period were offered standard of care treatment with Lupron Depot-PED® Monthly (either 7.5 mg, 11.25 mg, or 15 mg monthly) through the Safety Follow-up Visit, as deemed appropriate by the treating endocrinologist.

Number of Subjects (Planned and Analyzed): 70 planned; 72 enrolled and analyzed for safety; 71 analyzed for efficacy for this interim report

Diagnosis and Main Criteria for Inclusion:

Subjects had documented LH suppression as evidenced by peak-stimulated LH < 4 mIU/mL at the Month 6 study visit of the pivotal study; demonstrated suppression of the physical signs of puberty at Month 6 of the pivotal study (defined as regression or no progression of breast development according to pubertal staging in girls or regression or no progression in testicular volume and genital staging according to pubertal staging in boys). There was no age requirement; participation was based on whether the subject had the potential to benefit from an additional 12 months of GnRHa treatment.

Subjects were excluded if they had a diagnosis of incomplete precocious puberty, peripheral precocious puberty, or evidence of any abnormal pituitary, hypothalamic, adrenal, thyroid and gonadal function other than premature secretion of gonadotropins not adequately controlled, unstable intracranial tumors (unresponsive to treatment/expanding) except hamartoma; bone age ≥ 14.00 years for girls and ≥ 15.00 years for boys; had a chronic illness requiring treatment that may have interfered with growth; was receiving therapy with growth hormone, insulin-like growth factor, or an estrogen preparation.

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, each administered monthly) for standard-of-care treatment. Leuprolide acetate depot 11.25 mg and 30 mg were administered intramuscularly (IM) every 3 months. A dose of 20 mcg/kg of leuprolide acetate daily injection and/or the commercially available generic leuprolide acetate (Leuprolide Acetate Injection) was administered subcutaneously (SC) for the stimulation test. The lot numbers for study drug and other medications supplied to the sites are listed as follows.

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

	Formulation	Dosage	Mode of Administration	Finishing Lot Number	Manufacturer and Location
Investigational Product					
Leuprolide acetate depot 11.25 mg	11.25 mg syringe	11.25 mg (approximately 1.7 mL)	IM	699992E 879332E21	[redacted]
Leuprolide acetate depot 30 mg	30 mg syringe	30 mg (approximately 1.7 mL)	IM	688242E 880262E21	[redacted]
Other Medication					
Leuprolide Acetate Injection	5 mg/mL (1 mg/ 0.2 mL) supplied in a 2.8 mL multiple dose vial	20 mcg/kg (varied based on subject weight)	SC	08RP026	[redacted]
Leuprolide Acetate Injection	5 mg/mL (1 mg/0.2 mL) supplied in a 2.8 mL multiple dose vial	20 mcg/kg (varied based on subject weight)	SC	31305745B JKJ0299A JKJ0834A JKK2226A JKL0593A	[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 or 15 mg q month (approximately 1.1 mL)	IM	Not Available[a]	[redacted]

a. Commercial Lupron Depot-PED was provided to sites by Pharmacy Solutions or locally procured; lot numbers were not recorded in the study database.

Duration of Treatment: Subjects were to be administered investigational product at the study visit on Day 1. Subsequent injections were to be administered 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33 months later.

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

None

redacted information 10Jun2014

Criteria for Evaluation

Efficacy (N = 71): Subjects who received who received at least 1 dose of investigational product in this extension study and had at least 1 postbaseline measurement of any maintenance of suppression variable. Any subjects who were prematurely discontinued because they were subsequently found to have failed to have maintained suppression at Month 6 of the pivotal lead-in study (either based on peak-stimulated LH or bone age radiograph) were excluded from the intent-to-treat (ITT) population.

Safety (N =72): Subjects who received at least 1 dose of leuprolide acetate depot.

Statistical Methods

Efficacy:

The following analyses were performed: percentage of subjects suppressed and the 2-sided 95% binomial exact confidence intervals for LH (peak-stimulated < 4 mIU/mL), peak-stimulated LH concentrations at Months 6, 12, 24, 36 and the Final Treatment Visit; suppression of sex steroids (estradiol, < 20 pg/mL in girls; testosterone < 30 ng/dL in boys), and physical signs of puberty (regression or no progression of breast development in girls and genital development in boys according to pubertal staging, and testicular volume in boys by Prader beads); and the ratio of change from baseline in bone age/change from baseline in chronological age at Day 1, Months 12, 24, 36 and the Final Treatment Visit. The paired t-test was used to test the significance of the change versus no change for growth rate.

Safety:

The number and percentage of subjects with treatment-emergent adverse events were tabulated by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), and were further summarized by maximum severity and maximum investigator-assigned relationship to study drug. Clinical laboratory were summarized for mean changes to each study visit, by shifts relative to the laboratory normal ranges, and by the number and percentage of subjects with values that met the predefined criteria for potentially clinically significant (PCS) values. Vital sign results were summarized for mean changes to each study visit. The average number of days of bleeding, spotting or bleeding/spotting per month and the change from baseline in the average number of days were summarized by treatment group for girls. Data collected from the examinations of the injection sites corresponding to the first, second, third or fourth leuprolide acetate 3M depot injections in this extension study were summarized by treatment group. Data on hormonal flare response collected from assessments performed after each of the leuprolide acetate 3M depot injections were summarized by treatment group.

Summary/Conclusions

A total of 72 subjects who completed the treatment period of the pivotal Study L-CP07-167 enrolled in this study from 20 sites received the same investigational product they had received in the pivotal study. The majority of subjects were female (90.3%) and white (56.9%). The demographic characteristics were generally similar between dose groups, and between the subgroups of subjects based on previous GnRHa treatment status prior to the extension study. A total of 24 subjects completed the 36-month Treatment Period, and 48 subjects discontinued treatment. Seven (7) subjects had a gap between Protocol Amendment 1 and Amendment 2 and resumed treatment with the leuprolide acetate 3M depot after being on Lupron Depot monthly. One of these subjects received the 3M and monthly doses during the gap period. A total of 53 subjects completed the 12-week Safety Follow-Up Period, and 1 subject discontinued treatment.

Efficacy Results:

Sixty-seven of the 69 subjects (31/33 [94%] subjects in the 11.25 mg group and all 36 subjects [100%] in the 30 mg group) with peak-stimulated LH data after Day 1 were successfully suppressed with LH values < 4 mIU/mL at their Final Visit in this study. Seven subjects (5 subjects in the 11.25 mg dose group and 2 subjects in the 30 mg dose group) escaped LH suppression at any time during the study. All of these subjects maintained suppression of sex steroids to prepubertal levels and showed no clinical signs or symptoms of lack of suppression.

The mean peak-stimulated LH concentrations were consistently maintained at less than 2.24 mIU/mL for each dose group and were consistently lower in the 30 mg dose group (≤ 1.62 mIU/mL) than in the 11.25 mg dose group (≤ 2.24 mIU/mL).

The laboratory responsible for analysis of LH and sex steroids, altered the assay for estradiol during the conduct of the study to one with a different lower limit of quantitation (LLOQ) (changed from 1 pg/mL to 10 pg/mL). Estradiol suppression to prepubertal levels (< 20 pg/mL) was maintained in all female subjects for whom an LLOQ of 1 pg/mL was applied and for at least half of the female subjects for whom LLOQ of 10 pg/mL was applied, at every visit with the exception of: Months 12 and 36 as well as the Final Visit in the 11.25 mg dose group and Months 9, 24, and 26 as well as the Final Visit in the 30 mg dose group.

At any time during the study, 17 female subjects (6 subjects in the 11.25 mg group and 11 subjects in the 30 mg group) had progression of breast development and 3 male subjects in the 30 mg group had progression of genitalia development or increased testicular volume. For both sexes, progression of the clinical sexual characteristics of puberty during this extension study did not correlate with lack of peak-stimulated LH suppression. However, the progression did occur coincident with or after a visit where basal estradiol was not suppressed in several female subjects.

There was a rapid decrease from baseline in growth rate with leuprolide acetate 3M depot following treatment in the pivotal study with mean decreases of –1.67 and 1.65 cm/year by Day 1 of this extension study for the 11.25 mg group and 30 mg group, respectively. Mean decreases from baseline at subsequent visits ranged from –1.66 to –2.64 cm/yr for the 11.25 mg group and from –1.59 to –2.64 cm/yr for the 30 mg group.

The decrease in growth rate caused small mean decreases in height standardized score to bring subjects closer to the normal population height by the end of treatment for both the 11.25 mg and 30 mg dose groups. The mean body mass index (BMI) standardized scores showed little change during treatment in either dose group.

Overall, administering up to 36 months of additional treatment with leuprolide acetate 3M depot 11.25 mg or 30 mg maintained LH suppression in all but 7 subjects (5 subjects in the 11.25 mg group and 2 subjects in the 30 mg group). The majority of subjects did not exhibit clinical progression in physical signs of puberty or sex steroids during this 36-month extension.

Safety Results:

Leuprolide acetate 3M depot 11.25 mg and 30 mg, each administered IM every 3 months, were generally well tolerated in this population of 72 subjects (65 female, 7 male) with CPP who ranged from 2 to 11 years of age at the beginning of the pivotal lead-in Study L CP07-167. The safety profiles of the 2 dose groups were generally similar during this extension study based on the 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 97.1% (33/34) of subjects in the leuprolide acetate 3M depot 11.25 mg dose group and 89.5% (34/38) of subjects in the leuprolide acetate 3M depot 30 mg dose group. Treatment emergent adverse events reported for more than 20% of subjects in either dose group were cough (11.8% 11.25 mg group, 23.7% 30 mg group), injection site pain (29.4% 11.25 mg group, 23.7% 30 mg group), and upper respiratory tract infection (26.5% 11.25 mg group, 13.2% 30 mg group). Other adverse events reported for at least 10% of subjects in either dose group included arthralgia (11.8% 11.25 mg group, 13.2% 30 mg group), gastroenteritis (11.8% 11.25 mg group, 10.5% 30 mg group), headache (14.7% 11.25 mg group, 15.8% 30 mg group), nasal congestion (8.8% 11.25 mg group, 13.2% 30 mg group), pharyngitis streptococcal (14.7% 11.25 mg group, 10.5% 30 mg group), pyrexia (17.6% 11.25 mg group, 13.2% 30 mg group), and vomiting (0% 11.25 mg group, 10.5% 30 mg group).

The majority of adverse events were mild or moderate in intensity. A total of 7 adverse events were rated as severe by the investigator (1 event each of arthropod bite, headache, intracranial pressure, injection site pain, migraine, pharyngitis streptococcal, and sinusitis).

There were no deaths or adverse events that led to discontinuation of study drug. One treatment-emergent serious adverse event (SAE) (2 occurrences of the SAE of intracranial pressure increased in 1 subject and considered not related to study drug by the investigator) was reported. One subject had a SAE of depression that was not treatment-emergent in this study, but began in the pivotal study and ended on Day 1 of this extension study.

Injection site pain and weight increased were the only treatment-related adverse events (i.e., possibly or definitely related to study drug by investigator assessment) reported for more than 1 subject each. The incidence of weight increased, regardless of relationship to study drug, was present in the 30 mg dose group (7.9% of subjects [3/38]) and absent (0 subjects) in the 11.25 mg dose group.

In addition to injection site adverse event reports, the adverse event company MedDRA query (CMQ) of injection site reaction and separate symptom questionnaire were used to further evaluate events associated with the route of administration. The incidence of all adverse events in the CMQ of injection site reaction was similar in each dose group (29.4% for 11.25 mg dose; 26.3% for 30 mg dose). The incidence of injection site pain, regardless of relationship to study drug, was slightly more common in the 11.25 mg dose group (29.4% of subjects [10/34]) than the 30 mg dose group (23.7% of subjects [9/38]). The adverse events in the CMQ of injection site reaction were mild or moderate for all but 1 subject (in the 11.25 mg group) who had 1 severe adverse event of injection site pain.

Safety Results (Continued):

An assessment of the leuprolide acetate 3M depot injection sites separate from adverse event reporting (performed by the site using a nonvalidated study-specific symptom questionnaire at the site just after each injection and by phone call to the parents on the day after each injection) indicated injection site symptoms following any injection for 73.5% of subjects in the 11.25 mg dose group and 78.9% of subjects in 30 mg dose group, with no trend for increasing incidence over time. The high percentage of subjects with injection site symptom reports may be due to protocol-specified assessment collection instructions, solicited questions, and most were not reported as adverse events.

The signs and symptoms captured by the Injections Site Assessment questionnaire were most prevalent during the first few injections and generally declined with further follow-up. Approximately 28% of the subjects with symptoms reported on the injection site questionnaire also had an adverse event in the injection site reaction CMQ reported after the same injection. The most common symptoms reported on the questionnaire following any injection (> 15% in any dose group) were tender or painful feeling at site of injection, redness at injection site, swelling at injection site, and limitation of limb movement. Evaluation of injection site symptom information obtained by questionnaire did not reveal any unexpected findings.

Changes in behavioral or physical symptoms that may be expected based on increases in sex steroids following a potential acute-on-chronic response (first 14 days following each injection) were also collected via questionnaire, and included the following descriptions: more crying, more emotional, increased temperature, more mood swings, very tired, headache, anxiety, anxious, general achiness, hot flashes, increased emotional liability, increased moodiness, mild behavioral issues, and stomachache. None of the observations correlated with escapes from peak-stimulate LH suppression or failure to maintain prepubertal levels of sex steroids.

No safety concerns were identified based on laboratory testing and measurements of vital signs. Decreases in creatinine were observed with mean changes of –2.8 mcmol/L for the 11.25 mg dose group and –1.7 mcmol/L for the 30 mg dose group at Final Visit and no subject in either dose group with shifts from normal or high baseline values to values below the normal range at Final Visit. This decrease in creatinine is not in the direction of concern for renal function. Plasma creatinine levels increase during puberty and the observed changes may be due to hormonal suppression which in turn may decrease creatinine to prepubertal levels.

Despite some laboratory values meeting criteria for PCS, a single laboratory abnormality, in a female subject in the 11.25 mg group with transient hemoglobin decreased judged not related to study drug by the investigator, was reported as an adverse event.

Small changes from baseline with no trend with regard to direction of change from baseline over time were observed for vital signs in both leuprolide acetate 3M depot dose groups. Four events of increased weight and 1 event of blood pressure increased were vital sign abnormalities reported as adverse events.

There were no reports of bleeding and spotting was reported in 5 subjects (2 subjects in the 11.25 mg dose group and 3 subjects in the 30 mg dose group) during this extension study for any of the 56 female subjects with data from bleeding calendars.

Conclusions:

Overall, continued treatment with leuprolide acetate 3M depot 11.25 mg or 30 mg in this extension study maintained LH suppression in all but 7 subjects (5 subjects in the 11.25 mg dose group and 2 subjects in the 30 mg dose group) as well as sex steroid suppression in the majority of subjects in the study. Most subjects with progression of physical signs of puberty did not have associated increases in LH or sex steroids; however, several female subjects did have basal estradiol that was not suppressed coincident with or immediately preceding a progression in breast development. Growth rate was decreased and maintained at a rate appropriate for chronological age. No unexpected safety concerns were identified and the safety profile was similar between treatment groups. The results from this 36-month safety extension study provide evidence of continued maintenance of suppression for LH, sex steroids, and pubertal symptoms in the study population.