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Efficacy and Safety of Leuprolide Acetate 6-Month Depot for the Treatment of Central Precocious Puberty: A Phase 3 Study

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Abstract

Context: Treatment options for central precocious puberty (CPP) are important for individualization of therapy.

Objective: We evaluated the efficacy and safety of 6-month 45-mg leuprolide acetate (LA) depot with intramuscular administration.

Methods: LA depot was administered at weeks 0 and 24 to treatment-naïve (n = 27) or previously treated (n = 18) children with CPP in a phase 3, multicenter, single-arm, open-label study (NCT03695237). Week 24 peak-stimulated luteinizing hormone (LH) suppression (<4 mIU/mL) was the primary outcome. Secondary/other outcomes included basal sex hormone suppression (girls, estradiol <20 pg/mL; boys, testosterone <30 ng/dL), suppression of physical signs, height velocity, bone age, patient/parent-reported outcomes, and adverse events.

Results: All patients (age, 7.8 ± 1.27 years) received both scheduled study doses. At 24 weeks, 39/45 patients (86.7%) had LH suppressed. Six were counted as unsuppressed; 2 because of missing data, 3 with LH of 4.35–5.30 mIU/mL and 1 with LH of 21.07 mIU/mL. Through 48 weeks, LH, estradiol, and testosterone suppression was achieved in ≥86.7%, ≥97.4%, and 100%, respectively (as early as week 4 for LH and estradiol and week 12 for testosterone). Physical signs were suppressed at week 48 (girls, 90.2%; boys, 75.0%). Mean height velocity ranged 5.0 to 5.3 cm/year post-baseline in previously treated patients and declined from 10.1 to 6.5 cm/year at week 20 in treatment-naïve patients. Mean bone age advanced slower than chronological age. Patient/parent-reported outcomes remained stable. No new safety signals were identified. No adverse event led to treatment discontinuation.

Conclusion: Six-month intramuscular LA depot demonstrated 48-week efficacy with a safety profile consistent with other GnRH agonist formulations.

Key Words: central precocious puberty, leuprolide acetate, intramuscular depot, gonadotropin-releasing hormone agonist

Abbreviations: AE, adverse event; AESI, adverse event of special interest; AOC, acute-on-chronic; BA, bone age; BMI, body mass index; CA, chronological age; CPP, central precocious puberty; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; GnRHa, gonadotropin-releasing hormone agonist; IM, intramuscular; ISR, injection site reaction; LA, leuprolide acetate; LH, luteinizing hormone; MedDRA, ICH Medical Dictionary for Regulatory Activities; PedsQL, Pediatric Quality of Life Inventory; PROMIS, Patient Reported Outcomes Measurement Information System; SC, subcutaneous.

Central precocious puberty (CPP) occurs in 1 in 5000 to 10 000 children [1] and is one of the most common disorders presenting to pediatric endocrinologists. It manifests with hypothalamic pituitary activation, leading to precocious development of secondary sexual characteristics and accelerated advancement of bone age (BA) that can result in early cessation of linear growth [2, 3]. Pubertal timing is influenced by an interplay among genetic, environmental, nutritional, and other factors. However, compelling evidence has accumulated illustrating the role of genetic causal drivers on pubertal timing [4, 5] and mutations in the gonadotropin-releasing hormone (GnRH) axis are increasingly being identified in patients with CPP (most commonly in the *MKRN3* gene as well as in *KISS1*, *GPR54*, *PROKR2*, and *DLK1*) [6-11]. In CPP, the pulsatile release of hypothalamic GnRH that stimulates hypothalamic pituitary activation occurs prematurely. Continuous exposure to a GnRH agonist (GnRHa) suppresses gonadotropin release, most likely by desensitizing pituitary receptors to hypothalamic GnRH and altering the receptor function [2, 12]. GnRHa therapy is a standard treatment for CPP in appropriate patients, with treatment goals including suppression of luteinizing hormone (LH) and sex hormones, cessation of pubertal development, and normalization of BA advancement to preserve adult height [2, 12, 13].

Since the development of monthly intramuscular (IM) GnRHa for CPP [14, 15], further advances occurring in the

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past decade have led to additional long-acting GnRHa options with less frequent dosing becoming available to help individualize treatment, provide convenience, and potentially reduce morbidity associated with more frequent injections. Currently available GnRHa formulations in CPP include leuprolide acetate (LA) in a 1- or 3-month IM depot or 6-month subcutaneous (SC) depot, triptorelin pamoate in a 1- or 6-month IM depot, and histrelin acetate in a 12-month SC implant [3, 12, 16]. Here we present the initial 48-week efficacy and safety results from a phase 3 study of LA 45-mg 6-month IM depot use in children with CPP (NCT03695237) [17]. The primary efficacy objective was to evaluate suppression of LH after the first dose and at week 24; secondary efficacy objectives were to assess suppression of LH, sex hormones, and physical characteristics of puberty over 48 weeks of treatment, as well as changes in height velocity and BA advancement.

Methods

Study Patients

Children with a diagnosis of CPP were enrolled. They were either GnRHa-naïve or previously treated with a standard GnRHa. The diagnosis of CPP included the appearance of pubertal changes before chronological age (CA) of 8 years in girls or 9 years in boys and BA being advanced ≥1 year over CA. The GnRHa-naïve children had a peak-stimulated LH of ≥6 mIU/mL at screening and breast pubertal stage of ≥2 in girls or testicular volume of ≥4 cm^3 in boys. Girls had a BA of <13 years and CA of 2 to 8 years, if treatment naïve, or 2 to 10 years, if previously treated. Boys had a BA of <14 years and CA of 2 to 9 years, if treatment naïve, or 2 to 11 years, if previously treated. Exclusion criteria included a diagnosis of short stature, incomplete precocious puberty, peripheral precocious puberty, or any abnormalities in pituitary, hypothalamic, adrenal, thyroid, or gonadal function.

Study Design

A phase 3, single-arm, open-label, multicenter study was conducted in 2 parts at 16 sites in the United States including Puerto Rico. Part 1 consisted of a 48-week treatment period with 2 scheduled doses of study drug (1 dose at baseline and 1 dose at week 24) and was immediately followed by part 2, wherein patients received up to 4 additional doses over 96 weeks (Fig. 1). This paper presents efficacy and safety results for part 1 (first patient first visit October 24, 2018; last patient last visit October 18, 2021).

The study was conducted in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines, applicable regulations, and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki. Institutional review board approval was obtained at each participating site, written informed consent was provided by the patients' parents or legal guardians, and child assent was obtained as appropriate.

Study Treatment

The formulation used in this study was the same as the LA 45-mg 6-month IM depot approved for prostate cancer (LUPRON DEPOT, AbbVie, Inc., North Chicago, IL) [18]. It was administered as a single IM injection once every 24 weeks, in the same injection volume (1.5 mL) and using the same delivery system and sustained-release mechanism as the 3-month LA IM depot approved for CPP (LUPRON DEPOT-PED, AbbVie, Inc., North Chicago, IL) [19]. The delivery system consisted of a syringe and a prefilled dual chamber, with one chamber containing LA in a sterile lyophilized microsphere powder and the other a diluent that became reconstituted by pressing the plunger and gently shaking the syringe. Compared with the 3-month IM depot, the 6-month IM depot was designed to have a higher total dose of LA (45 mg vs 11.25 or 30 mg) and a slightly different chemical composition of the lyophilized microspheres (ie, includes stearic acid and different content of polylactic acid and D-mannitol [18, 19]) to release a similar monthly dose of LA over a longer dosing interval [20].

Study Outcomes and Assessments

The primary efficacy endpoint was the proportion of patients with aqueous leuprolide peak-stimulated LH suppressed to <4 mIU/mL at week 24 (before the second dose). The peak-stimulated LH suppression (<4 mIU/mL) at weeks 12, 20, 44, and 48 was assessed as part of secondary efficacy analyses. LH suppression was assessed robustly at all time points and any patient who had LH result missing was counted as a suppression failure; however, patients with missing LH results or those who were considered as suppression failures based on their peak-stimulated LH of ≥4 mIU/mL at any time point were allowed to continue in the study.

The proportions of patients with basal sex hormone suppressed (ie, basal estradiol to <20 pg/mL in girls; basal testosterone to <30 ng/dL in boys) were assessed at weeks 12, 20, 24, 44, and 48 as part of secondary efficacy analyses. Basal LH and basal and peak-stimulated follicle-stimulating hormone (FSH) concentrations obtained through week 48 and suppression of peak-stimulated LH and basal sex hormones at week 4 were assessed as part of other efficacy analyses. Additional secondary and other efficacy outcomes assessed from baseline through week 48 included physical signs of puberty, height- and BA-related measurements, and patient/parent-reported outcomes. Safety evaluations were performed through week 48.

Demographic variables collected in this study included age, sex, race, and ethnicity. Self-identified race and ethnicity categories were assessed to characterize the study population, since these factors have been associated with pubertal timing, and were collected via a questionnaire administered to patients and parents during baseline assessment. Ethnicity description included 2 mutually exclusive categories of Hispanic or Latino vs not Hispanic or Latino; race description included the following nonmutually exclusive categories: Asian (Chinese, Japanese, Korean, Taiwanese, and other), Black/African American, other (including American Indian/Alaska Native and multiple race categories) and White.

Hormone assays

Stimulation tests used 20-µg/kg generic aqueous LA SC injection and peak-stimulated LH and FSH concentrations were determined from their highest value obtained during serial blood draws at 30 and 60 minutes after the injection. Basal LH, FSH, and sex hormone concentrations were obtained immediately before the stimulation test. LH and FSH concentrations were measured by enzyme-linked immunosorbent assay

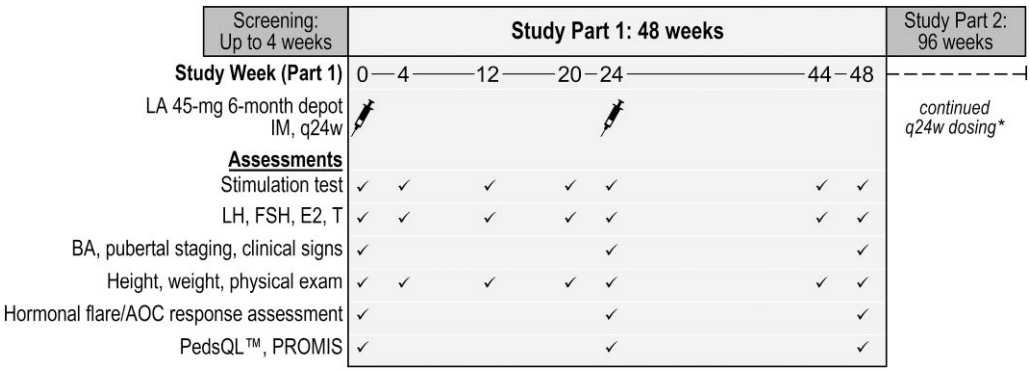

Figure 1. Study design and key part 1 assessments. Week 0 indicates baseline assessment before the first dose (ie, day 1 of treatment). Baseline stimulation test, BA radiograph, and pubertal staging were conducted during the screening period. Hormonal flare was evaluated via questionnaire on the day of, 48 hours after, and 7 days after treatment administration. AOC biochemical response assessments were performed 1 week after the first dose (week 0) and 48 hours after the second dose (week 24). *The dose at week 48 marked the first dose in Part 2 of the study and was administered after the indicated Part 1 assessments. Abbreviations: AOC, acute-on-chronic; BA, bone age; E2, estradiol; FSH, follicle-stimulating hormone; IM, intramuscular; LA, leuprolide acetate; LH, luteinizing hormone; PedsQL, Pediatric Quality of Life Inventory; PROMIS, Patient Reported Outcomes Measurement Information System; q24w, every 24 weeks; T, testosterone.

(ELISA; inVentiv/Syneos Health, Inc., Quebec, Canada) using commercially available assays (LH, Alpco Diagnostics Cat# 11-LUTHU-E01, RRID:AB_2936342, https://scicrunch.org/resolver/AB_2936342 and Diagnostics Biochem Canada Cat# CAN-LH-4040, RRID:AB_2936341, https://scicrunch.org/resolver/AB_2936341; FSH, Enzo Life Sciences Cat# ENZ-KIT108, RRID:AB_2909630, https://scicrunch.org/resolver/AB_2909630). A lower limit of quantitation (LLOQ) of 1 mIU/mL and concentration range of 1 to 100 mIU/mL were used for both. Estradiol and testosterone levels were measured using liquid chromatography–mass spectrometry (LC-MS; Bioanalysis, AbbVie, Inc., North Chicago, IL) with a LLOQ of 3 pg/mL for estradiol and 0.0250 ng/dL for testosterone.

Physical pubertal signs

Suppression of physical signs of puberty was assessed by breast palpation in girls and examination of genitalia in boys. Suppression was defined as regression or no progression in breast development according to pubertal staging for girls (Modified Tanner breast stages 1–5) and regression or no progression in testicular volume and genital staging for boys (Modified Tanner breast stages 1–5). Other measurements of suppression included regression or no progression of pubic hair (Modified Tanner breast stages 1–5); presence of menstrual bleeding; changes in uterine length/volume and endometrial stripe presence, as assessed by ultrasound in girls; and testicular length/volume, as assessed by examination and Prader/orchidometer beads in boys.

Height and BA measurements

Height was measured in triplicate using the same standard stadiometer equipment, such as Harpenden stadiometer or recumbent length table, and if possible, by the same study staff member. Height velocity (centimeter/year) was calculated prior to and during study treatment using 2 measurements separated ≥6 months; a historical height obtained ≥6 months prior to screening was used for the baseline height velocity calculation. BA radiographs of the left hand and wrist were performed at a facility specified by the study investigator and reviewed by a central reader using the FELS BA measurement [21, 22] obtained from the BoneXpert automated system (Visiana ApS, Hørsholm, Denmark) [23]. The BA/CA ratio was calculated for each patient at the time points of BA measurement, with a ratio of <1 indicating younger BA than CA. Ratio of change from baseline in BA divided by change from baseline in CA (ΔBA/ΔCA) was also calculated for each patient, with a ratio of <1 indicating a smaller advancement in BA compared to CA over time.

Patient/parent-reported outcomes

The Pediatric Quality of Life Inventory (PedsQL) Parent Report was collected for all patients, using a unique instrument for different age groups (2–4 years, PedsQL Parent Report for Toddlers; 5–7 years, PedsQL Parent Report for Young Child; 8–12 years, PedsQL Parent Report for Child). The overall PedsQL Parent Report score ranges from 0 through 100, with a higher score indicating a better quality of life. The Patient Reported Outcomes Measurement Information System (PROMIS) Peer Relationships Guardian Proxy was administered to children aged ≥5 years. A PROMIS Peer Relationship T-score of 50 indicates the mean for a healthy population, with higher values indicating better peer relationships.

Safety evaluations

Safety evaluations included assessment of adverse events (AEs) and AEs of special interest (AESI), physical and vital signs examinations, and clinical laboratory testing. AEs were collected and coded using the *Medical Dictionary for Regulatory Activities* Version 24.1 (MedDRA). AESI were retrieved by standard MedDRA query or company MedDRA query searches to identify AEs potentially related to the following: injection site reaction (ISR), hypersensitivity reaction, convulsion/seizure, neuropsychiatric event, epiphysiolysis, bone fracture, hormonal flare response and related psychiatric/mood event, and biochemical acute-on-chronic (AOC) response.

ISRs were evaluated through standard AE reporting, analysis of AESIs, and patient/parent questionnaire. The patient/parent questionnaire was administered by study staff on the day of each dose and 48 hours after and asked about

the presence of injection site pain or tenderness (and its severity), redness or swelling (and its size), drainage or abscess, and skin warmth. The events identified via the questionnaire were recorded as AEs, in addition to being further characterized in a detailed injection site assessment. The AESI analysis involved a company search of AEs using a number of MedDRA preferred terms (eg, administration site bruise, coldness, or anesthesia) to identify any events potentially representing ISRs. Finally, causality (ie, related to study treatment or stimulation tests) of AEs representing ISRs was also recorded. Similar to ISRs, AEs related to hormonal flare response were identified via a patient/parent questionnaire (administered on the day of each injection and 48 hours and 1 week after), in addition to standard AEs reporting. Using a company search of MedDRA preferred terms (eg, abdominal pain, bone pain, or constipation), AEs potentially related to hormonal flare occurring ≤14 days after each study drug dose were evaluated as AESIs. Biochemical AOC response was evaluated as part of the AESI analysis based on hormone blood concentrations (ie, LH >4.0 mIU/mL and estradiol >20 pg/mL [girls] or testosterone >30 ng/dL [boys]) obtained at week 1 after the first dose and 48 hours post-second dose.

Statistical Methods

No formal sample size calculation was performed. Based on previous studies and precedents used for registration, 40 patients were considered to be sufficient to support the efficacy and safety analysis for this therapeutic class and patient population. The sample size of 40 provides an observed response rate of suppression of peak-stimulated LH that is within 16.7% of the true response rate with 95% confidence.

The full analysis set and the safety analysis set were identical, with both including all patients who received ≥1 dose of study drug. Descriptive analyses were performed, and data were summarized overall and by treatment history group; inferential comparisons were not performed. The categorical primary and secondary efficacy endpoints were summarized with the 95% CI based on the binomial distribution (Clopper-Pearson exact method). The continuous secondary efficacy endpoints were summarized by sample size, mean, median, SD, standard error of the mean, minimum, and maximum. In the primary and secondary analyses describing the proportion of patients with peak-stimulated LH suppression at each visit, those with missing data were counted as suppression failures. For all other categorical data, missing data were not imputed. Statistical analyses were performed with SAS software package version 9.4 or later (SAS Institute Inc., Cary, NC) under the UNIX operating system.

Results

Patient Disposition and Characteristics

All 45 enrolled patients received 2 doses of LA and 44 completed the week 48 study visit. A previously treated 9-year-old girl discontinued study participation after receiving her second dose because she opted to start puberty. She completed the week 44 visit and had her final blood samples collected at week 48 for inclusion in the analysis of LH and estradiol concentration at week 48. Four patients had study visits impacted by COVID-19; 1 missed the week 44 visit because of COVID-19 infection and 3 had virtual visits because of logistical restrictions.

Baseline characteristics and demographics are shown in Table 1. Forty-five patients (41 girls and 4 boys) were enrolled; 18 were previously treated and 27 were GnRHa-naïve. None of the children had an adrenal gland abnormality identified at baseline. Six patients had a brain abnormality (per magnetic resonance imaging), namely hamartoma (n = 3; locations were hypothalamus, tuber cinereum, and inferior to third ventricle/left of midline/anterior to mammillary bodies), small simple pineal cyst (n = 1), arachnoid cyst in the pineal gland region (n = 1), and a hyperintensity in the right lateral ventricle and right posterior frontal white matter (n = 1). Of the 3 patients with hamartoma, 1 previously treated patient had hamartoma documented in their medical history.

LH, FSH, and sex Hormones

In the primary efficacy analysis, 86.7% (95% CI: 73.2%, 95.0%) of patients (n = 39/45) had peak-stimulated LH suppressed to <4 mIU/mL at week 24 (Table 2). Of the 6 patients counted as suppression failures in the primary analysis, 2 patients (treatment-naïve girls) had missing peak-stimulated LH data at week 24 due to not having the stimulation test performed (not due to COVID-19). Both girls had their LH concentrations assessed after the study drug injection at week 24, and their LH concentrations were <4 mIU/mL at 30 minutes and 1 hour after the study drug injection, and both also had their peak-stimulated LH suppressed to <4 mIU/mL at weeks 12, 20, 44, and 48. Three patients had peak-stimulated LH ranging from 4.35 to 5.30 mIU/mL and basal sex steroids suppressed at week 24, of whom 1 was a previously treated girl who was not suppressed at baseline with her prior GnRHa treatment (Table 3). The other 2 were treatment-naïve boys, one with peak-stimulated LH <4 IU/L by week 48, and the other with peak-stimulated LH of 4.5 IU/L at week 48. After treatment initiation, both boys had suppression of testosterone levels throughout. The remaining patient, a 7-year-old treatment-naïve girl, had a peak-stimulated LH of 21.07 mIU/mL at week 24 that declined to 4.35 and 4.62 mIU/mL at weeks 44 and 48, respectively, and basal estradiol of 65.40 pg/mL at week 24 that was below the LLOQ of 3.00 pg/mL at weeks 44 and 48 (Table 3). She had a Tanner breast stage of 3 at baseline through week 48, did not experience menarche (before or after baseline), and her height velocity declined from 13 cm/year at week 24 to 8 cm/year at weeks 44 and 48. One site administered fixed dosing for the GnRHa stimulation test (at 500 µg or 2500 µg instead of 20 µg/kg) to 5 patients, who all demonstrated LH, FSH, sex hormone, and pubertal suppression and were considered responders in the primary, secondary, and other efficacy endpoint analyses.

Suppression of peak-stimulated LH was observed in 86.7% to 91.1% of patients at week 4 through to week 48. In previously treated patients, 94.4% (n = 17/18) had peak-stimulated LH suppressed at 24 weeks and 83.3% to 94.4% from week 4 to 48 (Fig. 2A). Their mean concentration remained below the mean baseline value (≤2.1 mIU/mL) post week 4, including during the last month of each dosing interval, at week 20 (1.2 mIU/mL) and 24 (1.4 mIU/mL) and week 44 (1.4 mIU/mL) and 48 (1.9 mIU/mL) (Fig. 2B). In treatment-naïve patients, 81.5% (n = 22/27) were suppressed at week 24 and 81.5% to 96.3% at week 4 through 48 (Fig. 2A). Their mean peak-stimulated LH concentrations

Table 1. Patient characteristics in patients treated with LA 45-mg 6-month IM depot

Characteristic[a]	Previously treated	Treatment naïve	Overall
Girls and boys, n	18	27	45
Age, y	8.1 ± 1.73 (4.0, 10.0)	7.7 ± 0.83 (5.0, 9.0)	7.8 ± 1.27 (4.0, 10.0)
Race			
Asian	1 (5.6)	0	1 (2.2)
Black	4 (22.2)	3 (11.1)	7 (15.6)
Other	1 (5.6)	6 (22.2)	7 (15.6)
White	12 (66.7)	18 (66.7)	30 (66.7)
Hispanic ethnicity	2 (11.1)	9 (33.3)	11 (24.4)
Duration of prior GnRHa therapy,[b] days	558 ± 342.8 (179, 1384)	—	—
BMI, kg/m^2	20.8± 4.51 (13.6, 31.0)	19.2 ± 3.92 (13.0 28.4)	19.8 ± 4.19 (13.0, 31.0)
BMI standardized score	1.1 ± 1.04 (−1.5, 2.0)	0.8 ± 1.12 (−2.0, 2.0)	0.9 ± 1.08 (−2.0, 2.0)
Height, cm	141.1 ± 14.18 (108.8, 158.2)	138.7 ± 6.62 (127.5, 153.0)	139.7 ± 10.25 (108.8, 158.2)
Height standardized score	1.4 ± 0.97 (−1.0, 2.0)	1.4 ± 0.74 (−0.5, 2.0)	1.4 ± 0.83 (−1.0, 2.0)
Girls, n	17	24	41
Tanner breast stage			
1	4 (23.5)	0	4 (9.8)
2	4 (23.5)	1 (4.2)	5 (12.2)
3	6 (35.3)	18 (75.0)	24 (58.5)
4	3 (17.6)	5 (20.8)	8 (19.5)
Time from puberty onset to treatment, y	1.2 ± 0.92 (0.1, 2.7)	1.4 ± 0.94 (0.2, 5.3)	1.3 ± 0.93 (0.1, 5.3)
Height velocity, cm/y	5.8 ± 2.44 (0.9, 9.4)	10.0 ± 3.27 (5.3, 19.8)	8.3 ± 3.61 (0.9, 19.8)
BA, y	10.4 ± 1.80 (6.9, 12.6)	10.9 ± 0.76 (9.4, 13.0)	10.7 ± 1.30 (6.9, 13.0)
BA/CA	1.3 ± 0.18 (0.9, 1.6)	1.4 ± 0.13 (1.2, 1.8)	1.3 ± 0.16 (0.9, 1.8)
BA − CA, y	1.9 ± 1.01 (−0.7, 3.8)	2.8 ± 0.82 (1.5, 4.7)	2.5 ± 1.00 (−0.7, 4.7)
Boys, n	1	3	4
Testicular volume, cm^3	3.0	8.0 ± 2.00 (6.0, 10.0)	6.8 ± 2.99 (3.0, 10.0)
Time from puberty onset to treatment, y	6.0	2.4 ± 1.52 (1.2, 4.1)	3.3 ± 2.22 (1.2, 6.0)
Height velocity, cm/y	6.2	10.8 ± 1.51 (9.1, 11.9)	9.7 ± 2.65 (6.2, 11.9)
BA, year	11.5	12.6 ± 1.28 (11.2 13.7)	12.3 ± 1.17 (11.2, 13.7)
BA/CA	1.1	1.4 ± 0.07 (1.3, 1.4)	1.3 ± 0.13 (1.1, 1.4)
BA − CA, y	1.4	3.4 ± 0.48 (3.0, 3.9)	2.9 ± 1.07 (1.4, 3.9)

Abbreviations: BA, bone age; BMI, body mass index; CA, chronological age; CPP, central precocious puberty; GnRHa, GnRHa agonist; LA, leuprolide acetate.
[a]Data are expressed as mean ± SD (range) or number (%).
[b]All previously treated patients received prior GnRHa therapy for ≥6 months prior to enrollment (n = 15, leuprorelin; n = 3, triptorelin; n = 3, histrelin).

Table 2. Suppression of peak-stimulated LH (<4.0 mIU/mL) at week 24: primary efficacy analysis

Parameter	Previously treated (N = 18)	Treatment naïve (N = 27)	Overall (N = 45)
Suppression responder, n (%)	17 (94.4)	22 (81.5)	39 (86.7)
Two-sided 95% CI[a], %	72.7, 99.9	61.9, 93.7	73.2, 95.0
Suppression failures, n			
Missing assessment	0	2	2
Peak-stimulated LH ≥4 mIU/mL	1	3	4

[a]Based on the binomial distribution (Clopper-Pearson exact method).

declined rapidly post-baseline to <4 mIU/mL at week 4 (1.6 mIU/mL), remaining below this cutoff through week 48 (Fig. 2B). Relative to the mean levels observed most immediately after their first dose, at week 4 (1.6 mIU/mL), a small upward trend in the mean concentration was evident at weeks 20 and 24 (2.5 and 2.7 mIU/mL), but not at weeks 44 and 48 (1.7 and 1.9 mIU/mL). LH was not assessed at week 28 (the most immediate visit following the second dose).

Consistent with the observed peak-stimulated LH profile, mean basal LH levels remained relatively stable post-baseline and close to the baseline level of 1.2 mIU/mL in previously treated patients (1.1–1.5 mIU/mL) (Fig. 2C). Levels also remained stable in treatment-naïve patients after a rapid decline from baseline (4.1 mIU/mL) to week 4 (1.0–1.1 mIU/mL) (Fig. 2C). The mean peak-stimulated and basal FSH levels also paralleled the peak-stimulated LH profile. They remained consistently below post-baseline levels in both patient groups, with small post-baseline decreases observed in previously treated patients (peak-stimulated: baseline, 3.1 mIU/mL and post-baseline, 1.1–2.4 mIU/mL; basal: baseline, 1.8 mIU/mL and post-baseline 1.0–1.2 mIU/mL) and, as expected, a larger numeric decrease in treatment-naïve patients (peak-stimulated:

Table 3. Patients failing LH suppression at week 24

Sex (age, y)	Treatment status	Visit/ Week	Basal LH, mIU/mL	LH peak, mIU/ mL	Basal E2, pg/ mL	Basal T, ng/ dL	Tanner stage[a]	Pubic hair[a]	Testicular volume, mL[a]	Height velocity, cm/y	BA, y	BA/ CA
F (8)	Previously treated	Baseline	5.51	7.73	<3.00[b]	n/a	3	1	n/a	8.11	9.86	1.22
		20	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
		24	3.96	4.35	<3.00[b]	n/a	3	1	n/a	7.94	10.62	1.18
		44	3.70	4.36	<3.00[b]	n/a	n/a	n/a	n/a	7.77	n/a	n/a
		48	3.73	4.39	<3.00[b]	n/a	3	1	n/a	7.76	10.99	1.21
F (7)	Treatment naïve	Baseline	1.35	11.00	6.27	n/a	3	2	n/a	7.43	11.00	1.55
		20	3.93	23.68	61.10	n/a	n/a	n/a	n/a	14.72	n/a	n/a
		24	3.10	21.07	65.40	n/a	3	3	n/a	13.64	12.20	1.52
		44	1.51	4.35	<3.00[b]	n/a	n/a	n/a	n/a	8.88	n/a	n/a
		48	0.97	4.62	<3.00[b]	n/a	3	3	n/a	8.70	11.95	1.48
M (9)	Treatment naïve	Baseline	2.46	19.85	n/a	335.0	2	1	10	9.13	12.87	1.41
		20	1.00	3.22	n/a	6.52	n/a	n/a	n/a	6.69	n/a	n/a
		24	1.00	5.00	n/a	5.70	2	1	7	5.54	13.36	1.33
		44	0.95	2.87	n/a	5.70	n/a	n/a	n/a	5.98	n/a	n/a
		48	0.95	2.88	n/a	6.30	2	1	6	6.17	13.54	1.34
M (9)	Treatment naïve	Baseline	0.95	16.98	n/a	418.0	3	3	8	11.45	13.68	1.50
		20	0.95	3.42	n/a	12.00	n/a	n/a	n/a	4.23	n/a	n/a
		24	0.95	5.30	n/a	7.00	4	4	12	3.77	13.81	1.38
		44	1.00	4.14	n/a	10.40	n/a	n/a	n/a	3.95	n/a	n/a
		48	1.00	4.51	n/a	10.40	4	4	8	4.72	13.99	1.39

Abbreviations: BA, bone age; BA/CA, bone age/chronological age ratio; E2, estradiol; LH, luteinizing hormone; n/a, not available/applicable; T, testosterone.
[a]Pubic hair, breast stage, and testicular volume were assessed at baseline, week 24, and week 48. Tanner stage was determined via assessment of breasts (girls) or genitalia (boys).
[b]Lower limit of quantitation (LLOQ).

baseline, 6.2 mIU/mL and post-baseline 1.3–2.8 mIU/mL; basal: baseline, 2.3 mIU/mL and post-baseline 1.0–1.2 mIU/mL).

Basal estradiol was suppressed to <20 pg/mL in 97.4% (n = 37/38) of girls at week 24 (97.4%–100% from week 4 through week 48). In previously treated girls, all were suppressed post-baseline, with a mean concentration of ≤1.9 pg/mL (Fig. 3A and 3B). In treatment-naïve girls, all were suppressed post-baseline, except for the aforementioned 7-year-old girl who became suppressed later at weeks 44 and 48; their mean levels remained at ≤4.3 pg/mL post-baseline (Fig. 3A and 3B). All boys had basal testosterone suppressed to <30 ng/dL from week 12 through week 48; the mean (SD) baseline, week 24, and week 48 concentrations were 3.9, 3.4, and 6.1 ng/dL in the single previously treated boy and 255.1 (214.38), 6.1 (0.77), and 7.4 (2.61) ng/dL in the 3 treatment-naïve boys, respectively.

Suppression of Physical Characteristics of Puberty

At weeks 24 and 48, respectively, suppression of breast development was observed in 94.1% (n = 16/17) and 88.2% (n = 15/17) of previously treated girls and 91.7% (n = 22/24) and 91.7% (n = 22/24) of treatment-naïve girls (92.7% [n = 38/41] and 90.2% [37/41] overall), and suppression of pubic hair distribution was observed in 82.4% (n = 14/17) and 88.2% (n = 15/17) of previously treated girls and 79.2% (n = 19/24) and 66.7% (n = 16/24) of treatment-naïve girls (80.5% [n = 33/41] and 75.6% [31/41] overall). One previously treated girl without prior history of menstrual bleeding experienced spotting at week 12. This 9-year-old girl was on prior GnRHa therapy for 1.5 years and, at baseline, her LH/estradiol was suppressed, BA was 12 years, and Tanner breast stage was 4. Her LH and estradiol remained suppressed through week 48 and Tanner breast stage declined to stage 3 at week 24 and rebounded to stage 4 at week 48. Two treatment-naïve girls experienced menstrual bleeding at baseline and week 4, but not thereafter. Uterine length and volume remained generally unchanged in previously treated girls; their mean (SD) change from baseline to week 48 was 0.1 (1.47) cm and 0.7 (6.46) mL, respectively. In treatment-naïve girls, the mean (SD) change from baseline to week 48 was −0.7 (1.52) cm for uterine length and −6.3 (11.39) mL for uterine volume. An endometrial stripe was present in 25 girls at baseline (mean [SD] thickness 4.3 [4.22] mm), and of these girls, most had persistent endometrial stripes present at weeks 24 (n = 20/24) and 48 (n = 17/25). Among 16 girls without an endometrial stripe at baseline, a third or less had an endometrial stripe reported at weeks 24 (n = 5/15) or 48 (n = 5/16).

In boys, 50.0% (n = 2/4) and 75.0% (n = 3/4) had physical signs of puberty suppressed at week 24 and 48, respectively. The single previously treated 10-year-old boy had testosterone suppressed to 3.4 ng/dL at week 24 but experienced progression of genital stage from 1 to 2, returning back to stage 1 at week 48. His pubic hair growth was not suppressed at week 24 or 48 and testicular length increased by 0.4 cm from baseline to week 24 (48-week missing data), but his testicular volume of 3 mL remained unchanged. In treatment-naïve boys, 2 of 3 showed suppression of physical signs and pubic hair at weeks 24 and 48. Their mean (SD) testicular length declined by −0.8 (0.28) cm and testicular volume by −1.3 (2.31) mL from baseline to week 48.

Height, BA/CA, and Body Mass Index

The mean incremental height velocity remained generally unchanged from a baseline mean of 5.8 cm/year through week

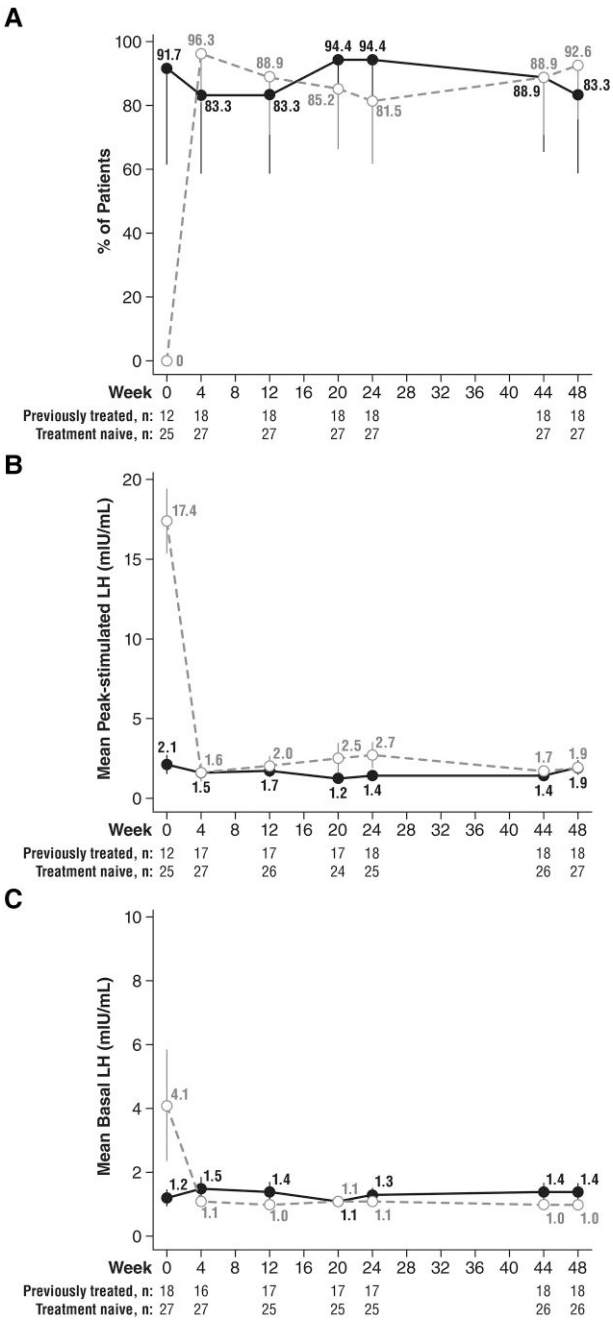

Figure 2. Suppression* of peak-stimulated LH (A) and mean concentrations† of peak-stimulated LH (B) and basal LH (C) in previously treated (black) and treatment-naïve (gray) patients. Week 0 indicates baseline assessment prior to the first dose (ie, day 1 of treatment). *Error bars are lower 95% CIs. †Error bars are ± SEM.

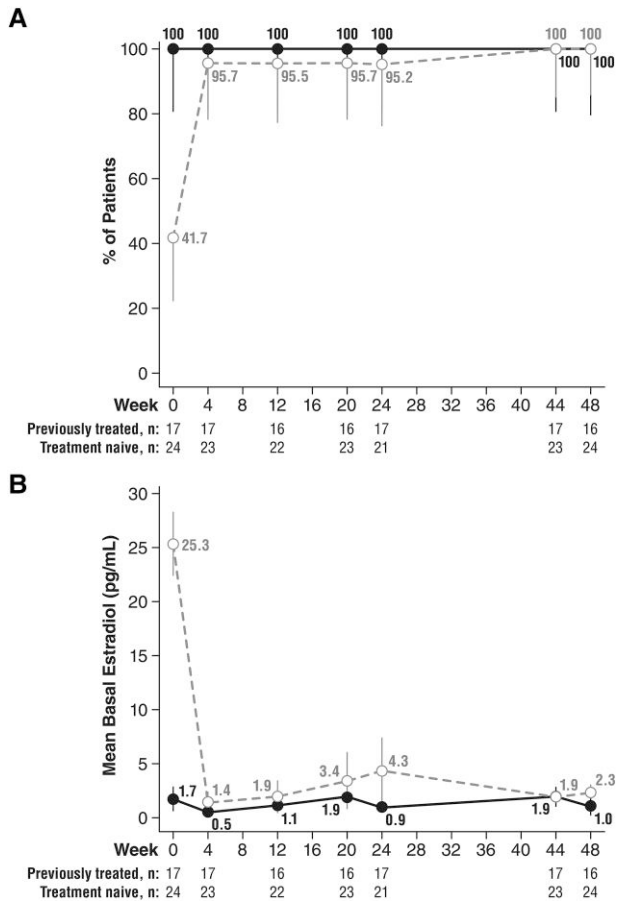

Figure 3. Suppression* (A) and mean concentration† (B) of basal estradiol in previously treated (black) and treatment-naïve (gray) patients. Week 0 indicates baseline assessment prior to the first dose (ie, day 1 of treatment). *Error bars are lower 95% CIs. †Error bars are ± SEM.

48 in previously treated patients and declined from 10.1 cm/year at baseline to a normalized prepubertal level [24] of 6.5 cm/year in treatment-naïve patients at week 20, remaining relatively stable thereafter (Fig. 4A). The mean BA/CA ratio was observed to decline by 0.1 in each group at week 48 (Fig. 4B), as 94.4% (n = 17/18) of previously treated and 92.6% (n = 25/27) of treatment-naïve patients experienced a decline in BA/CA ratio at week 48. The mean of ΔBA/ΔCA was 0.2 to 0.7 in both groups at weeks 24 and 48, indicating smaller advancement in BA compared to CA over time. Mean height standardized scores were generally stable post-baseline.

Baseline body mass index (BMI) standardized scores were >0 in each study group (Table 1), indicating above-average BMI for the study population relative to the standard population, with no clinically meaningful post-baseline changes occurring at week 24 or 48 in previously treated patients (0.0 and −0.1, respectively) or treatment-naïve patients (0.4 and 0.4, respectively).

Patient/Parent-Reported Outcomes

In general, numeric increases were observed during 48 weeks of treatment in the mean overall PedsQL Parent Report score (higher score indicates better quality of life; highest possible score: 100). The mean (SD) scores at baseline, week 24, and week 48 were, respectively, 80.7 (10.47), 85.3 (9.64), 88.1 (8.80) in previously treated children aged 8 to 12 years; 74.3 (14.06), 80.7 (15.44), 84.6 (10.71) in treatment-naïve children aged 8 to 12 years; and 69.3 (19.88), 76.2 (17.69), 77.5 (22.10) in treatment-naïve young children aged 5 to 7 years. Owing to the small number of patients enrolled per group, only 2 previously treated young children (age 5–7 years) and 1 toddler (age 2–4 years) had the PedsQL Parent Report scores available at baseline and post-baseline assessments, limiting observation of trends for these subgroups. Numeric increases were also observed in the mean PROMIS Peer Relationship T-score (higher values indicate better relationship; healthy population score: 50); the mean (SD)

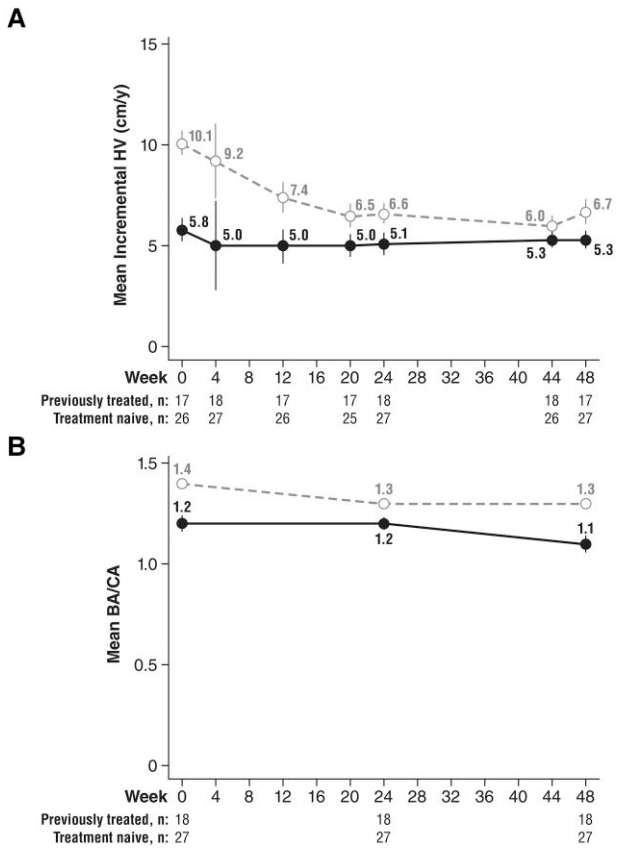

Figure 4. Mean height velocity (A) and BA/CA (B) in previously treated (black) and treatment-naïve (gray) patients. Week 0 indicates baseline assessment prior to the first dose (ie, day 1 of treatment). Error bars are ± SEM. BA/CA, bone age/chronological age ratio; HV, height velocity.

T-scores at baseline, week 24, and week 48 were, respectively, 52.6 (9.58), 54.2 (8.90), and 55.8 (8.87) in previously treated patients and 48.6 (11.99), 50.8 (10.33), and 50.3 (9.83) in treatment-naïve patients.

Safety

No patients experienced AEs leading to drug discontinuation and no clinically meaningful changes in laboratory or vital signs were observed. One patient had a serious AE reported (Table 4). Specifically, a treatment-naïve 8-year-old boy experienced a serious AE of altered mood on day 155, and a concurrent nonserious AE of disruptive mood dysregulation disorder, both resolving on day 170, prior to the second study drug dose. Both events were assessed by the site investigator as having a reasonable possibility of relationship to study drug; however, no changes to study drug administration occurred and the boy had a medical history of posttraumatic stress disorder, attention-deficit/hyperactivity disorder, adjustment disorder, and chronic mood disturbance.

Most AEs were deemed to be unrelated to study drug by the investigators and were mild or moderate in severity. Two patients had severe AEs reported (Table 4). One was the aforementioned boy, with both of the above-described AEs (ie, altered mood and disruptive mood regulation disorder) reported as severe. The other patient (a treatment-naïve girl) experienced a severe intermittent trichotillomania deemed to be unrelated to study drug.

Table 4. Summary of treatment-emergent AEs

Parameter, n (%)	Previously treated (n = 18)	Treatment naïve (n = 27)	Overall (n = 45)
Any AE	17 (94.4)	27 (100)	44 (97.8)
AEs related to treatment	14 (77.8)	23 (85.2)	37 (82.2)
Any severe AEs	0	2 (7.4)	2 (4.4)
Any serious AE	0	1 (3.7)	1 (2.2)
Any COVID-19–related AE	1 (5.6)	2 (7.4)	3 (6.7)
Deaths and AEs leading to death	0	0	0
AEs occurring in ≥4 patients overall			
Injection site pain	10 (55.6)	21 (77.8)	31 (68.9)
Headache	8 (44.4)	7 (25.9)	15 (33.3)
Cough	3 (16.7)	4 (14.8)	7 (15.6)
Oropharyngeal pain	4 (22.2)	3 (11.1)	7 (15.6)
Abdominal pain upper	1 (5.6)	5 (18.5)	6 (13.3)
Pyrexia	3 (16.7)	3 (11.1)	6 (13.3)
Vomiting	3 (16.7)	2 (7.4)	5 (11.1)
Gastroenteritis	3 (16.7)	1 (3.7)	4 (8.9)
Mood altered	1 (5.6)	3 (11.1)	4 (8.9)
Nasopharyngitis	2 (11.1)	2 (7.4)	4 (8.9)
Pain in extremity	2 (11.1)	2 (7.4)	4 (8.9)
Rhinorrhea	1 (5.6)	3 (11.1)	4 (8.9)

Abbreviation: AE, adverse event.

Injection site reactions

Injection site pain was the most common AE, occurring in 31 children (68.9%, Table 4) and was deemed to be related to study drug in 30 children (66.7%). The AESI analysis identified 4 additional patients (total n = 35, 77.8%) with injection site reactions (ISRs) or other AEs potentially related to ISRs, including injection site erythema, warmth, bruising, discomfort, and/or swelling. In the more detailed injection site assessment based on the patient/parent questionnaire conducted on the day of each dose and 48 hours after, none of the ISRs required follow-up and the events of injection site pain were identified as having mild or moderate severity in majority of cases (96%–100%).

AEs of special interest

Six patients were identified with AEs potentially related to hypersensitivity, which was most commonly a rash (n = 3). No previously treated patients experienced a biochemical AOC response. Among treatment-naïve patients, 4 experienced an AOC response within 1 week after the first dose and 1 within 48 hours after the second dose. Of the patients who experienced AEs potentially related to hormonal flare within 14 days post-dose (n = 9), the majority experienced these events after their first dose (n = 8), with headache being most common (n = 4); the most common psychiatric AE potentially related to hormonal flare was altered mood (n = 4). No patient experienced convulsion, neuropsychiatric, or epiphysiolysis events. Two patients experienced a bone fracture, with each being assessed as nonserious and unrelated to study drug.

Discussion

In this phase 3, open-label, multicenter study of LA 45-mg 6-month IM depot formulation, the primary efficacy endpoint, a suppression of peak-stimulated LH to <4 mIU/mL, was achieved at week 24 in 87% of patients. Of the 6 children who were considered as suppression failures in the primary analysis, 2 had missing stimulation test data but were suppressed to <4 mIU/mL after their study drug injection at week 24 and were also suppressed at all other post-baseline assessments. Three had peak-stimulated LH concentration of 4.35 to 5.30 mIU/mL and suppressed sex steroids. A single treatment-naïve patient remained unsuppressed at week 24, but at week 44 and 48, her peak-stimulated LH concentration was 4.35 mIU/mL and 4.62 mIU/mL, respectively, and estradiol was suppressed to <3.00 pg/mL. She did not experience menarche or increase pubertal breast stage and her height velocity declined substantially by week 48. These results were supported by the secondary analyses of post-baseline hormonal levels through week 48, which demonstrated suppression of peak-stimulated LH in ≥86.7% of patients, basal estradiol in ≥97.4% of girls, and testosterone in 100% of boys; suppression was observed as early as week 4 for peak-stimulated LH and basal estradiol and week 12 for testosterone. Consistent mean concentration profiles were observed over 48 weeks for peak-stimulated and basal LH and FSH. LH suppression of <4 mIU/mL was not achieved in 2 of 4 boys at 24 weeks. One boy reached LH suppression by 48 weeks, whereas the other had LH of 4.5 mIU/mL at 48 weeks (slightly above the criterion for LH suppression), and both had testosterone suppressed post-baseline. Physical characteristics of puberty were suppressed at week 48 in 90.2% of girls and 75.0% of boys.

Overall, these data support a 6-month IM administration of LA as another therapeutic option for CPP that, similar to the 3-month LA IM depot, does not require the usage of multiple syringes or vials, external filling, or surgical placement. The results are similar to those observed for the LA 3-month 30-mg IM depot, with peak LH suppression (<4 mIU/mL) during 6 months of treatment [25]. These formulations have the same active ingredients with a different depot formulation. In the 6- and 3-month IM formulations, specifically, LA is released from lyophilized microspheres, first quickly from their surface for initial dosing and then slowly through their "digestion" for maintained monthly dosing of approximately 7.5 mg [20]. Consistent with this biphasic LA dose release, a mean peak-stimulated LH of <4 mIU/mL was observed at week 4 after each dose in both patient groups that remained below this level throughout both dosing intervals.

LA 45-mg 6-month IM depot also decreased the rate of BA advancement. The mean of ΔBA/ΔCA was 0.2 to 0.7 through week 48 in previously treated and treatment-naïve children, indicating smaller advancement in BA than CA over time. Height velocity remained generally unchanged from a baseline mean of 5.8 cm/year through week 48 in previously treated patients, suggesting continued suppression of puberty, and declined by week 20 (ie, after a single dose) in treatment-naïve children, after which it remained relatively stable at a mean of 6.5 cm/year at week 48, similar to height velocity reported with other 6-month preparations [16, 26]. Stable prepubertal height velocity and decreased BA advancement together are generally associated with increase in predicted adult height in patients with receiving GnRHa treatment.

LA 45-mg 6-month IM depot formulation was observed to have an overall safety profile that was consistent with those of other GnRHa formulations [15, 16, 25-28]. It was well tolerated, with no new or additional safety concerns identified; most AEs were mild or moderate in severity and none led to withdrawal of study treatment. AEs of injection site pain were more commonly reported here (68.9%) than for the 3-month LA IM depot (22.6%–26.4%) [5, 6], warranting several considerations. The same needle (23 gauge) and injection volume (1.5 mL) were used with the 3- and 6-month IM depot formulations, and while it is possible that the total dose and/or microsphere composition contributed to these results, part of the variation was likely due to the differences in ISR reporting. Both studies used the same comprehensive questionnaire to further assess ISRs related to study treatment; however, per their protocols, the identified reactions were reported as AEs only per investigator discretion in the 3-month depot study, whereas the investigators were required to enter all potential injection site events as AEs in the current study. Overall, injection site pain events identified in the current study did not require a follow-up and were predominantly mild to moderate in severity, and quality-of-life scores did not appear to decline.

Strengths of this study include a relatively large sample size for this patient population (though smaller than the typical phase 3 study due to the uncommon nature of CPP), 48-week duration (which is clinically meaningful for efficacy and safety assessments), assessments at week 20 and 44 time points (to examine the last month of both dosing intervals), and inclusion of previously treated patients. A robust primary analysis was performed with patients with missing data being counted as treatment failures. Finally, this is one of few studies of GnRHa treatment for CPP that evaluated quality-of-life measures, which is important considering that children who experience earlier puberty, particularly girls, are more likely to report mental health problems [29, 30]. Limitations of the study are that no direct comparisons were performed with other LA formulations or GnRHa treatments for CPP and inclusion of a small number of boys. With only 4 boys included, caution is needed when interpreting their data. Four patients had study visits impacted by COVID-19, but none discontinued from the study because of COVID-19 infection, and the impacted visits were not considered to have affected the study outcome or interpretation of the study results or conclusions.

In conclusion, LA 45-mg 6-month IM depot demonstrated efficacy over 48 weeks through suppression of hormones and physical signs of puberty, slower BA advancement relative to CA, and normal prepubertal height velocity in children with CPP. Treatment was well tolerated, and the overall safety profile was consistent with other GnRHa formulations. The LA 6-month IM depot formulation provides an additional option for individualized treatment decisions that may benefit patients by reducing the number of injections required to maintain suppression, which can potentially improve treatment compliance and quality of life.

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Disclosures

K.O.K. is a consultant for AbbVie, Inc. and has been paid for participating in speakers bureaus and educational presentations for AbbVie, Inc. and has had travel/accommodations paid for by AbbVie, Inc. N.M., S.N., and B.S. have no conflicts of interest to disclose. B.M.M.-P., S.D., M.B., Q.Z., and A.R.K. are employees of AbbVie, Inc. and may own AbbVie, Inc. stock or stock options. C.B. (Clifford Bloch, see "Acknowledgments") owns AbbVie, Inc. stock.

Data Availability

AbbVie, Inc. is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the United States and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvieclinicaltrials.com/hcp/data-sharing/.html.

Clinical Trial Information

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