

2.0 SYNOPSIS

STUDY INFORMATION:

Name of Sponsor: Independent Investigators

Title of Study: Combined Results of Independent Investigators' Studies Leuprolide in the Treatment of Central Precocious Puberty

Name of Active Ingredient: Leuprorelin acetate

Name of Finished Product: Leuprorelin acetate 3.75mg 1-month depot injection

Investigator: 44 Investigators treated children under this program at 38 sites in the USA.

Publication Based on the Study (Citation): NA

Study Period: Study was started in November 1985 and as ended in 1992

Objectives:

Primary: The objective of this study was to evaluate the safety and efficacy of leuprolide acetate in the treatment of central precocious puberty.

Methodology: An open, noncomparative, multicenter study Lupron® (leuprolide acetate) Injection and Lupron Depot® (leuprolide acetate for depot suspension) in children with central precocious puberty. Children were treated under the individual investigator's protocol under a private IND. No central laboratory facilities were utilized in this study.

The study consisted of an open treatment period during which subjects received either daily injections of Lupron Injection, or monthly injections of Lupron Depot.

There was variability in objective and subjective parameters. The need for therapeutic intervention was often assessed based on clinical symptoms and secondary sexual characteristics. It was the individual investigator's judgement when and whom to treat.

Multiple commercial assays were used for determination of luteinizing hormone (LH) or follicle stimulation hormone (FSH), with differing results.

Radiographs of the left wrist and hand were made at the investigator's site, and all bone age determinations were made at the local site.

Number of Subjects:

Data for these children were collected retrospectively. Three hundred sixty-five patients were enrolled and 226 patients were evaluable for efficacy analysis. All patients were evaluated for safety.

Diagnosis and Main Criteria for Inclusion: Subjects had to meet criteria set forth in the individual investigator's protocols. The population generally consisted of children with central precocious puberty; developed secondary sexual characteristics consistent with puberty, an advanced bone age and either pubertal basal or stimulated gonadotrophin measurements. Estradiol levels may or may not have been elevated in females, testosterone levels were generally elevated in females. Ages varied by protocol.

Duration of Treatment: All subjects received leuprorelin acetate in varying doses. The planned treatment period was 2 years.

Children continued to receive treatment until they reached the appropriate age for puberty as determined by the individual investigator, or until therapy was discontinued at the discretion of the physician, parent or guardian.

Test Product, Dose and Mode of Administration, and Lot Number:

Study Medication	Product Dose Strength and Form	Mode of Administration	Drug Product Lot Number
Lupron Injection	Sterile, aqueous solution 5mg/ml or 1mg/ml	Subcutaneous or Intramuscular injection	Not Stated
Lupron Depot	Single-dose vial of sterile lyophilized microspheres of leuprolide acetate (3.75mg or 7.5mg) and an ampoule of diluent for reconstitution.	Subcutaneous or Intramuscular injection	Not Stated

Each investigator determined the dose of drug to be administered as dictated by the investigator's protocol.

Criteria for Evaluation:

Efficacy was evaluated based on Tanner staging, decrease of gonadotrophins and sex steroids to prepubertal levels, and other parameters that the investigator set forth in his/her individual protocol.

Statistical Methods:

All p-values were based on two-tailed tests. P-values ≤ 0.050 are reported as "significant". P-values $>$ than 0.050 but ≤ 0.100 are reported as "marginally significant".

SUMMARY OF RESULTS:

Baseline Demographics and Other Relevant Characteristics:

For the 226 evaluable subjects: age ranged from 0.8 to 9.8 years; 29 (13%) were male, 195 (86%) were female and 2 (1%) were of unknown sex. Females were slightly younger than the males with respective mean ages of 6.1 years and 6.3 years. Among subjects for whom race was provided, 83% were Caucasian, 7% were Black, 8% were Hispanic and 1% was Oriental.

Efficacy Results:

The effectiveness of leuprolide acetate and leuprolide acetate for depot suspension was evidenced by suppression of gonadotrophins and sex steroids (where pubertal) to pre-pubertal levels with therapeutic dosing, by decreases in Tanner staging, and by a decrease in linear growth velocity (height and bone age).

During the early days of therapy, many of these children were not effectively treated. This was the result of dosing that was too low and/or the fact that the laboratory tests used to evaluate suppression were not sensitive enough to accurately reflect the status of suppression.

Once adequate suppression of the pituitary-gonadal axis was achieved, the children demonstrated regression of sexual maturation both physically and psychologically. There was a slowing of linear growth velocity and a decrease in the ratio of bone age to chronological age; changes in these measurements would be anticipated to lead to an increase in final adult height. None of these children have attained adult age to verify this hypothesis.

Of the female children who were post-menarchial, all became amenorrheic once adequate suppression had been established.

Treatment was discontinued for 91 of these children, including 34 who had reached an age appropriate for puberty. Many have re-entered puberty with reinstatement of menarchy, and other secondary sexual characteristics and elevation of gonadotrophins and sex hormones.

Safety Results:

Adverse events were reported in 95/365 (26%) of the study population. Adverse events potentially related to study drug were reported in 66/365 (18.1%) of subjects. The most frequently reported event 19/365 (5.2%) was related to an injection site reaction. These reactions included mild reactions such as inflammation or erythema at the injection site, or those which may have resulted in inflammation, induration and sterile abscess.

CONCLUSIONS:

Leuprolide acetate was shown to be safe and effective in suppressing gonadotrophins and sex steroids in children with central precocious puberty, who were properly diagnosed, aggressively treated and accurately monitored.

DATE OF SYNOPSIS: 11 August 2011

REASON FOR SYNOPSIS: Prepared in ICH format for submission to Competent Authorities (Article 45)

DATE OF CLINICAL STUDY REPORT: Not stated on report.