# An Observational, Retrospective Study to Evaluate Long Term Safety and Effectiveness of Leuprorelin in the Treatment of Central Precocious Puberty

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## Background

Central precocious puberty (CPP) occurs when the hypothalamic-pituitary-gonadal axis (HPGA) is prematurely activated, before 8 years in girls and 9 years of age in boys [1]. Leuprorelin is a gonadotropin releasing hormone analogues, produces desensitization of pituitary gonadotropin receptors, resulting in a decrease in the secretion of gonadotropins and sex hormones (such as testosterone and estradiol), widely used for the therapy of CPP [2, 3].

## Aim

To describe safety and effectiveness of high (≥ 90-180 μg/kg) and low (< 90-30 μg/kg) dose Leuprorelin in treating CPP.

## Methods

- This was an observational, retrospective medical chart review to determine the effectiveness and safety of Leuprorelin in treating CPP in Chinese children.
- Data from medical records were organized into a treatment phase in which subjects were treated with at least 9 continuous months of Leuprorelin and a follow up phase up to the day of last follow-up data for the subject.
- The main safety outcomes were adverse events (AEs) and serious adverse events (SAEs) in the medical records during and after treatment with Leuprorelin.
- The primary efficacy outcome was regression or no progression of Tanner staging during and after Leuprorelin treatment.
- luteinizing hormone (LH), follicle stimulating hormone (FSH) and estradiol (E2) or testosterone suppression, and decrease in bone age to chronological age (BA/CA) ratio were secondary efficacy outcomes.
- LH suppression was considered to be a peak LH ≤ 2 U/L for females and LH ≤ 2.7 U/L for males. FSH suppression was considered to be a peak FSH ≤ 6.7 U/L for females and FSH ≤ 3.7 U/L for males.

## Results

- During the treatment phase, all subjects (104 females and 4 males) were treated with Leuprorelin. In the follow up phase, 44 (62.9%) subjects who were no longer on CPP treatment had a mean follow-up duration of 8.75 months; another 26 (37.1%) subjects were continuing their CPP treatment with another GnRH agonist (**Figure 1**).
- The mean exposure time was 22.3 months and 97.2% subjects received the maximum dose of 3.75 mg.
- At the end of the treatment period, 69.4% of subjects recorded AEs, the most common being upper respiratory tract infection (16.7%). No SAEs were related to Leuprorelin (**Table 1**). In the follow up phase, 10 AEs reported, none of which were related to Leuprorelin.
- At the end of the treatment period, 1 of 4 male patients had sufficient data for evaluation and showed progression of the Tanner stage, while 79.7% (63/79) of females showed regression or no progression (**Table 2**). In the follow-up phase, Of the 2 female subjects who had sufficient data for evaluations of Tanner staging, the percentage of regression or no progression was 50.0% (1/2) at month 9 and 0% (0/2) at month 12.
- LH and FSH peak levels were suppressed in 98.1% (52/53) and 100% (53/53) of subjects while suppression of E2 occurred in 74.8% (77/103) of females and testosterone was suppressed in 100% (4/4) of males. 75% (3/4) of the male and 90.2% (83/92) of the female patients had decrease from baseline in the BA/CA ratio at the end of the Leuprorelin treatment phase (**Table 3**).

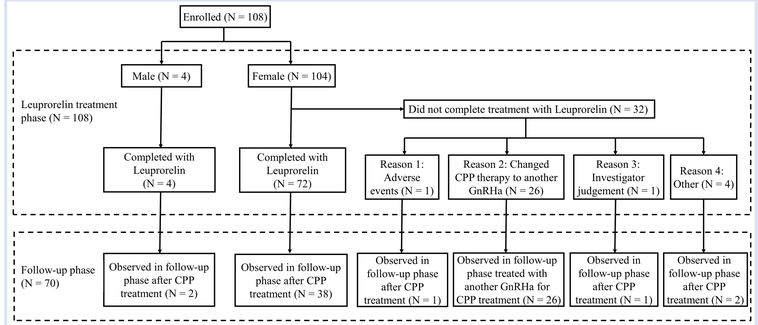


**Figure 1. Flow chart of the disposition of patients**

**Table 1. Overview of AEs during the Leuprorelin treatment phase**

| | Male (N = 4) | | Female (N = 104) | | Total (N = 108) | |
|---|---|---|---|---|---|---|
| | Events | Patients (%) | Events | Patients (%) | Events | Patients (%) |
| **AEs** | 7 | 4 (100) | 250 | 71 (68.3) | 257 | 75 (69.4) |
| **Drug withdrawn** | 0 | 0 (0) | 2 | 1 (1.0) | 2 | 1 (0.9) |
| **Relationship with Leuprorelin** | | | | | | |
| **TRAEs** | 1 | 1 (25.0) | 20 | 15 (14.4) | 21 | 16 (14.8) |
| **Not related** | 6 | 3 (75.0) | 230 | 56 (53.8) | 236 | 59 (54.6) |
| **SAEs** | 0 | 0 | 2 | 2 (1.9) | 2 | 2 (1.9) |
| **Drug withdrawn** | 0 | 0 | 0 | 0 | 0 | 0 |
| **Relationship to Leuprorelin** | | | | | | |
| **Treatment-related SAEs** | 0 | 0 | 0 | 0 | 0 | 0 |
| **Not related** | 0 | 0 | 2 | 2 (1.9) | 2 | 2 (1.9) |
| **Deaths** | 0 | 0 | 0 | 0 | 0 | 0 |
| **Most frequent AEs by preferred term occurring in ≥ 3% of patients** | | | | | | |
| **Preferred term** | **Male (N = 4) (PY = 7.384)** | | **Female (N = 104) (PY = 181.44)** | | **Total (N = 108) (PY = 188.824)** | |
| | Events (IR) | Patients (%) | Events (IR) | Patients (%) | Events (IR) | Patients (%) |
| **Total** | 2 (27.1) | 2 (50.0) | 143 (78.8) | 61 (58.7) | 145 (76.8) | 63 (58.3) |
| **Upper respiratory tract infection** | 0 | 0 | 27 (14.9) | 18 (17.3) | 27 (14.3) | 18 (16.7) |
| **Growth retardation** | 1 (13.5) | 1 (25.0) | 14 (7.7) | 14 (13.5) | 15 (7.9) | 15 (13.9) |
| **Bronchitis** | 0 | 0 | 25 (13.8) | 14 (13.5) | 25 (13.2) | 14 (13.0) |
| **Pharyngitis** | 0 | 0 | 17 (9.4) | 13 (12.5) | 17 (9.0) | 13 (12.0) |
| **Pyrexia** | 0 | 0 | 10 (5.5) | 9 (8.7) | 10 (5.3) | 9 (8.3) |
| **Refraction disorder** | 0 | 0 | 9 (5.0) | 9 (8.7) | 9 (4.77) | 9 (8.3) |
| **Cough** | 0 | 0 | 7 (3.9) | 7 (6.7) | 7 (3.71) | 7 (6.5) |
| **Rhinitis** | 0 | 0 | 10 (5.5) | 7 (6.7) | 10 (5.3) | 7 (6.5) |
| **Tonsillitis** | 0 | 0 | 8 (4.4) | 7 (6.7) | 8 (4.2) | 7 (6.5) |
| **Nasopharyngitis** | 1 (13.54) | 1 (25.0) | 3 (1.7) | 3 (2.9) | 4 (2.12) | 4 (3.7) |
| **Bone density decreased** | 0 | 0 | 4 (2.2) | 4 (3.8) | 4 (2.12) | 4 (3.7) |
| **Conjunctivitis** | 0 | 0 | 4 (2.2) | 4 (3.8) | 4 (2.12) | 4 (3.7) |
| **Gastritis** | 0 | 0 | 5 (2.8) | 4 (3.8) | 5 (2.65) | 4 (3.7) |

**Note:** The percentage of patients was based on the total number of patients per gender in the safety analysis set. The frequent AEs listed in the table are those that occurred in ≥ 3% of patients. PY = total time at risk in years; AEs per 100 person years; IR = incidence rate per 100 person years.

**Table 2. Number and percentage of regression or no progression from baseline in Tanner staging during the Leuprorelin treatment phase**

| Observational interval (months) | Tanner stage | Male (N = 4) | | Female (N = 104) | |
|---|---|---|---|---|---|
| | | **Genitals n/N (%) [95% CI]** | **Pubic hair n/N (%) [95% CI]** | **Breast n/N (%) [95% CI]** | **Pubic hair n/N (%) [95% CI]** |
| **Month 9 (226-315 days)** | **Tanner score per parameter** | | | | |
| | Regression/no progression | 3/3 (100) [29.24, 100] | 2/2 (100) [15.81, 100] | 71/75(94.7) [86.90, 98.53] | 59/63 (93.7) [84.53, 98.24] |
| | Progression | 0/3 [0, 70.76] | 0/2 [0, 84.19] | 4/75 (5.3) [1.47, 13.10] | 4/63 (6.3) [1.76, 15.47] |
| | **Tanner stage evaluation** | | | | |
| | Regression/no progression | 1/1 (100) [2.50, 100] | | 55/63 (87.3) [76.50, 94.35] | |
| | Progression | 0/1 [0, 97.50] | | 8/63 (12.7) [5.65, 23.50] | |
| **At the end of treatment** | **Tanner score per parameter** | | | | |
| | Regression/no progression | 2/3 (66.7) [9.43, 99.16] | 1/2 (50.0) [1.26, 98.74] | 88/95 (92.6) [85.41, 96.99] | 67/79 (84.8) [74.97, 91.90] |
| | Progression | 1/3 (33.3) [0.84, 90.57] | 1/2 (50.0) [1.26, 98.74] | 7/95 (7.4) [3.01, 14.59] | 12/79 (15.2) [8.10, 25.03] |
| | **Tanner stage evaluation** | | | | |
| | Regression/no progression | 0/1 [0,97.50] | | 63/79 (79.7) [69.20, 87.96] | |
| | Progression | 1/1 (100) [2.5, 100] | | 16/79 (20.3) [12.04, 30.80] | |

**Note:** Tanner stage evaluation was determined by the greater of the 2 evaluations for the Tanner score (specifically, breast development and pubic hair for females, and genital development and pubic hair for males) at a given time point compared to the baseline Tanner stage. A post baseline value greater than baseline for either breast/genitals or pubic hair was classified as progression, otherwise it was classified as regression/no progression. The percentage of regression/progression was calculated by the number of responses / (total number of patients) × 100%; 95% confidence intervals (CIs) were derived using an exact Clopper-Pearson method.

**Table 3. Changes in gonadotropin and hormone levels, and patients with a decrease in the BA/CA ratio during the Leuprorelin treatment phase**

| | Male (N = 4) | Female (N = 104) |
|---|---|---|
| **FSH (U/L)** | | |
| Baseline (n) | 3 | 78 |
| Mean (SD) | 3.36 (0.93) | 3.96 (3.41) |
| End of treatment | 3 | 77 |
| Mean (SD) | 0.92 (0.75) | 2.57 (4.93) |
| Change from baseline, mean (SD) | -2.35 (0.91) | -1.06 (6.77) |
| Number and percentage of FSH suppression, n/N (%) [95% CI] | 1/1 (100) [2.50, 100.00] | 52/52 (100) [93.15, 100.00] |
| **LH (U/L)** | | |
| Baseline (n) | 3 | 78 |
| Mean (SD) | 6.59 (7.55) | 1.78 (5.46) |
| End of treatment (n) | 3 | 77 |
| Mean (SD) | 2.32 (3.90) | 0.67 (0.64) |
| Change from baseline, mean (SD) | -3.54 (10.79) | -1.05 (5.42) |
| Number and percentage of LH suppression, n/N (%) [95% CI] | 1/1 (100) [2.50, 100.00] | 51/52 (98.1) [89.74, 99.95] |
| **Testosterone (male, nmol/L) or E2 (female, pg/mL)** | | |
| Baseline (n) | 4 | 89 |
| Mean (SD) | 70.47 (127.74) | 23.35 (18.16) |
| Min, max | 3.51, 262.02 | 0.18, 88.95 |
| End of treatment (n) | 4 | 88 |
| Mean (SD) | 0.61 (0.55) | 13.47 (9.63) |
| Change from baseline, mean (SD) | -69.86 (127.40) | -9.86 (18.46) |
| Number and percentage of testosterone or E2 suppression, n/N (%) [95% CI] | 4/4 (100) [39.76, 100.00] | 77/103 (74.8) [65.24, 82.80] |
| **Number (%) of patients with a decrease in the BA/CA ratio, n/N (%) [95% CI]** | | |
| Month 9 (226-315 days) | 0/1 [0.00, 97.5] | 15/19 (78.9) [54.43, 93.95] |
| At the end of treatment | 3/4 (75.0) [19.41, 99.37] | 83/92 (90.2) [82.24, 95.43] |

**Note.** LH suppression was considered to be a peak LH ≤ 2 U/L for females and LH ≤ 2.7 U/L for males. FSH suppression was considered to be a peak FSH ≤ 6.7 U/L for females and FSH ≤ 3.7 U/L for males. The percentage of regression/progression was calculated by the number of responses / (total number of patients) × 100%; 95% confidence intervals (CIs) were derived using an exact Clopper-Pearson method.

## Conclusion

The safety profile observed was consistent with the known profile of leuprorelin and no concerns were identified regarding long term administration. The majority of subjects received a maximum dose of 3.75 mg. Leuprorelin appeared to have been effective in the treatment of CPP.

## References

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## Conflict of Interest

Winston Wang is a former staff of Takeda Development Center Asia and does not have a current affiliation. Ziheng Guo is employed by Takeda (China) International Trading Co., Ltd. The remaining authors declare no conflict of interest.

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