Triptorelin 6-month Formulation Shows Good Efficacy and Safety in Patients with Central Precocious Puberty (CPP)

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Clinical Trial Registration Number: NCT01467882

Background
Triptorelin is an established treatment of Central Precocious Puberty (CPP) as 1- and 3-month formulations. This is the first study of the triptorelin emboinate (pamatoe) 6-month formulation in CPP, previously approved for prostate cancer therapy.

Objectives
- The efficacy and safety of the triptorelin 6-month formulation in CPP were investigated.
- The primary objective was to evaluate the efficacy in achieving LH suppression to pre-pubertal levels ≥5 IU/L at month 6.

Methods
Design
This was an international, multicenter, non-comparative phase III study over 48 weeks conducted at 18 medical centers in the US, Mexico and Chile. Forty-four treatment naïve patients (39 girls and 5 boys) were included.

Inclusion Criteria
- Onset of puberty <8 years in girls and <9 years in boys
- Age at treatment start 2-8 (<9) years for girls and 2-9 (<10) years for boys
- Puberal LH response to leuprolide stimulation of ≥6 IU/L
- Clinical evidence of puberty (Tanner ≥2 for breast in girls and <9 years in boys)

Intervention
Two consecutive intramuscular triptorelin injections were administered at an interval of 24 weeks.

Hormone Levels
Hormone levels (LH, FSH [basal & stimulated], estradiol [girls], testosterone [boys]) and auxological parameters and clinical signs of puberty and safety were assessed.

Results

Patient Characteristics

<table>
<thead>
<tr>
<th>Sex</th>
<th>Race</th>
<th>N</th>
<th>Mean (SD)</th>
<th>Median (min-max)</th>
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<td>Other</td>
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<td>1.33 (1.20)</td>
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<td>White</td>
<td>39</td>
<td>1.34 (1.33)</td>
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<tr>
<td></td>
<td>White</td>
<td>12</td>
<td>1.35 (1.30)</td>
<td>1.30 (0.60)</td>
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<tr>
<td></td>
<td>Other</td>
<td>2</td>
<td>1.35 (1.30)</td>
<td>1.30 (0.60)</td>
</tr>
</tbody>
</table>

Table 1. Demographic, baseline and auxological characteristics at baseline and at month 12.

Hormonal Parameters

In the ITT (Intention-to-treat) population, 41 patients out of 44 (93.2%; 95% CI 81.3%; 98.6%) showed pre-pubertal LH levels at month 6 and maintained LH suppression until month 12 (Fig. 1).

The percentage of girls with pre-pubertal estradiol ranged from 79.5% to 92.3%, while the percentage of boys with pre-pubertal testosterone ranged from 80.0% to 100.0% from month 1 to 12 (Fig. 2).

Fig. 1. Individual serum LH levels

Fig. 1. A, Mean (SD) serum estradiol levels in girls (ITT population). B, Mean (SD) LH, FSH and testosterone levels in boys (ITT population).

Three patients failed to suppress LH at month 6 (Table 2).

- A 9-year-old boy (0802) had a non-suppressed LH at month 6 and 12.
- Another boy (0803) had an LH of 5.1 IU/L at month 6, but it was suppressed to 3.2 IU/L at month 12.
- An 8-year-old girl (2404) encountered a technical problem with the LH stimulator.

Non-hormonal Parameters

- The percentage of children with reduction in bone age/chronological age ratio on-treatment was 56.8% at month 6 and 90.9% at month 12.
- Mean growth velocity was 6.8 cm/year at month 6 and 6.1 cm/year at month 12 suggesting slowing down of accelerated growth.
- The Tanner stage was stable or reduced in 90.9% of patients between baseline and month 6 and in 88.6% between baseline and month 12.

Safety
- All patients completed the study and there were no treatment interruptions. A total of 62 mostly mild (89.0%) treatment-emergent AEs (Adverse Events) for 33 (75.0%) out of 44 patients during the study.
- Five of the AEs reported for 4 (9.1%) patients were considered as triptorelin-related: 2 patients with mild vaginal bleeding shortly after treatment start, 1 girl [LH non-suppressed at month 6 following technical problems] with menstrual bleeding twice between the 1st and 2nd injections, 1 patient with mild injection site pain.
- One serious non-drug AE (infection of a vagus nerve stimulator) was reported.

Conclusions

- The results show that triptorelin emboinate 22.5 mg 6-month formulation is efficacious in suppressing the pubilary release of LH and FSH, and consequently the gonadal secretion of estradiol in girls and testosterone in boys to pre-pubertal levels, with a favorable effect on progression of clinical signs of puberty.
- Administration of the triptorelin 6-month formulation was well tolerated and safe with no unexpected AEs reported.
- The reduced injection frequency has the potential advantage of improving compliance to treatment and increasing comfort for children with CPP.

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Fig. 2. Mean (SD) serum testosterone levels in boys (ITT population).