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

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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 embonate (pamoate) 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
- Pubertal LH response to leuprolide stimulation of ≥6 IU/L
- Difference between bone and chronological age ≥1 year
- Clinical evidence of puberty (Tanner ≥2 for breast in girls and testicular volume ≥4 mL for boys)

Intervention

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

Main Outcome Measures

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

Clinical Trial Registration Number: NCT01467882

Results

Patient Characteristics

		Baseline	
Sex	Female Male	39 (88.6%) 5 (11.4%)	
Age (completed years)	N Mean (SD) Median (min-max)	44 7.41 (1.28) 8.00 (2.00-9.00)	
Weight (kg)	N Mean (SD) Median (min-max)	44 32.83 (8.40) 34.00 (15.30-54.00)	
BMI (kg/m²)	N Mean (SD) Median (min-max)	44 17.76 (2.66) 18.00 (11.77-23.76)	
Height (cm)	N Mean (SD) Median (min-max)	44 134.77 (10.88) 137.00 (103.00-155.00)	
Race	Asian Black /African American Other White	2 (4.55%) 12 (27.27%) 4 (9.09%) 26 (59.09%)	
		Baseline	**Month 12**
Bone age (months)	N Mean (SD) Median (min-max)	44 129.55 (18.16) 132.00 (82.00-156.00)	44 136.92 (19.34) 144.00 (82.00-162.00)
BA/CA ratio	N Mean (SD) Median (min-max)	44 1.40 (0.25) 1.36 (1.15-2.65)	44 1.30 (0.19) 1.26 (1.03-1.95)
Height for age (Z-score)	N Mean (SD) Median (min-max)	44 1.33 (1.20) 1.34 (-1.63-3.31)	44 1.33 (1.15) 1.50 (-1.88-3.23)

Table 1. Demographic (baseline) and disease characteristics at baseline and at month 12.

- At baseline, 13.6% of the patients were defined as Tanner stage 2, 65.9% as stage 3 and 20.5% as stage 4.

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).

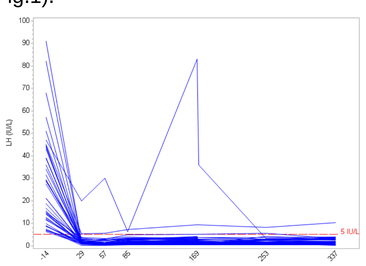

Fig. 1. Individual serum LH levels

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).

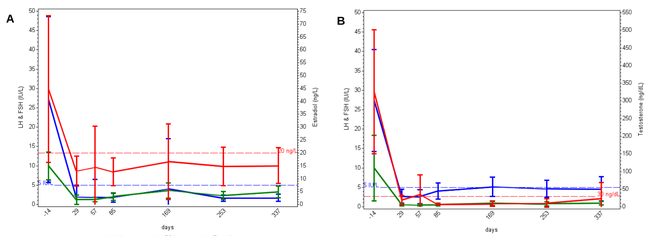

Fig. 2. A. Mean (SD) LH, FSH and estradiol levels in girls (ITT population). **B.** Mean (SD) LH, FSH and testosterone levels in boys (ITT population).

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

- A 9-year-old boy (0802) had a non-suppressed LH at months 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 1st triptorelin injection (LH: 83 IU/L at month 6). There were no difficulties with the 2nd injection and at month 12, LH was suppressed to a pre-pubertal level (3.6 IU/L).

Patient	Age (years at baseline)	Sex	Body Weight (kg)	BMI (kg/m²)	Race	Time (month)	LH (IU/L)	FSH (IU/L)	E2 (ng/L)	Test (ng/dL)
0802	9	M	54	23.1	Black	0	45.0	4.9	-	142.0
						1	5.4	0.4	-	40.0
						2	5.6	0.5	-	134.0
						3	7.3	0.5	-	9.7
						6	9.4	0.9	-	17.9
						9	8.1	0.4	-	32.0
						12	10.2	1.0	-	104.0
0803	9	M	28.5	15.2	Asian	0	34.0	12.0	-	247.0
						1	2.4	0.6	-	12.5
						2	3.0	0.6	-	11.8
						3	4.9	0.7	-	4.6
						6	5.1	1.1	-	2.0
						9	5.5	1.3	-	5.1
						12	3.2	1.1	-	3.3
2404	8	F	45.8	21.2	Black	0	47.0	13.0	38.0	-
						1	20.0	8.0	27.0	-
						2	30.0	2.5	105.0	-
						3	6.3	3.2	14.0	-
						6	83.0	8.6	99.0	-
						9	3.2	2.1	14.0	-
						12	3.6	2.7	37.0	-

Table 2. Patients considered as failures for the primary endpoint.

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% patients between baseline and month 12.

Safety

- All patients completed the study and there were no treatment interruptions. A total of 82 mostly mild (89.0%) treatment-emergent AEs (Adverse Events) were reported 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-related AE (infection of a vagus nerve stimulator) was reported.

Conclusions

- The results show that triptorelin embonate 22.5 mg 6-month formulation is efficacious in suppressing the pituitary 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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