Effects on growth, body composition, motor and cognitive development and safety of recombinant human growth hormone in infants or toddlers with Prader-Willi syndrome: A randomized, active-comparator controlled Trial

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INTRODUCTION

- Growth hormone therapy is beneficial for children with Prader-Willi Syndrome (PWS) in a height (Ht) and body composition improvement as well as motor and cognitive development.

OBJECTIVES

- To evaluate efficacy and safety of recombinant human growth hormone (rhGH) (Eutropin® Inj., LG Chem, Ltd.) in children with PWS compared to the approved rhGH (Genotropin® Inj., Pfizer, Inc.)

METHODS

- A Phase Ⅲ, Multi-center, Randomized, Active-comparator controlled, Parallel, Open-label study
- Pre-pubertal subjects were to be randomly assigned to Eutropin® Inj. or Genotropin® Inj., and the study drug was administered for 1 year (52 weeks).
- The subjects visited at 4, 8, 16, 28, 40, 52 weeks after randomization to evaluate efficacy and safety parameters. After the last administration, subjects were followed-up for 4 weeks.
- Body composition was measured by dual energy x-ray absorptiometry, and motor and cognitive developments were assessed by Bayley Scales of Infant Development (BSID-II/ Korean BSID-II).

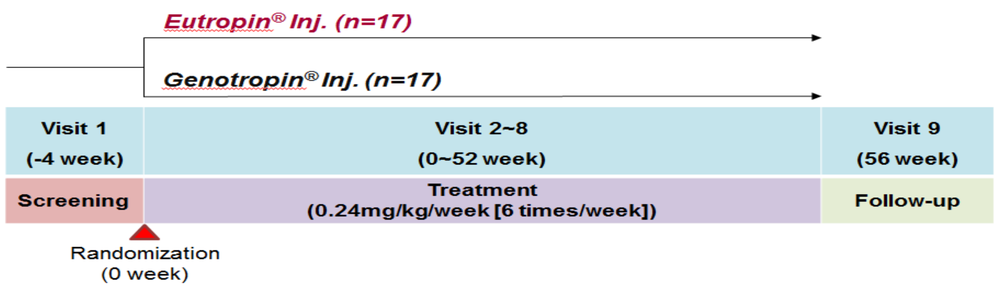
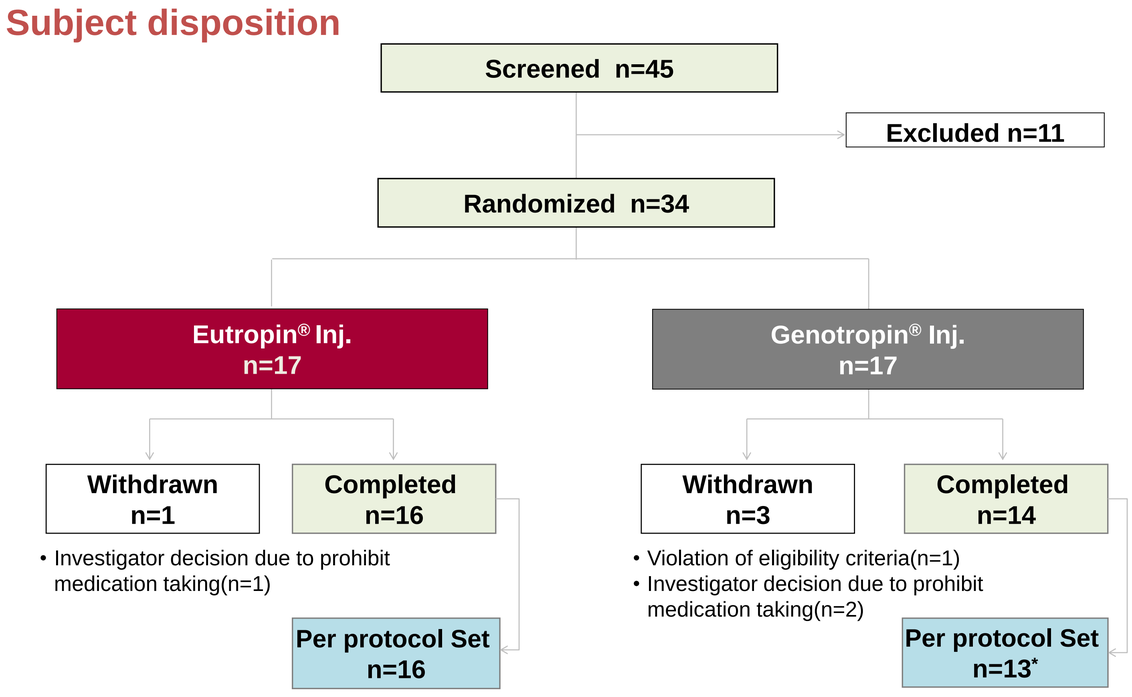


Figure 1. Study design

RESULTS

Subject disposition



* One subject was excluded due to the deviation from eligibility criteria and taking prohibited medications.

Figure 2. Subject disposition

Demographic characteristics

Table 1. Characteristics (*N or mean* ± (SD))

Treatment group	Eutropin® Inj. (N=16)	Genotropin® Inj. (N=13)	P-value (intercomparison)
Gender, Male/Female	5/11	6/7	0.4657 §§
Age, month	4.81 (± 2.04)	8.04 (± 5.81)	0.0483 **
Weight at Birth, kg	2.86 (± 0.34)	2.49 (± 0.48)	0.0219 *

*: *p*-value obtained from two sample t-test, **: *p*-value obtained from Wilcoxon's rank sum test, §§: *p*-value obtained from Fisher's exact test

Efficacy Results

- After 52 weeks of treatment, Ht SDS (Standard Deviation Score) and Lean Body Mass increased significantly, Percent Body Fat also decreased significantly in both groups.
- The mean changes in other auxological parameters as well as Insulin-like Growth Factor 1(IGF-1) and IGF-binding Protein 3 (IGFBP-3) values were also comparable between the groups.
- The scores for motor and cognitive developments were also improved in both groups after the 1 year treatment.

RESULTS(Cont'd)

Efficacy Results (Cont'd)

Table 2. Change from baseline at Week 52 (Mean (±SD))

Treatment group	Eutropin® Inj. (N=16)	Genotropin® Inj. (N=13)	Mean difference (95% CI)
HtSDS			
At each time point			
Baseline	-1.040 (± 0.940)	-2.082 (± 0.923)	1.043 (0.328, 1.757)
Week 52	-0.289 (± 0.883)	-1.134 (± 0.920)	0.845 (0.156, 1.534)
Change from Baseline			
Week 52	0.751 (± 0.588)	0.948 (± 0.663)	-0.197 (-0.674, 0.279)
p-value (intracomparison)	0.0001 †	0.0002 †	
Lean Body Mass, g			
At each time point			
Baseline	3438.86 (± 600.18)	3691.72 (± 745.93)	-252.87 (-765.33, 259.60)
Week 52	5816.65 (± 738.28)	6298.82 (± 946.53)	-482.17 (-1123.63, 159.28)
Change from Baseline			
Week 52	2377.79 (± 536.25)	2607.10 (± 641.36)	-229.31 (-677.73, 219.12)
p-value (intracomparison)	<.0001 †	<.0001 †	
Percent Body Fat, %			
At each time point			
Baseline	41.53 (± 8.51)	40.04 (± 10.30)	1.49 (-5.67, 8.65)
Week 52	33.41 (± 5.26)	32.56 (± 5.59)	0.85 (-3.29, 5.00)
Change from Baseline			
Week 52	-8.12 (± 9.86)	-7.48 (± 10.26)	-0.64 (-8.33, 7.05)
p-value (intracomparison)	0.0049 †	0.0398 ‡	
Head Circumference, cm			
At each time point			
Baseline	40.76 (± 1.30)	42.23 (± 2.45)	-1.47 (-3.06, 0.12)
Week 52	45.46 (± 1.38)	46.85 (± 1.56)	-1.39 (-2.51, -0.27)
Change from Baseline			
Week 52	4.69 (± 1.04)	4.62 (± 1.47)	0.08 (-0.88, 1.03)
p-value (intracomparison)	<.0001 †	<.0001 †	
Motor Development, Score			
At each time point			
Baseline	14.1 (± 10.6)	26.2 (± 18.1)	-12.2 (-23.2, -1.1)
Week 52	54.5 (± 10.9)	59.2 (± 11.8)	-4.7 (-13.3, 4.0)
Change from Baseline			
Week 52	40.4 (± 7.8)	32.9 (± 10.5)	7.5 (0.5, 14.5)
p-value (intracomparison)	<.0001 †	<.0001 †	
Cognitive Development, Score			
At each time point			
Baseline	28.0 (± 16.6)	48.5 (± 28.9)	-20.5 (-39.5, -1.6)
Week 52	84.8 (± 13.9)	96.2 (± 19.2)	-11.3 (-24.0, 1.3)
Change from Baseline			
Week 52	56.8 (± 14.6)	47.6 (± 13.8)	9.2 (-1.7, 20.1)
p-value (intracomparison)	<.0001 †	<.0001 †	

†: p-value obtained from Paired t- test, ‡: p-value obtained from Wilcoxon's signed rank test

Safety Results

- Adverse events (AEs) were reported 17 subjects in Eutropin® Inj. group and 16 subjects in Genotropin® Inj. group, and most AEs were mild to moderate intensity.
- The most common AE was upper respiratory tract infection in both groups (11 [64.71%] and 10 [58.82%] subjects, respectively).
- Among AEs, 9 and 6 events were reported as Adverse Drug Reactions (ADRs) in each group, respectively. Hypothyroidism (3 [17.65%] and 1 [5.88%] subjects, respectively) was the major ADR.
- Two SADRs (congestive cardiomyopathy and urinary tract infection) in Eutropin® Inj. group and one SADR (bronchitis) in Genotropin® Inj. group were reported. All SADRs were unlikely related to study drugs.
- One AE of sleep apnoea syndrome was reported in Eutropin® Inj. group, but was not a SAE, and had No relationship with the study drug.

Table 3. Summary of AEs

Treatment group	Eutropin® Inj. (N=17)		Genotropin® Inj. (N=17)	
	n (%)	Number of AEs	n (%)	Number of AEs
AE	17 (100.00)	151	16 (94.12)	107
ADR	6 (35.29)	9	6 (35.29)	6
SAE	8 (47.06)	15	7 (41.18)	13
SADR	2 (11.76)	2	1 (5.88)	1

AE, Adverse event; ADR, Adverse drug reaction; SAE, Serious AE; SADR, Serious ADR

CONCLUSION

- Eutropin® Inj. showed comparable efficacy and safety outcomes in infants and toddler with PWS with Genotropin® Inj.
- Hence, Eutropin® Inj. is expected to provide safe and clinically meaningful improvement in children with PWS.

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