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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Genotropin®/Genotonorm®/Somatropin (recombinant)

PROTOCOL NO.: 90-076

PROTOCOL TITLE: A Multicentre Study of Genotonorm® treatment in children with familial short stature

Study Centres: Eleven centres in France.

Study Initiation Date and Completion Dates: 1991 to 2002

Phase of Development: Phase 3

Study Objectives: Objectives of the study were to evaluate the effect of a 2-year Genotonorm® treatment on height Standard Deviation Score (SDS) for chronological age (CA) in non growth hormone (GH) deficient children with familial short stature compared to no Genotonorm® treatment; to compare the growth promoting effect of 2 different doses of Genotonorm®; and, to evaluate the safety of two different doses of Genotonorm®.

METHODS

Study Design: This was a French, open, multi-centre, parallel group, randomised trial which included an untreated control group throughout the duration of the trial. Subjects were randomised into 3 groups: no treatment (group A), 1.0 IU/kg/week of Genotorm® (group B), 2.0 IU/kg/week of Genotorm® (group C).

The design of the study was to be:
(1) Month 0 to month 24 (M0-M24): active GH treatment period for group B and C (visit every 3 months), for the untreated group visit every 6 months.
(2) After M24: for all subjects, follow-up after treatment until final height.

Number of Subjects (Planned and Analysed): Planned: 70 subjects [30 subjects untreated (group A), 20 subjects treated by 1.0 IU/kg/week (around 0.043 mg/kg/day, group B) and 20 subjects treated by 2.0 IU/kg/week (around 0.086 mg/kg/day, group C)]. During the study a total of 73 subjects were pre-selected and 64 randomised subjects were included in the study.

Diagnosis and Main Criteria for Inclusion: Criteria for inclusion were: Height for CA at baseline < -2.5 SDS, bone age (BA) at baseline within 2 SDS of the mean for CA, CA ≥6 ≤11 for boys and ≥6 ≤10 for girls, GH peak at stimulation test ≥ 12 ng/ml before randomisation, measured height <2SDS: < 163 cm for the father and/or <152 cm for the
mother, birth length according to gestational age > -3 SDS, growth rate between P10-P50 and no pubertal sign.

**Study Treatment:** Genotonorm® 16 IU, 1 daily subcutaneous injection. The duration of treatment was 24 months.

**Efficacy Evaluations:** The main criterion for efficacy evaluation was height in SDS for CA at M24. Other criteria were height in SDS for CA at month 12 (M12), height in cm, height in SDS for BA, final height (cm, SDS), growth rate (cm/year), delta BA (years), BMI (kg/m²).

**Safety Evaluations:** Measured safety variables were adverse events (AEs), biological parameters such as insulin-like growth factor 1 (IGF-1), thyroid stimulating hormone (TSH), free thyroxin (FT4), and insulin every 6 months in active treatment groups, triglycerides, free fatty acids and cholesterol every 6 months in active treatment groups and every year in non-treated subjects, dehydroepiandrosterone sulphate (DHAS), blood cells every 6 months in all groups, and Oral Glucose Tolerance Test (OGTT) for all children every year. Derived/computed safety variables were hyperglycemia, OGTT hyperglycemia, and changes in laboratory parameters.

**Statistical Methods:** The statistical methods used included:

- Descriptive statistics of efficacy and safety data.
- Comparisons between groups at M12, M24 and final height, were performed using pairwise comparisons between each group according to Holm’s sequentially rejective Bonferroni procedure with an overall α-error of 0.05 followed by explanatory analysis (Anova, covariance analysis). A post-hoc analysis on the possible influence of puberty was performed after splitting the GH treated children into two subgroups according to age at inclusion (<9 years, ≥9 years).
- The estimated sample size was 20 subjects per active group and 30 subjects in the control group (total of 70 subjects), based on the following assumptions: Main criterion height in SDS for CA at M24, standard deviation (SD) = 0.8 SDS, delta between groups = 0.75 SDS, drop-out rate of 30% in the control group.
- Efficacy analysis was performed on Intent-To-Treat (ITT) and Per Protocol (PP) populations. ITT population was defined as all patients randomised to active treatment who received at least one injection of study medication and all patients randomised to the untreated group who continued in the study after the baseline visit. Furthermore, an informed consent should be available. PP population was defined as all ITT patients who remained in their randomization group 2 years at least and with no major protocol violation.
- The definition of the safety population corresponds to the definition of the ITT population.
RESULTS

Subject Disposition and Demography: Out of 73 pre-selected subjects for the study a total of 64 subjects were included in the study. Nine subjects were excluded because of lack of written informed consent. A total of 12 subjects (18.8%) were dropped out before M24 mostly due to other reasons or lost to follow up. Details are provided in Table 1.

Boys represented 70% of the ITT population. Age at inclusion was 8.8 ± 1.5 yrs, birth length was –1.4 ± 0.7 SDS, Height for CA was –2.8 ± 0.6 SDS corresponding to 114.5 ± 7.5 cm, the target height was –1.9 ± 0.7 SDS.

Table 1: Randomised subjects, drop-outs (before M24) and study populations

<table>
<thead>
<tr>
<th></th>
<th>A (control)</th>
<th>B (1.0 IU/kg/week)</th>
<th>C (2.0 IU/kg/week)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of subjects</td>
<td>24</td>
<td>22</td>
<td>18</td>
<td>64</td>
</tr>
<tr>
<td>Total number of subjects in the study at least until M24</td>
<td>19</td>
<td>18</td>
<td>15</td>
<td>52</td>
</tr>
<tr>
<td>Number of subjects drop out from study before M24</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Reason of premature discontinuation :</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No compliance</td>
<td>0</td>
<td>0</td>
<td>1 (33.3)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>- Consent withdrawn</td>
<td>0</td>
<td>1 (25.0)</td>
<td>0</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>- Subject lost to follow-up</td>
<td>2 (40.0)</td>
<td>1 (25.0)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>- Other reason</td>
<td>3 (60.0)</td>
<td>2 (50.0)</td>
<td>2 (66.7)</td>
<td>7</td>
</tr>
<tr>
<td>Study populations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects included in ITT population</td>
<td>22 (91.7)</td>
<td>20 (90.9)</td>
<td>18 (100.0)</td>
<td>60 (93.8)</td>
</tr>
<tr>
<td>Subjects included in PP population compared to the ITT population</td>
<td>19 (86.4)</td>
<td>18 (90.0)</td>
<td>14 (77.8)</td>
<td>51 (85.0)</td>
</tr>
</tbody>
</table>

Abbreviations: ITT = intent to treat, PP = per protocol.

Efficacy Results: Sixty (94%) subjects were included in the ITT population and 51 (80%) in the PP population. Twenty-two subjects were randomised in the A group, 20 in the B group and 18 in the C group (ITT population).

After 24 months of treatment, the mean height in SDS for CA (main criterion of efficacy) was significantly higher in group B (1.0 IU/kg/week Genotorm®) and in group C (2.0 IU/kg/week Genotorm®) than in group A (control):

- pAB <0.0001 and pAC =0.0005, A: -2.8 ± 0.5, B: -1.6 ± 0.5, C: -1.6 ± 1.3 in ITT population.
• pAB <0.0001 and pAC =0.0008, A: -2.8 ± 0.5, B: -1.6 ± 0.5, C: -1.6 ± 1.4 in PP population.

A significant difference between treated and untreated groups was shown for the followings criteria, in PP (see figures below) and in ITT populations:

**Height in SDS for CA at 12 months**: -2.7 ± 0.5 in control group, -1.9 ± 0.5 in group 1.0 IU/kg/week and -2.1 ± 1.4 in group 2.0 IU/kg/week (pAB<0.0001, pAC =0.0098)

**Delta height in SDS for CA at 24 months**: 0.0 ± 0.3 in control group, 1.2 ± 0.3 in group 1.0 IU/kg/week and 1.5 ± 0.5 in group 2.0 IU/kg/week (pAB<0.0001, pAC <0.0001)

**Height in cm at 24 months**: 123±8 in control group, 130± 8 in group 1.0 IU/kg/week and 133±8 in group 2.0 IU/kg/week (pAB =0.0096, pAC =0.001)

**Delta height in cm at 24 months**: 9±2 in control group, 16±2 in group 1.0 IU/kg/week and 18±4 in group 2.0 IU/kg/week (pAB <0.0001, pAC <0.0001)

**Growth rate in cm/year at 12 months**: 4.8±1.4 in control group, 8.8±1.1 in group 1.0 IU/kg/week and 9.9±2.5 in group 2.0 IU/kg/week (pAB <0.0001, pAC <0.0001)

**Growth rate in cm/year at 24 months**: 4.3±0.9 in control group, 7.0±1.0 in group 1.0 IU/kg/week and 7.7±1.5 in group 2.0 IU/kg/week (pAB <0.0001, pAC <0.0001)

For height in SDS for BA at 12 months (BA is missing in more than 11% of the children at 24 months) and predicted final height in SDS at 24 months, significant differences were shown between group A and group B only, in PP (see figures below) and in ITT populations:

**Height in SDS for BA at 12 months**: -1.0±0.9 in control group, -0.2±0.9 in group 1.0 IU/kg/week and -0.2±1.4 in group 2.0 IU/kg/week (pAB =0.0102)

**Predicted final height in SDS at 24 months**: -2.3±0.9 in control group, -1.4±0.8 in group 1.0 IU/kg/week and -1.4±1.6 in group 2.0 IU/kg/week (pAB =0.0042)

Pre-final height was available in 46 (72%) children and final height in 35 (55%) children out of the 64 randomised children. Final height was available in 34 (57%) of the ITT population and 31 (61%) children of the PP population. No statistically significant difference in final height was shown between the groups:

Mean final height in SDS was -2.5±0.9, -2.0±0.7, -2.7±1.5 in the A, B and C group respectively (all randomised children with available pre-final or final height). Mean final height in SDS was -2.4±0.7, -2.0±0.6, -2.4±1.2 in the A, B and C group respectively (PP population).

Final height tended to be higher in early treated children but the difference was not statistically significant (p=0.10).

**Safety Results**: A total of 28 subjects (46.7%) presented at least 1 event during the first 24 months (A: 3 [13.6%], B: 12 [60.0%], C: 13 [72.2%]); significantly more treated subjects presented 1 or more AE compared to the untreated subjects during the treatment period.
(p=0.0004). Almost 25% of subjects presented at least 1 drug related event (during all the study). No event resulted in termination of the study medication.

A total of 71 AEs (during all the study) were reported; 1 subject presented a serious adverse event (SAE) (fracture, musculoskeletal system disorders) 3 years after GH discontinuation. The main AEs concerned were insulin increase (metabolic and nutritional, 8.5% of AEs), free fatty acids increased (8.5% of AEs) and hypercholesterolemia (7% of AEs).

As far as laboratory data were concerned, only OGTT Insulin at T120 (120 minutes) was increased in the 2 active treated groups after 1 and 2 years of treatment. No GH treatment was stopped because of an AE. No case of diabetes was reported.

CONCLUSION: Height was significantly increased after 2 years of GH treatment with no apparent dose effect. GH treatment efficacy is not confirmed when children are followed until near final height, with no significant difference between control group and GH treated groups. Safety of 2 years GH treatment is acceptable. The efficacy of a 2-year GH treatment on final height cannot be ruled out in this population since:

- The number of patients with available final height (61% of the PP population) is small and a bias is possible. Long-term follow-up is difficult in children with familial short stature.

- An insufficient duration of treatment or late start of treatment. Children have been treated only 2 years and half and most of them were near puberty onset at start of GH treatment.

- Other unexplained factors including not reported GH treatment in the control group after 2 years.