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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: sanofi-aventis **Drug Substance:** Somatropin	**Study Identifier:** NCT00452725 **Study Code:** MAX08
Title of the study: Effect of growth hormone, Maxomat®, on the growth of children and adolescents with small stature (≤ 2 SD) due to Noonan syndrome	
Study Centers: Saint Vincent de Paul Hospital – Paris; Armand Trousseau Hospital – Paris; Centre Hospital – Nevers; Necker Hospital – Paris; Children's Hospital – Nancy; Purpan Children's Hospital – Toulouse; Robert Debré Hospital – Paris; Pellegrin Hospital – Bordeaux; Jeanne de Flandres Hospital – Lille; South Hospital – Lyon; Debrousse Hospital – Lyon; Saint Jacques CHU – Besançon; Clocheville CH – Tours; Dupuytren Hospital - Limoges; Saint Louis CHG – La Rochelle; La Timone Hospital – Marseille; Centre Robert Debré – Angers; Flaubert Hospital – Le Havre; American Hospital – Reims; North Hospital CHU – Amiens; CHG - Compiègne.	
Study Period: - Date first patient enrolled: 16 October 1997 - Date last patient completed: 08 March 2010	**Phase of development:** IV
Objectives: - To verify the efficacy of growth hormone in the treatment of small stature related to Noonan syndrome - To study the genetics of this syndrome - To verify the safety of the growth hormone for the duration of treatment	
Methodology: open-label, multicenter study. - Group I: children older than 3 years of age with bone age < 13 years for boys and < 11 years for girls - Group II: adolescents with bone age between 13 and 15 for boys and between 11 and 13 for girls	
Number of patients: - Number of patients planned: 40 - Number of patients analysed: 36	
Investigational medicinal product: Maxomat® (somatropin), presented in the form of a bottle containing 4 IU/2 mL of solvent, administered by subcutaneous route 7 days out of 7, from 0.9 to 1.2 or 1.4 IU/kg/week (group I) and 1.4 IU/kg/week (group II)	
Duration of treatment: two years and more.	
Criteria for evaluation: - Efficacy: change in size, gain in stature, weight, bone age and rate of growth - Safety: clinical and biological safety - Other: genetic study of Noonan syndrome	
Statistical methods: Statistical analyses were performed by RPS using SAS software, version 9.1.3, and were essentially descriptive. The quantitative variables are described in terms of the number of patients, number of missing values, mean, standard deviation, ranges, quartiles and median. The qualitative variables are described in terms of the number of patients and percentage. Initial	

parameters correspond to the criteria found at pre-enrolment and enrolment visits. Analysis of parameters is descriptive per group of children.

In terms of efficacy, the analysis of variables related to the growth of the children (growth rate (cm/year and SDS/year), height (cm and SDS), weight (kg and SDS), bone age (year), and statural gain (cm and SDS)) was performed in a descriptive manner by group of children.

Safety was studied according to 4 endpoints: biological safety, cardiac safety, clinical safety and local safety.

These parameters are described at every odd-numbered visit (every 6 months). Changes in relation to initial values are indicated at each odd-numbered visit for each parameter. The incidence of values outside of the norms is also calculated for each parameter at each odd-numbered visit in a "shift table."

The results of cardiac clinical evaluations (normal/abnormal) are reported every 3 months. Comments concerning abnormal ElectroCardioGrams are listed.

Local safety, i.e., the number of painful injections (quantitative variable) and whether or not there were other local complaints are reported every 6 months. Specifications are also provided for the other local complaints.

Clinical safety is analysed using the occurrence of adverse events. Those are analysed overall by system organ and preferred term.

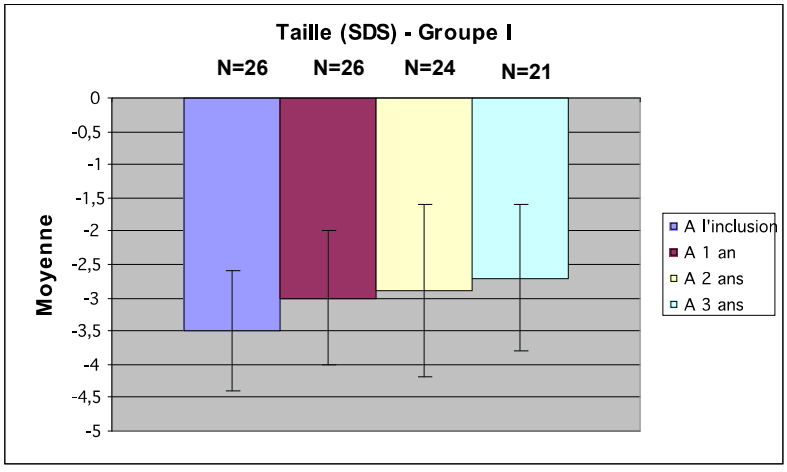
Summary

Out of a total of 39 selected patients, 36 patients were enrolled in the study: 26 in group I and 10 in group II. Group I had 15 boys and 11 girls; group II, 4 boys and 6 girls.

- *Results of the efficacy evaluation*

Upon enrolment, the children are from 10.4 ± 3.0 years of age on average in group I and 14.8 ± 1.5 years in group II. Their heights are 118.0 ± 14.9 cm on average for the children in group I and 139.1 ± 4.4 cm for the adolescents in group II. In terms of cardiology, 18 subjects (51.4%) presented with a normal profile whereas 17 (48.6%) had cardiac abnormalities. We wish to emphasise that, in a population of this type, it is normal to encounter a previous history of cardiac disorders in 50 to 80% of children affected.

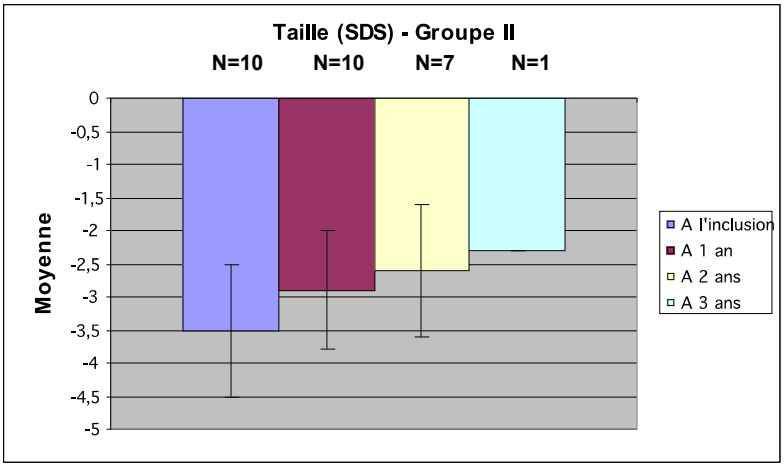
During follow-up, in terms of height expressed in SDS, we noticed a tendency of the effect of the treatment to wear off over time, while the outcome in cm in this parameter showed regular progression.



Height (SDS) – Group I

Mean

Upon enrolment, At 1 year, At 2 years, At 3 years



Height (SDS) – Group II

Mean

Upon enrolment, At 1 year, At 2 years, At 3 years

The mean height at the final visit is 156.2 ± 10.2 cm in group I and 153.4 ± 4.3 cm in group II. Only 3 of the 29 patients, i.e. 10.3% (exact 95% CI: [2.2% - 27.4%]), reached their definitive height at the end of treatment with Maxomat® in this study.

Considering the very small sample size, no conclusion is possible on the efficacy of Maxomat® in this population of patients.

- *Results from the safety evaluation*

Out of all of the 95 Adverse Events (AEs) observed in the study, 38 correspond to Serious Adverse Events (SAEs), all causalities taken together: 21 SAEs occurred in group I (10 patients) and 17 in group II (7 patients). Of these 38 SAEs observed, whatever their causality, imputability to treatment is ruled out in 23 cases, but plausible in 1 case, unknown in 2 cases and doubtful in 10 cases in 3 patients. Data are missing in 2 cases.

The SAEs that could be imputable to the treatment involve 7 patients. They are the following SAEs: hospitalisation for surgical intervention, severe scoliosis, mild dishydrosis, mild skin spots, severe thrombocytopenia, mild laryngitis, limping, epiphysiolysis of the right hip, ablation of screw and subglottic stenosis, moderate encopresis, and portal hypertension.

We also counted 15 AEs having led to a definitive discontinuation of treatment in 5 patients. Their imputability to the treatment is ruled out in 7 cases and doubtful in 8 cases.

In terms of biological safety, while the majority of laboratory parameters are in line with the accepted norms, we observe a significant number of high values beyond the limits of normal on lab tests, which seem to regress, nevertheless, over time (glycaemia, triglyceridaemia, etc.).

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