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Sponsor / Company : Sanofi-aventis	**Study Identifier** : NCT00452491
Generic drug name : Somatropin	**Study Code** : FH5126A

Title of the study:
A cohort of prepubertal children for the study of optimisation of administration methods of the biosynthetic growth hormone Maxomat® in the treatment of severe early onset intrauterine growth retardation (height below or equal to –2.5 SD)

1st part of the study

Study Center(s):
Aix-en-Provence (C19), Angers (C21), Argenteuil (C07), Arras (C09), Bagnols-sur-Cèze (C20), Besançon (C14), Bordeaux – Medical centre (C28), Bordeaux – Pellegrin University Hospital (C08), Bourges (C15), Brest (C10), Brive (C16), Caen (C10), Calais (C09), Cambrai (C09), Chambéry (C12), Colmar (C05), Dieppe (C23), Dijon (C29), Dunkerque (C09), Evreux (C23), Fécamp (C23), Firminy (C12), Fréjus Saint-Raphaël (C22), Freyming Merlebach (C04), Grenoble (C13), Hyères (C19), La Roche-sur-Yon (C17), La Rochelle (C17), Le Havre (C23), Le Mans (C21), Le Puy (C11), Lens (C09), Liège (C13), Lille (C09), Limoges (C16), Lisieux (C23), Lorient (C10), Lyon 05 (C12), Mâcon (C12), Marseille – Medical centre (C19), Marseille - Saint-Joseph Hospital (C19), Marseille - La Timone medical centre (C19), Montceau-les-Mines (C11), Montélimar (C11), Montpellier – Arnaud de Villeneuve Hospital (C20), Montpellier – Prof. Sultan (C25), Morlaix (C10), Moulins (C11), Nantes (C17), Nice (C22), Niort (C15), Orléans (C15), Oyonnax (C11), Palavas-les-Flots (C30), Paris (C07), Paris - Armand-Trousseau Children's Hospital (C02), Paris - Necker Hospital for Sick Children (C03), Paris - Saint Vincent de Paul Hospital (C01), Périgueux (C16), Perpignan (C30), Pierre-Bénite (C11), Reims (C31), Rennes (C10), Roanne (C13), Romans (C11), Roubaix (C09), Rouen (C23), Saintes (C17), St Priest-en-Jarez (C27), Strasbourg (C05), Toulouse – Purpan Regional Hospital (C06), Toulouse – Medical centre (C06), Tours (C15), Vandoeuvre-Les-Nancy (C04), Vesoul (C14), Villefranche-sur-Saône (C11).

Study period : Date of first inclusion: 26-Jan-1993 Date of Last data collected: 12-Dec-1998	**Phase of development**: Phase 3

Objectives:

To test for equivalence in terms of catch-up growth comparing a continuous treatment regimen and a sequential treatment regimen (six months of treatment, six months without) of Maxomat using the same dose 0.2 IU/kg/day, seven days out of seven, in the management of prepubertal children presenting IUGR (Intrauterine Growth Retardation) with a growth retardation ≤ 2.5 SD.

Methodology:

A randomised, comparative, open, multicenter study on two parallel groups. The duration of treatment according to the protocol is 36 months with a selection visit and an inclusion visit, and then visits every three months (3, 6, 12, 15, 18, 21, 24, 27, 30, 33, 36 months).

Number of patients (expected and analysed):

400 patients in each group according to the protocol, then 210 patients in total following amendment #3 of 04-Jan-1994, which revalidated the number of subjects further to the results of Sanofi study P1023. The intention to treat population comprised 304 patients.

Diagnosis and criteria for inclusion:

Girls aged > 3 years and ≤ 9 years, boys aged > 3 years and ≤ 11 years at the time of selection. Impuberty may be confirmed by a dose of testosterone plasma (< 0.25 ng/ml) or by ultrasound assessment of uterine height (< 38 mm). Height ≤ -2.5 SD (curves following Sempé 1979). Absence of somatotrope deficiency, defined as a GH secretion level greater than 10 ng/ml during a conventional stimulation test carried out during the previous two years. Absence of chromosome abnormality, dysmorphic syndrome other than Silver-Russell, or skeletal pathology. Absence of severe chronic inflammatory disease, or any chronic digestive, pulmonary or cardiac pathology that could affect growth. Informed written consent from the parents and from children when they are aged over seven.

Experimental medicinal product: dose and administration route:

Maxomat (vials dosed at 4 IU – solvent 2 ml). The posology of administration is 0.2 IU/kg/day, seven days out of seven.

Treatment duration:

36 months for the Continuous group. Three six-month periods separated by medication-free intervals of six months for the sequential group, to a total duration of 36 months.

Criteria for evaluation:

Efficacy:
Height measured at selection, inclusion and then at each of the three-monthly visits. Height in cm and in SD. Rate of growth in SD assessed over the 12 months before treatment and the six months after inclusion. Bone age assessed by centralised readings following the Greulich and Pyle method using an X-ray of the left hand and wrist.

Safety:
Information that enabled safety to be assessed was collected at each assessment and entered on specific pages of the case report form. If undesirable events occurred, the following information was collected: description of the undesirable event, date of start and end, intensity of the undesirable event, seriousness, consequences for the treatment, corrective treatment, outcome and imputability.

Statistical methods:

Initial comparability of the groups after randomisation (selection and inclusion). Analysis of efficacy comparing the Continuous group (C) and the Sequential group (S). Analysis of increase in height carried out on the intention to treat population and on the per-protocol population. Study of normality of the distributions: Shapiro-Wilk test, symmetry coefficients (skewness) and curve symmetry (kurtosis). Confidence interval of 95 % for the equivalence study. Non-parametric Mann-Whitney U-test, Chi2 or Fisher's exact test. Two-tailed comparisons are carried out. Threshold of significance 5 %. Software SAS 8.1.

Summary :

Efficacy :

The study population was made up of 306 patients: 169 boys (55.2 %) and 137 girls (44.8 %) selected at 28 main centers. The ITT (Intend To Treat) population was made up of 304 patients split into 153 patients in the Continuous group and 151 patients in the Sequential group. 15 patients who were selected were not included in the study (consent withdrawn). The figures at inclusion were 144 patients in the Continuous group and 145 patients in the Sequential group, making a total of 289 patients at inclusion. 50 patients (17.3 %) stopped treatment prematurely after inclusion; 23 were from the Continuous group (16.0 %) and 27 from the Sequential group (18.6 %). The main reasons were that it was the investigator's decision (15 patients), the patients were lost to follow-up (12 patients) or it was the patient's decision (7 patients).

Initial comparability. The mean chronological age of the boys at selection was 6.9 ± 2.6 years and height age was 4.4 ± 2.0 years. The chronological age of the girls was 5.8 ± 2.1 years and height age was 3.8 ± 1.6 years. At selection the groups were comparable for chronological age, height age, bone age, progression of the pregnancy, neonatal history, medical and surgical history and associated pathologies. A difference was seen in the mother's height among the boys. This was, for the selected population, 153.9 ± 6.9 cm or –1.01 ± 1.16 SD for the Continuous group boys and 156.3 ± 6.8 cm or –0.62 ± 1.14 SD for the Sequential group boys (p=0.12). At inclusion, on average 5.2 ± 2.5 months after selection (extreme values of 1 and 15 months), the mean height of the boys was -3.31 ± 0.77 SD in the Continuous group and -3.25 ± 0.72 DS in the Sequential group (p=0.56). The mean height of the girls at inclusion was -3.28 ± 0.69 SD in the Continuous group and -3.18 ± 0.74 SD in the Sequential group (p=0.20). The Continuous and Sequential treatment groups were comparable at inclusion in terms of the other parameters and, most importantly, in terms of the parameters related to growth.

Height increase:

At 24 months, the difference seen in the ITT between the groups (C – S) was 0.61 ± 0.05 SD. 95 % CI of [0.51 - 0.71 SD]. The difference reported was greater than 0.3 SD (equivalence acceptance threshold at 24 months). The per-protocol analysis showed a difference (C - S) of 0.60 ± 0.06 SD. 95 % CI of [0.48 – 0.72 SD].

At 36 months, the difference seen (C – S) was 0.75 ± 0.07 SD in ITT. 95 % CI of [0.61 – 0.89 SD]. The difference seen was greater than 0.4 SD (equivalence acceptance threshold at 36 months). The per-protocol analysis showed a difference (C - S) of 0.74 ± 0.07 SD. 95 % CI of [0.60 – 0.88]. The two treatments cannot be considered to be equivalent. At the end of study, after 36 months, the difference in mean height increase between C and S was highly statistically significant (p=0.0001). The analysis of height increase by six-month periods shows a positive height increase for each six-month period in the Continuous group with a progressive fall in treatment benefit from the beginning to the end of the study. The height increase was positive at the end of each six-month treatment phase in the Sequential group. It returned to negative (below average) during each of the six-month treatment-free phases. As with the Continuous group, the increase reported in the Sequential group during the treatment phases fell progressively as the study went on.

Height in terms of SD. A statistically significant difference was seen in the height in terms of SD between the Continuous and Sequential groups. At the end of the study, mean height was -1.33 ± 0.96 SD in the Continuous group as against -2.04 ± 0.82 SD in the Sequential group (p<0.0001). This difference was seen in both the boys and the girls.

Rate of growth. The rate of growth expressed in terms of SD for the chronological age was positive (above the average) at each of the assessments in the Continuous group. It exceeded 4.71 ± 2.55 SD at six months and 1.24 ± 1.83 SD at 36 months. The fall in rate of growth shown over six-month periods was uniform in the Continuous group. In the Sequential group the rate of growth was positive after the treatment phases and became negative after the six-month treatment-free phases. It should be noted that the rate of growth in the Sequential group outstripped that of the Continuous group at the 18-month and 30-month assessments, which corresponded to the ends of the second and third treatment phases. The rates of growth at 18 months were 3.27 ± 2.42 SD in the Sequential group and 2.46 ± 1.99 SD in the Continuous group (p=0.011). At the 30-month assessment, the rates of growth were 2.40 ± 2.09 SD in the Sequential group and 1.72 ± 1.84 SD in the Continuous group (p=0.003).

Safety :

Safety was assessed in the 289 patients of the ITT population included in the study who were monitored for a mean duration of 34.2 ± 6.9 months. 158 patients (54.7 %) reported one undesirable event; 83 of these patients were from the Continuous group (57.6 %) and 75 were from the Sequential group (51.7 %), with no difference between the groups (p=0.31). The respiratory system was the most common site of undesirable events (30.8 %) followed by other infections, grouped together under the heading "problems of the body's mechanisms of defence" (16.3 %). There did not appear to be any difference between the groups in terms of the types of events reported. Five patients dropped out of the study due to undesirable events; four of these were from the Continuous group and one from the Sequential group. Standard blood test data. The study of standard blood test parameters that were not carried out in a centralised way did not allow any particular systematic trends to be drawn out concerning the glycaemia or glycosolated haemoglobin figures. Centrally collected blood test data. 88.2 % of patients whose IGF1 was tested had levels below the norm at inclusion. An increase in IGF1 was reported during the study in the Continuous treatment group. This rise was also seen in the Sequential group after each of the six-month treatment phases. At the end of each six-month treatment-free phase, the patients in the Sequential group had returned to a profile comparable to the basal state. The percentage of patients in the Continuous group who presented anti-hGH antibodies above the normal level was 5.1 % at 12 months, 5.8 % at 24 months and 6.3 % at 36 months. These figures were 1.1 %, 0 and 2.5 % respectively in the Sequential group. The difference is statistically significant at 24 months (p=0.029). It should be noted that the anti-hGH levels were measured after six months without treatment in the Sequential group.

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Generic drug name : Somatropin	**Study Code** : FH5126A
Title of the study :	A cohort of prepubertal children for the study of optimisation of administration methods of the biosynthetic growth hormone Maxomat® in the treatment of severe early onset intrauterine growth retardation (height below or equal to –2.5 SD) **2nd part of the study – Follow-up of growth up to the final height of patients after discontinuation of treatment with MAXOMAT®**
Study centers :	Aix-en-Provence, Angers, Argenteuil, Arras, Bagnols-sur-Cèze, Besançon, Bordeaux, Bordeaux - C.H.U. Pellegrin, Bourges, Brest, Brive, Caen, Calais, Cambrai, Chambéry, Colmar, Dieppe, Dijon, Dunkerque, Evreux, Fécamp, Firminy, Fréjus Saint-Raphaël, Freyming Merlebach, Grenoble, Hyères, La Roche-sur-Yon, La Rochelle, Le Havre, Le Mans, Le Puy, Lens, Liège, Lille, Limoges, Lisieux, Lorient, Lyon, Mâcon, Marseille, Marseille - Hôpital Saint-Joseph, Marseille - Clinique médicale La Timone, Montceau-les-Mines, Montélimar, Montpellier – Hôpital Arnaud de Villeneuve, Morlaix, Moulins, Nantes, Nice, Niort, Orléans, Oyonnax, Palavas-les-Flots, Paris – Hôpital Robert Debré, Paris - Hôpital d'enfants Armand Trousseau, Paris - Hôpital Necker Enfants Malades, Paris - Hôpital Saint Vincent de Paul, Périgueux, Perpignan, Pierre-Bénite, Rennes, Roanne, Romans, Roubaix, Rouen, Saintes, St Priest-en-Jarez, Strasbourg, Toulouse - C.H.R. Purpan, Toulouse, Tours, Vandoeuvre-Les-Nancy, Vesoul, Villefranche-sur-Saône.
Study period :	Date of the first follow-up visit: October 29, 1996 Date of the last follow-up visit: April 23, 2010
Objectives :	The primary objective of this 2nd part is to evaluate the efficacy of the treatment on the final height of the patients.
Methodology :	The FH5126A study is an open, randomised, multi-centric study with a 1st part of 3 years comparing MAXOMAT® administered continuously to MAXOMAT® administered for 6 month periods with 6 month treatment-free intervals. The patients were divided into the Continuous and Sequential groups according to a centralised randomisation carried out by minimisation. For 3 years, evaluation visits took place every quarter. A clinical study report concerning the first part of the study was published on December 31, 2002. The 2nd part of the study, which is the subject of this report, concerns the follow-up of growth up to the final height of patients after discontinuation of treatment with Maxomat® (follow-up visits every 6 months).

Number of patients :	Only the 239 patients who received all of the treatment during the first part of the study were followed-up with regard to growth and are therefore part of the analysed population of this second part of the study.
Diagnosis and criteria for inclusion :	Only the patients who received the 3 years of treatment during the 1st part of the study were followed-up in this 2nd part up to their final height.
Duration of observation :	From the end of treatment with MAXOMAT® to the final height of the children.
Criteria for evaluation :	
Efficacy	Primary endpoint • Height measured during the clinical examination at each of the consultations every 6 months (mean of 3 measurements or mean of available measurements) Secondary endpoints • Weight measured during the clinical examination at each of the consultations every 6 months • Clinically evaluated stage of puberty (pubic and axillary hair according to the Tanner scale, volume of the testis and testosterone levels for boys, breasts according to the Tanner scale and menstruation for girls) • Bone age evaluated on the radiography of the left hand-wrist • Treatment resumed: yes, no
Safety	Description of the adverse event • Symptomatic treatment: yes, no • Treatment with MAXOMAT®: continued, discontinued • Causal relationship to treatment with MAXOMAT®: ruled out, doubtful, sure
Statistical methods :	Efficacy The increase in height in cm and in SD as well as the final height are described overall and for each monitoring duration category (defined by median, 25th percentile and 75th percentile) for all of the patients and for each treatment group. The height (mean of 3 measurements), weight, pre-puberty evaluation, bone age and whether or not treatment was resumed are described for each treatment group and for each monitoring visit. The duration of follow-up is described continuously and for each category (as per quartiles) for all of the patients and for each treatment group. Safety The number of adverse events and the number of patients with at least one adverse event are described for each treatment group overall then by system organ class and preferential term. The causal relationship to the treatment is also available.

Summary :	<u>Efficacy results</u> The mean duration of follow-up was seen to be 1 year shorter in the Continuous group (6.1 ± 2.3 years) compared to the Sequential group (7.0 ± 2.8 years). With a mean duration of follow-up that was 1 year shorter in the Continuous group, the increase in height rose depending on the different categories of follow-up duration in the same way in both groups. For patients with duration of follow-up greater than 8.1 years, it is lower in the Continuous group on average. If we compare the 2 groups, the final heights were slightly greater in the Continuous group on average if the duration of follow-up was less than 8.1 years, and there was no real difference if the duration of follow-up was greater than 8.1 years. For weight and bone age, the data increased over time in the same way in both groups. <u>Safety results</u> 21 patients reported adverse events in the Sequential group (18.3% of the 115 analysed patients), i.e. 58 Adverse Events (51% of AEs) and 16 patients reported adverse events in the Continuous group (13.9% of the 119 analysed patients), i.e. 55 Adverse Events (49% of AEs). It should be noted that the duration of follow-up is greater by a mean of 1 year in the Sequential group (mean: 6.1 years in the Continuous group and 7.0 years in the Sequential group). On the other hand, no difference was observed between the 2 groups with regard to the type of adverse events and no deaths were reported. Two patients in the Sequential group had an adverse event with a sure causal relationship to the MAXOMAT® treatment (limb pain, pain and bleeding at the injection site) and 8 with a doubtful causal relationship to the treatment. In the Continuous group, 7 patients had an adverse event with a doubtful causal relationship to the treatment and there were no adverse events with a sure causal relationship to the treatment.
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