London, 28 January 2008
Product Name: **Nutropin AQ**
Procedure No: **EMEA/H/C/315/II/24**

WITHDRAWAL ASSESSMENT REPORT FOR NUTROPIN AQ

International Nonproprietary Name:
(Somatropin)

Procedure No. EMEA/H/C/000315/II/24

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. INTRODUCTION

NutropinAq is a human growth hormone (hGH) produced by recombinant DNA technology. The amino acid sequence of the product is identical to pituitary-derived hGH. The protein is synthesised by a specific laboratory strain of *E. coli* as a precursor consisting of the recombinant human growth hormone (rhGH) molecule preceded by the secretion signal from an *E. coli* protein. This precursor is directed to the plasma membrane of the cell. The signal sequence is removed and the native protein is secreted into the periplasm so that the protein is folded appropriately as it is synthesised.
Human GH is secreted throughout life and is involved in many processes such as fat, protein, carbohydrate, muscle and bone metabolism. These processes do not function normally if hGH is missing. Lack of GH can start during childhood (childhood-onset), or may appear later (adult-onset).
Recombinant human growth hormone products have been used clinically over 20 years for a number of indications. Primarily a therapy of childhood growth hormone deficiency (GHD), rhGH products have over the years been approved for other indications not associated with childhood GHD (such as Turner´s syndrome and chronic renal insufficiency).

NutropinAq has been approved in the European Union (EU) for use in the following indications:

- Long-term treatment of children with growth failure due to inadequate endogenous GH secretion.
- Long-term treatment of growth failure associated with Turner syndrome.
- Treatment of in prepubertal children with growth failure associated with chronic renal insufficiency up to the time of renal transplantation.
- Replacement of endogenous GH in adult with GH deficiency of either childhood- or adult-onset aetiology. Growth hormone deficiency should be confirmed appropriately prior to treatment.

The MAH submitted on 18 April 2006 a type II variation to extend the indication for NutropinAq in the treatment of children with severe short stature not explained by growth hormone deficiency or other non-GHD associated disorders with growth retardation. The proposed indication evolved during the procedure to:
"Long-term treatment of children with severe ISS ≥ 5 years of age. Short children should have a current height below -3.0 standard deviation score (SDS). In case height is below -2.5 SDS but above -3.0 SDS, a height velocity below the 25th percentile (measured at least twice over a period of at least one year) has to be shown in addition to be considered for treatment. The predicted adult height should be at least 1 SD below the target height. Diagnostic evaluation should have excluded other causes of short stature before starting treatment."

Four lists of questions were addressed to the MAH successively on the 27th July 2006, 15th November 2006, 22nd February 2007, and 26th April 2007 on which the MAH responded in writing. The response to the list of Questions adopted by the CHMP at the February 2007 plenary meeting was also presented by the MAH at the SAG endocrinology meeting during which discussions and responses on the below questions took place (SAG meeting held on 23rd March 2007):

1. *Is it generally acceptable to subject short "normal" children to long-term treatment with GH?*
2. *Are there acceptable criteria for treating certain children with severe ISS (e.g. cut-off for age, current height SDS, current height velocity SDS, predicted adult height, deviation of predicted adult height from target height or specific defined genetic parameters)?*
3. *Is it possible to define response / stopping criteria (e.g. first year treatment response) to avoid long-term treatment of children with a likely overall poor treatment success?*
4. *A recommendation on whether the term "idiopathic short stature" or the term "non-GH deficient short stature" or another terminology is preferred in the SPC should be discussed.*
5. *Is there a specific age beyond which the therapy should not be initiated (i.e. due to insufficient gain in height)?*

2. CLINICAL ASPECTS

This type II variation for the indication of NutropinAq in children with severe idiopathic short stature (ISS) is proposed based on the results of:
- a pivotal study (the phase II study FR 86-053, treating 118 children who did not meet the criteria for classic GHD);
- an interim report (study 85-036), from an ongoing observational post-marketing surveillance study, the National Cooperative Growth Study (NCGS), in a subset of patients (n=8018) identified as having ISS.

Subgroup analyses have been performed on these data in order to define a more restricted target population. The proposed dose by the MAH for this new submitted indication is up to 0.043 mg/kg bodyweight given as a daily subcutaneous injection.

2.1 - GCP aspects

The MAH states that all clinical studies have been conducted in accordance with GCP and are consistent with published EMEA and ICH guidelines in place at the time.

2.2 - Population

A heterogeneous group of children with growth impairment ("short stature", defined as height more than 2 standard deviations below the population mean) without GH deficiency and without other known causes of reduced height was included in the submitted clinical studies. However these children should be distinguished from small for gestational age (SGA) patients since birth weight was > 2.5 kg.

2.3 - Clinical pharmacology

The clinical pharmacology has been characterized in other paediatric indications and the pharmacokinetics is identical from other indications for NutropinAq. No new information on the clinical pharmacology was provided for the proposed new indication.
The dosage used for the proposed new indication is 0.3 mg/kg/week, initially administered in three divided doses, later changed to daily injections. The daily dose of up to 0.043 mg/kg NutropinAq is in agreement with other approved indications of non-GHD disorders.

The CHMP is in agreement that no new PK data are needed and that it is justified to apply the same dosage to the proposed new indication.

2.4 - Clinical efficacy

A - Main studies

To support the new indication the MAH submitted results from the 2 below trials:

1. The **pivotal clinical trial (study FR 86-053)** was a phase II, multicenter, open-label, randomised controlled study treating 118 pre-pubertal children ≥ 5 years of age and a bone age (BA) of ≤ 10 years in boys and ≤ 9 years in girls with short stature (height standard deviation score, HSDS, ≤ -2) who did not meet the criteria for classic GHD. The trial was originally designed as a 2-years, randomised, controlled study. At study start, subjects were randomised to receive either Nutropin 0.3 mg/kg/week divided into three doses per week (TIW) or no treatment. The study was subsequently amended to add a daily dosing regimen, and to provide long-term treatment and follow-up for all subjects until adult height was achieved. Therefore, subjects of both treatment groups were re-randomised after one year in the study to either daily or TIW administration of NutropinAq.

2. The **supportive study (study 85-036)** was based on an interim report from the post-marketing surveillance study NCGS. Study 85-036 focused on a subset of subjects (n=8018) from the NCGS study identified as having ISS and treated with different Nutropin formulations. Results of the latter study have been submitted by an interim report dated 4 December 2003.

B - Subgroup analyses

The table below gives a summary of the post hoc subgroup analyses were performed. The goal was to try to better define a group of children who were not just small but showed characteristics that could be related to a pathophysiology.
Height cut-off at the level of -2.5 SDS was selected based on the precedent for the approved GH indication granted for SGA. IGF-1 cut-off was based on the assumption of a disturbance in the GH-IGF-1 axis for values < 0 SDS.
The **cohort 1** within the NCGS study represents subjects who had baseline characteristic criteria similar to those of subjects in Study 86-053, received a starting GH dose of at least 0.25 mg/kg weekly, and had baseline and Year 1 results. However, as IGF-1 levels were not routinely measured in the NCGS, further subgroups could not be identified.

Table 1: Additional Subgroup Analyses

Study 86-053
• All subjects with short stature (defined as height less than –2.0 SDS at study entry) reported in Genentech Study 86-053 [a].
• Subjects with severe short stature (i.e. height ≤–2.5 SDS) at study entry.
• Subjects with IGF-1 levels below the mean (<0 SDS) at study entry.
• Subjects with IGF-1 levels above the mean (≥0 SDS) at study entry.
• Subjects with severe short stature ≤–2.5 SDS and whose IGF-1 levels were below the mean (<0 SDS) at study entry.
• Subjects with severe short stature ≤–2.5 SDS and whose IGF-1 levels were above the mean ≥0 SDS at study entry.
NCGS Study 85-036 [b]
• Subjects with baseline height ≤–2.5 SDS from Cohort 1

[a] Clinical study report dated 3 December 2003.
[b] Clinical study report dated 4 December 2003.

C – Pivotal study FR 86-053

The objective of this study was to evaluate the safety and efficacy of Nutropin in children with short stature (SS) who did not meet the criteria for classic GHD.
Study 86-053 was initially designed as an open label study with an untreated control. Due to the difficulties associated with conducting a long-term controlled study, and the high risk of withdrawal in an untreated group, the study design was modified to allow all subjects the opportunity of receiving Nutropin treatment for their second and subsequent years in the study.

C-1 Methods

- **Population**

The main inclusion criteria were as follows:
- Boys or girls age ≥ 5 years with height SDS ≤ -2 (≤ 3rd percentile), and a Bone Age (BA) of ≤ 10 years in boys and ≤ 9 years in girls
- Growth rate ≤ 50th percentile
- Weight 10th-90th percentile of height
- Birth weight ≥ 2.5 kg
- Normal body proportion (sitting height, arm span) and absence of significant phenotypic abnormalities, as well as normal karyotype in girls

- Documented GH level ≥ 10 ng/mL after pharmacological stimulation or during sleep or exercise on at least one occasion.

The inclusion and exclusion criteria aimed at a study population of children with idiopathic short stature (ISS) are principally acceptable to the CHMP.

- **Treatments**

Subjects were randomized into two treatment groups of equal size:
- one group was treated with NutropinAq 0.3mg/kg weekly divided into three doses per week (TIW),
- the other group was an untreated control group.

After the first year, the continuing subjects were re-randomized to receive a total weekly dose of NutropinAq 0.3mg/kg administered either daily or TIW.
The dose was adjusted annually for change in body weight.

Treatment was continued until a subjects bone age (BA) was >15.0 years in boys or >14 years in girls and the growth rate was < 2cm/yr. At that point, treatment was discontinued and follow-up visits were performed at 6-month intervals for measurement of height until adult height was attained.

The BA determination and predicted final height calculations was centralised and performed in a blinded fashion.

- **Outcomes/endpoints**

Primary endpoint
The **primary efficacy endpoint** of this study was the **gain in adult height**, determined by comparing the near adult height with the pre-treatment Bayley-Pinneau predicted adult height.

Additional endpoints
- **Study Year 1**: Comparison of annualized growth rate and change in height SDS of the Nutropin treated and untreated control groups; similar comparisons for change in BA, height age change minus BA change, and change in predicted adult height.
- **Treatment Years 1-7**: Comparison of the daily treated and TIW-treated groups for growth rate, change in height SDS, cumulative change in BA, height age change minus BA change, and cumulative change in predicted adult height.
- Adult Height: Effect of treatment frequency (TIW versus daily) on adult height gain; assessment of adult height minus mid-parental target height

- **Randomisation**

For the **first year** of the study, subjects were randomized into treatment and control groups of equal size. A variant of Efron's biased coin randomization method was performed to maintain balance between treatment and control group with respect to the following prognostic variables (based on treatment experience with children with GHD):
- pre-treatment IGF-1,
- height age,
- adiposity,
- mother's height,
- the subject's chronological age minus height age deficit.

For their **second year** of the study all subjects were re-randomized to receive the same total weekly dose of Nutropin at daily or TIW intervals.
The randomization was based on whether subjects had received Nutropin during the first year and if they were prepubertal (Tanner stage 1). This randomization was designed to maintain balance between the daily and TIW treatment groups with respect to:

- mothers height,
- pre-treatment IGF-1,
- 6-month height,
- Weight,
- chronological age,
- height age,
- growth rate.

The randomization was performed by the data management at biostatistics group at Genentech. Dynamic randomisation procedures have been used for the randomisation at the start of the study to allocate the children either to the active treatment group (TIW) or to the group, that remained untreated during the first year of the study as well as for the randomisation taking place after the first study year, when all continuing children were re-randomised either to a TIW or to a daily dosing scheme. For the first randomisation, five variables were taken into account, whereas for the second one seven variables were considered to be necessary to assure that the population is balanced.

The CHMP is of the opinion that the commented algorithms used for randomisations have to be provided and the MAH needs to clarify the reasons why for both randomisation procedures different sets of variables were considered to be important to ensure that the sampled treatment groups are balanced. The CHMP requested the MAH to carefully evaluate and discuss this issue. The CHMP also requested the MAH to discuss on the impact of the open-label nature of the study on the randomisation process and how the complex and difficult process of randomisation itself was organised.
The MAH responded to the above concerns. Based on the MAH's response, the CHMP considers that the randomization procedure to be overly complex: the variables used for randomization do not seem to possess predictive power. This is rather unexpected at first, since their assumed impact on the primary outcome justified their inclusion in the randomization process in the first place. However, looking post-hoc at the baseline values related to the variables used for the randomizations, no hints for unusual imbalances can be seen by the CHMP. Therefore, based on the submitted response, this point is considered resolved by the CHMP.

However the CHMP requested further justification with regards to the table "Growth rate comparison for TIW treatment group vs. daily treatment group" provided in the study report. The CHMP considers that a justification on statistical and clinical grounds is needed for pooling children according to their first active treatment year, irrespective if this was during their first or second year in the study.
To this request, the MAH reported the primary endpoint based on the data resulting from the two randomizations. The primary endpoint was the gain in adult height determined by comparing the near-adult height with the pre-treatment Bayley-Pinneau predicted adult height. The MAH stated that their data revealed some numerical differences. Whereas for the group being untreated during the first year the dosing scheme does not seem to have an impact on the outcome, the outcome is slightly higher for the daily dosing scheme for the group being treated with NutropinAq during the first year.
The CHMP considers that the analysis does not show that patients having started active treatment at study start, do have a better outcome compared to patients receiving active treatment delayed by one year. The CHMP did not consider this question as resolved.

- **Statistical methods**

Treatment Year 1 results refer to the first year of treatment. Thus, for subjects who were initially randomized to the control group (at the start of the study), treatment Year 1 is the second year of their participation in the study.

Treatment Years 2-7 are defined similarly. For subjects who were initially treated with NutropinAq TIW, treatment year and year of the study are the same.

Efficacy Analyses for Study Year 1
Mean **growth rates** of the treatment and control group were compared by using a t-test.

Efficacy Analysis for Treatment Years 1-7
The primary endpoint **adult height gain** was measured by the difference between the adult height and the pre-treatment Bayley-Pinneau predicted adult height. Subjects treated for ≥ 2 years who achieved a measured or estimated BA of ≥ 16.0 years in boys and ≥ 14.0 years in girls and were either Tanner stage 4 or 5 or had a chronological age (CA) >17.0 years were designated as having reached near-adult height (hereafter referred as adult height).
Mean growth rates of the TIW and daily treatment groups for each year were compared using t-tests.
Interaction was assessed between treatment frequency (TIW vs. daily) and each of the following covariates:

- sex
- pre-treatment IGF-1
- height age
- BMI SD score
- target height
- chronological age minus height age.

Within each treatment group, the mean change in BA was compared with the mean change in height age using paired t-tests. Treatment difference between these two measures was assessed by t-test.
Additional analyses were performed using t-test for group comparison. No adjustments were made for multiple comparisons.

C-2 Results from the pivotal study FR 86-053

Of the 118 Nutropin-treated subjects, 83 (70%) were followed for 2-10 years until they reached adult height. The last measured height, including post-treatment follow up, was obtained at the mean age of 18.3 years in males and 17.3 years in females (mean duration of therapy was 6.2 and 5.5 years, respectively).

In the overall Nutropin treated subjects the mean gain in adult height compared to pre-treatment predicted adult height was 5.2 ± 5.0 cm in males ($p < 0.001$) and 6.0 ± 5.0 cm in females ($p< 0.001$). This represents an increase in adult height of 0.7 SD in boys and 0.9 SD in girls resulting in a mean adult height SD score within the normal range (-1.5 in males and -1.6 in females). Although the mean increase in adult height was numerically larger in subjects treated with daily injections vs. those treated TIW (5.9 ±5.4 cm vs. 4.9±4.6 cm, respectively), the difference was not significant. There was no gender effect on gain in adult height.

Adult height was greater than pre-treatment predicted adult height in 49 of 60 males (82%) and 19 of 23 females (83%). Over 80% of subjects were able to achieve adult heights that were within the normal range and within their target height range (defined as target height ± 10 cm). Mean adult height minus target height SDS was -0.7 in males and -0.9 in females; thus, mean adult height was within 1 SD of mean target height.

As the inclusion criteria in study 86-053 defining short stature as a height ≤-2 SDS could be considered too broad, a subgroup analysis was performed on subjects with more severe growth retardation (height ≤-2.5 SDS at baseline, in line with the SGA indication approved for other GH-containing medicinal products). In addition, the study population was not in line with the target population for the proposed indication, which excluded pure familial SS. Therefore, the MAH was asked to provide a new subgroup analysis regarding gain in final height including only children with a height ≤ -2.5 SDS whose predicted adult height is at least 1 SDS below the target height and

irrespective of their IGF-1 levels since, based on the submitted analyses, IGF-1 levels were not considered predictive of treatment response.

This subgroup analysis included adult height measurements on 25 males and 15 females. Mean gain in final height over predicted height was 6.5 ± 4.2 cm (0.9 ± 0.58 HSDS) in boys and 7.7 ± 4.7 cm (1.2 ± 0.71 HSDS) in girls, and therefore was slightly better than in the overall group.

Further analyses requested by CHMP showed that the difference of predicted final height minus target height was the best predictor of overall treatment success in terms of final height gain (the smaller the child's predicted adult compared to midparental target height the better the overall treatment success). This analysis supported the conclusion that children with pure familial short stature are less likely to benefit from GH treatment and therefore should not be treated with GH. The proposed indication excludes children with pure familial SS.

It was also noted by the CHMP that 39% of children discontinued the treatment prematurely.

D – Supportive study: the National cooperative growth Study (NCGS) 85-036

D-1 Description

The **post-marketing surveillance study NCGS,** is an ongoing observational postmarketing surveillance study in the United States and Canada for subjects treated with Nutropin Depot, NutropinAq, Nutropin or Protropin. The purpose of this open-label, multicenter (500 centers in the USA and Canada) study is to address questions relating to the safety and efficacy of GH therapy. An interim report dated 4 December 2003 focused on the subset of NCGS subjects identified as having ISS (n=8018) and was used as the source of data for the supportive subgroup analysis. This report constitutes Study 85-036.

- An efficacy comparison was performed between subjects from the main study 86-053 and a cohort of 2520 subjects (Cohort 1) from Study 85-036 who met similar diagnostic criteria to those used in the main study and were treated with prolonged rhGH therapy.
- Patients in efficacy Cohort 2 met the same criteria as Cohort 1, except that patients in Cohort 2 had a baseline chronological age that was <5 years old.
- Patients in efficacy Cohort 3 also met the same criteria as those in Cohort 1, except that patients in Cohort 3 were pubertal at baseline.

The supportive NCGS study included male or female subjects treated with one of the following somatropin-containing Genentech preparations Nutropin Depot, NutropinAq and Protropin.

Endpoint

Annualised growth rate and height SD are the primary efficacy outcome measures for this interim report.

D-2 Results

A comparison of the demographic and baseline characteristics between both studies is summarized in the tables 2 and 3 below. BA measurements and predicted adult height calculations as well as IGF-1 measurement were not available from study 85-036.

Table 2: Demographics and Baseline Characteristics (Mean ± SD)

Characteristic	Study 86-053 (n=122)	NCGS Cohort 1 [a] (n=2520)	NCGS Cohort 2 [a] (n=283)	NCGS Cohort 3 [a] (n=940)
Sex (males/females)	90/32	1907/613	191/92	668/272
Chronologic age (yr)	9.4 ± 2.1	10.5 ± 2.7	3.7 ± 0.9	13.8 ± 1.6
Bone age (yr)	7.8 ± 2.0	—	—	—
Growth rate (cm/yr)	4.4 ± 1.1	4.0 ± 1.7	5.6 ± 2.3	4.5 ± 2.1
Height SDS	-2.8 ± 0.6	-2.9 ± 0.6	-3.2 ± 0.8	-2.8 ± 0.6
Predicted adult height SDS	-2.3 ± 0.8	—	—	—
Target height SDS	-0.7± 0.6	—	—	—

Note: N varies slightly for individual characteristics.
[a] Efficacy cohorts were defined as: 1) similar to Study 86-053; 2) baseline age <5 years; 3) pubertal at baseline.

Table 3: comparison of the demographic and baseline characteristics between both studies

	Study 86-053				Study 85-036	
	All subjects		Height ≤–2.5 SDS		Cohort 1	Height ≤–2.5 SDS
	Nutropin (N=63)	Untreated control (N=59)	Nutropin (N=40)	Untreated control (N=40)	Nutropin (N=2520)	Nutropin (N=1801)
Gender Male Female	 46 (73%) 17 (27%)	 44 (75%) 15 (25%)	 25 (63%) 15 (38%)	 26 (65%) 14 (35%)	 1907 (76%) 613 (24%)	 1304 (72%) 497 (28%)
	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD
Predicted adult height SDS	–2.4 ± 0.8 (n=63)	–2.2 ± 0.9 (n=59)	–2.7 ± 0.8 (n=40)	–2.5 ± 0.8 (n=40)	–	–
Target height SDS	–0.7 ± 0.7 (n=61)	–0.7 ± 0.5 (n=57)	–0.9 ± 0.5 (n=38)	–0.8 ± 0.5 (n=38)	–	–
Predicted adult height minus target height SDS	–1.7 ± 0.8 (n=61)	–1.4 ± 0.8 (n=57)	–1.8 ± 0.8 (n=38)	–1.7 ± 0.8 (n=38)	–	–
Age at first visit (years)	9.4 ± 1.9 (n=63)	9.4 ± 2.4 (n=59)	9.5 ± 1.7 (n=40)	9.8 ± 2.4 (n=40)	10.5 ± 2.7 (n=2520)	10.4 ± 2.8 (n=1801)
Bone age (years)	7.9 ± 1.8 (n=63)	7.6 ± 2.2 (n=59)	7.9 ± 1.7 (n=40)	7.9 ± 2.1 (n=40)	–	–
Baseline IGF-1 SDS	–0.7 ± 0.9 (n=62)	–1.1 ± 1.1 (n=59)	–0.8 ± 1.0 (n=39)	–1.3 ± 1.2 (n=40)	–	–
Baseline height SDS	–2.7 ± 0.5 (n=63)	–2.8 ± 0.6 (n=59)	–3.0 ± 0.4 (n=40)	–3.1 ± 0.4 (n=40)	–2.9 ± 0.6 (n=2520)	–3.2 ± 0.6 (n=1801)
Growth rate (cm/year)	4.4 ± 1.2 (n=63)	4.5 ± 1.1 (n=59)	4.4 ± 1.3 (n=40)	4.3 ± 1.0 (n=40)	4.0 ± 1.7 (n=1721)	4.0 ± 1.7 (n=1232)

Results from Cohort 1

An efficacy comparison was performed between subjects from the main study 86-053 and a cohort of 2520 subjects (**Cohort 1**) from Study 85-036 who met similar diagnostic criteria to those used in the main study and were treated with prolonged GH therapy.
The course of growth rates and Height SDS over the 7 treatment years was similar in cohort 1 compared to study 86-053 (see Figures 1 and 2 below). The mean growth rates increased from 4.0 cm/yr at baseline to 8.6 cm/yr during the first year of treatment which represents an increase of 4.6 cm/yr. The mean height SDS increased from baseline -2.9 to -2.4 at the end of the first year of treatment which represents an increase of 0.5 SDS.
For patients who completed 7 years of treatment mean height SD scores improved during all treatment years. The mean height SD scores after seven years of treatment were 1.2 which represents an increase of 1.8 SDS.

Results from Cohort 2

Patients in efficacy **Cohort 2** met the same criteria as Cohort 1, except that patients in Cohort 2 had a baseline chronological age that was <5 years old.
Annualized growth rates were presented by the MAH. These patients were younger than patients enrolled in Study 86-053 (see Figures 1 and 2 below). Growth rates were greater than pretreatment for each year of GH treatment.
Height SDS increased with each year of treatment, indicating that these very young patients with ISS responded to treatment with GH.
Changes from baseline in growth rate and height SDS for Cohort 2 were similar to those for Cohort 1.

Results from Cohort 3

Patients in efficacy **Cohort 3** also met the same criteria as those in Cohort 1, except that patients in Cohort 3 were pubertal at baseline.
Height SDS improved with each year of treatment, including the fifth year of treatment. Thus, with the exception of the growth rate during the fifth year of treatment, the changes from baseline in Cohort 3 were similar to those for Cohorts 1 and 2.

Figure 1: Growth Rate for Subjects in Study 86-053 and NCGS Efficacy Cohort 1 by Treatment Year (Mean ± SD)

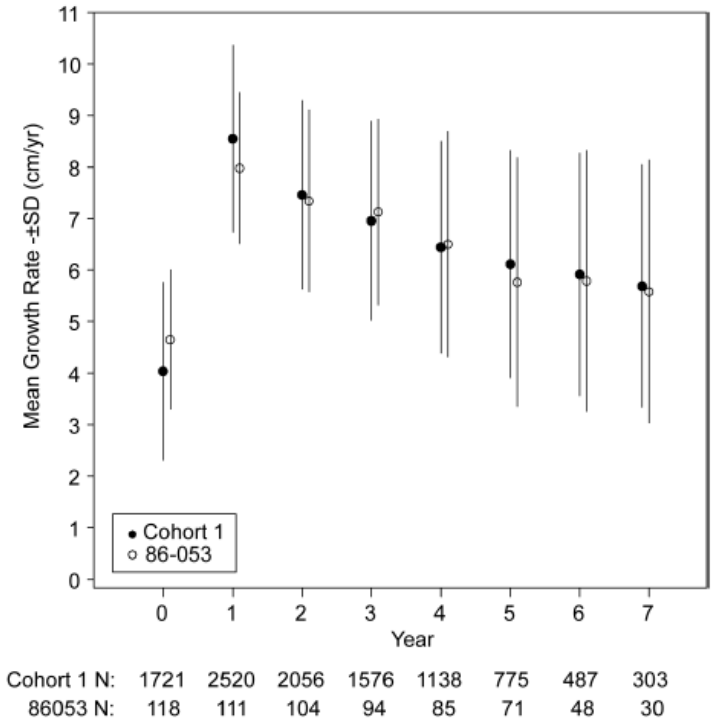
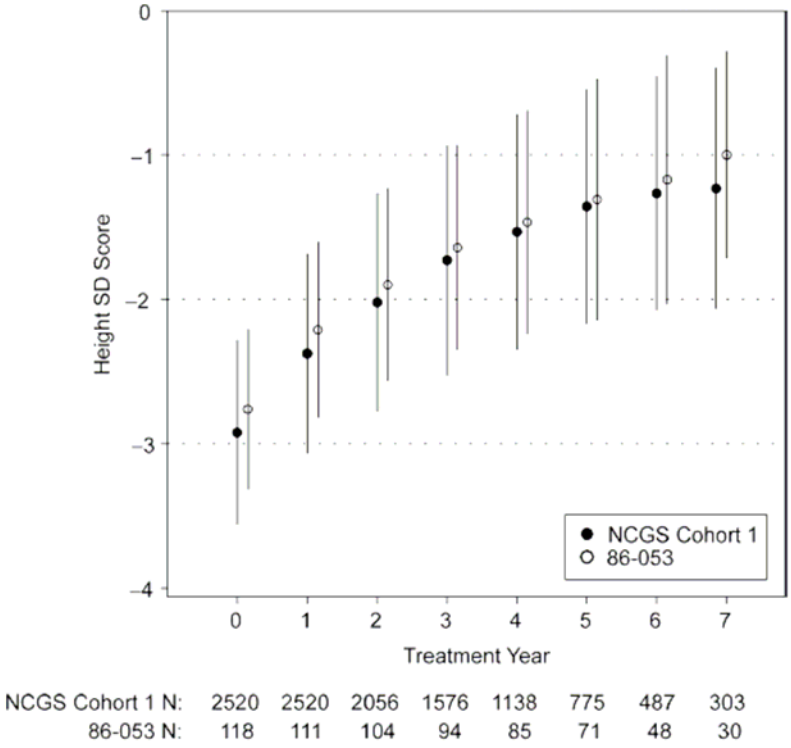


Figure 2: Height SDS for Subjects in Study 86-053 and NCGS Efficacy Cohort 1 by Treatment Year (Mean ± SD)



CHMP requested that an additional subgroup analysis was performed in children from Cohort 1 with a baseline height ≤ -2.5 SDS. Children treated with Nutropin Depot (not licensed in the EU) were also excluded from this analysis.

Similar patterns of growth increase were observed in this subgroup of Cohort 1 (n=1776), as shown in figures 3 and 4 below. The greatest gain in height SDS was achieved in the first year of treatment, with smaller increases recorded in subsequent years.

Figure 3: Growth rate by treatment year (mean ± SD) (Subjects treated with lyophilised Nutropin, NutropinAq and Protropin)

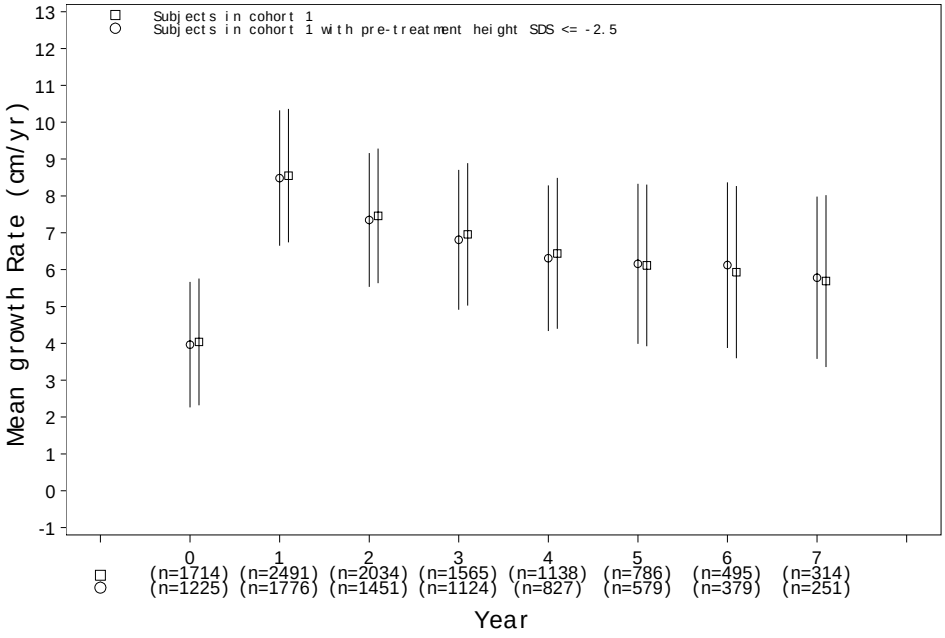
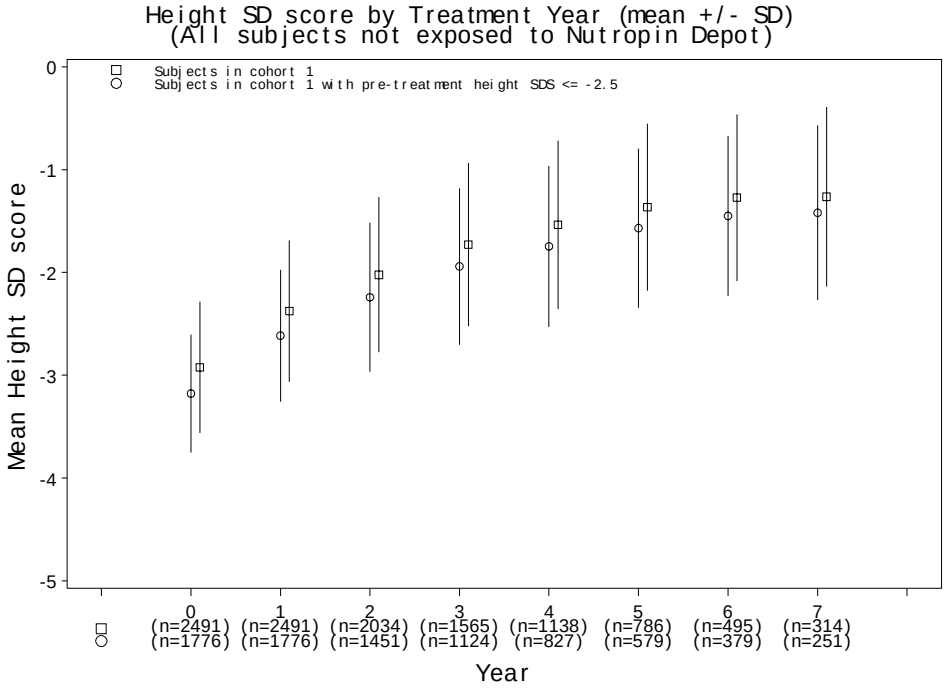


Figure 4: Height SDS by treatment year (mean ± SD) (Subjects treated with lyophilised Nutropin, NutropinAq and Protropin)



Data for subjects less than 5 years old and subjects in puberty at baseline were similar to those in pivotal study 86-053 for growth rate and gain in height SDS.

There was insufficient evidence from the data on cohort 2 that start of GH treatment before age 5 provides additional benefit compared to starting treatment after age 5. In addition, data from cohort 3

were not sufficient to recommend start of GH treatment in children with ISS already in puberty. The primary objective of cohort 2 and 3 analyses was to determine safety in these subgroups of ISS patients.

2.5 - Clinical safety

A - Patient exposure

In the pivotal study 86-053 a total of 118 subjects received Nutropin 0.3 mg/kg/week administered either TIW or daily for an average of 5.3 years, for a total of 620 subject-years of exposure. During the study many patients discontinued therapy, and only 40% of subjects completed the study protocol until final adult height. A total of 11 patients discontinued treatment due to adverse events. Of these, five were discontinuated for adverse events considered as possibly related to study drug.
In the supportive study 86-036 a total of 8018 subjects were treated with one or more of Genentech's four marketed recombinant GH formulations: Protropin (5128 subjects), Nutropin (1591), Nutropin AQ (2233) or Nutropin Depot (153) for an average of 3.1 years representing 24817 patient-years of exposure.

B - Common Adverse Events (AEs)

The table below (Table 4) presents the incidence of all AEs by preferred term reported for ≥ 5% of subjects in the Nutropin-treated and/or untreated control groups during Study Year 1. The most commonly reported AEs in both groups included common childhood infections, headache and arthralgia. The events were mostly classified by the investigators as mild to moderate in severity and unrelated to the study drug.

Table 4: Study 86-053: Adverse Events Occurring in ≥5% of Subjects in One or Both Treatment Groups during Study Year 1

Preferred Term	No. (%) of Subjects	
	Nutropin-Treated (n=63)	Untreated Control (n=59)
Any adverse event	52 (83%)	21 (36%)
Infection	24 (38%)	7 (12%)
Pharyngitis	10 (16%)	3 (5%)
Gastroenteritis	8 (13%)	0
Headache	8 (13%)	1 (2%)
Otitis media	8 (13%)	2 (3%)
Flue syndrome	5 (8%)	2 (3%)
Rhinitis	5 (8%)	3 (5%)
Fever	4 (6%)	1 (2%)
Arthralgia	4 (6%)	1 (2%)
Cough increased	4 (6%)	0
Sinusitis	4 (6%)	0

Note: Follow-up visits for data collection were more frequent for the Nutropin group (every 3 months) than the control group (every 6 months).

Conclusion:
The majority of AEs reported in study 86-053 are commonly observed illnesses in childhood. No new safety signals (not yet listed in the SPC of NutropinAq) have been identified.

C - Serious adverse events and deaths

Deaths
No deaths were reported in **Study 86-053.**
In the **NCGS** population of subjects with non-GH deficient short stature, two deaths were reported.

Other Serious Adverse Events

Study 86-053
At first, the only AE reported as serious during the study was a case of appendicitis.
An examination of the narrative comments on the AEs and Study Discontinuation revealed 19 subjects with AEs that should have been classified as serious according to the protocol criteria. Therefore events were reassessed.
In summary there were 20 SAEs (e.g. surgical intervention in case of appendicitis, bone fractures, torsion of the testicle or repair of urethral fistula, hospitalisation), only one of them considered related.

Study 86-036
Fifty-three SAEs were reported for 52 subjects in the NCGS population. Of these, 23 were considered possibly or probably related to GH treatment. These events, amongst others, included: papilledema, orbital pseudotumour, insulin-dependent diabetes mellitus, Legg-Calve-Perthes disease, muscle atrophy and weakness, scoliosis, Hodgkin's lymphoma, squamous cell carcinoma of tongue, low-grade glioma, cholesteatoma behind the ear, intracranial hypertension (2 subjects), seizure (2 subjects), psychiatric disorder (2 subjects), and gynecomastia.

Conclusion:
Benign intracranial hypertension, asthenia and gynecomastia are listed AEs. There was no concerning increased incidence of tumours or clustering of tumours. The unusual case of squamous cell carcinoma of the tongue was reported in an 18-year old patient who was treated with GH for 1 year prior to this event. Overall, in view of the submitted data, the CHMP considers that the safety data don't elicit new safety concerns.

D - Laboratory findings

As anticipated from the physiological mechanism of action increases in IGF-1 concentrations were observed in the majority of subjects during active treatment. A compensatory increase in insulin levels was observed. Two subjects discontinued due to abnormal post-prandial glucose levels. However, no case of sustained glucose intolerance or diabetes mellitus was observed.

Conclusion:
The effect of GH on glucose metabolism is well-know and is included in the SPC of NutropinAq.

E – Immunological events

Of the 118 subjects in Study 86-053 who were treated with Nutropin and had follow-up data, 31 (26%) had positive GH antibody titres at one or more visits. Peak antibody incidence occurred at approximately Month 9 of treatment.
Antibody binding capacity was determined for one or more samples with positive antibody titres in 11 subjects. These values were all below 2 mg/L and were thus unlikely to cause growth attenuation. Poor growth was observed in 1 subject who had positive antibody titres; however, binding capacity measurements were well below 2 mg/L. No antibody formation with high binding capacity or neutralising effects was detected.

The possible effect of anti-GH antibodies on growth was assessed using multivariate repeated-measures regression analysis, with growth rate between consecutive visits as the dependent variable and the presence or absence of antibodies at the end of each interval as an independent variable. In this analysis, antibody status at the end of each interval had no significant effect on growth rate during that interval.
Overall, no formation of antibodies with high binding capacity or neutralising effects was detected.

The CHMP considers that the incidence of 26% in anti GH antibodies is high and asked the MAH to discuss this issue: the MAH was requested to clarify how many patients had transient antibodies and how many subjects had antibodies on more than 1 occasion, and also why antibody binding capacity was only determined in samples from 11 patients.
The MAH provided a response on this issue: most of the identified 31 patients were anti GH antibody positive on more than one occasion . Seven of these patients were still antibody positive at the last measured time point. However, most antibodies were of rather low titre and didn't increase over time. The CHMP agrees with the threshold decision of the company for determination of antibody binding capacity. However overall, the CHMP considers that these data not only confirm the high antibody frequency observed with this product but also suggest that the incidence in the newly proposed indication may be even higher than in the presently approved indications. Therefore, in case of a positive opinion, the CHMP would have proposed to amend the current wording in the section 4.8 of the SPC and asked the MAH to consider that the antibody frequency in the table be stated as "very common".

F – Discontinuation due to AEs

In Study 86-053, 11 subjects had a medical condition reported on the Treatment Discontinuation Forms, including two cases (suicide attempt and ulcerative colitis) described above as SAEs. The other conditions were the following: elevated postprandial glucose (2 subjects); concern with size of feet; fatigue and increased liver enzymes; depression (2 subjects); knee pain (possible metaphyseal dysplasia); headache and dizziness; and mild swelling of the right side of the subject's mouth and left ear.

G – Overall safety conclusion

Over the complete reported observation period in study 86-053, no unlisted adverse events were reported. The safety database from supportive study 85-036 did not reveal any new safety concerns. However the high incidence of low-titre anti-GH antibodies was noticed by the CHMP in this indication. The CHMP considers the short-term risks of GH treatment acceptable but is concerned about possible long-term risks such as tumour promotion and diabetes in this indication..

2.6 – Summary of issues and conclusion of the benefit-risk profile

A total of four lists of questions were addressed to the MAH successively on the 27 July 2006, 15 November 2006, 22 February 2007, and 26 April 2007 to which the MAH responded in writing and in an Oral Explanation. In addition, a SAG meeting was held on 23 March 2007.

The following main issues were discussed:

1) The CHMP acknowledged that GH treatment for the condition of SS with no identifiable cause was controversial, since SS itself may not necessarily be associated with psychological problems or require treatment, and treatment would not necessarily have any other benefits beyond height gain such as improving the child's psychological wellbeing.

The SAG discussed this issue as follows:
Short stature *per se* is not necessarily associated with psychosocial problems, but those referred for medical investigation are more likely to experience such problems than those who are not referred. The only randomised double blind placebo controlled study of the psychosocial effects of GH in ISS concluded that "GH treatment was associated with a *trend* toward improvement in problem behaviours, as measured by questionnaires completed by study participants' parents. It remains to be determined whether GH treatment significantly impacts adaptation, psychosocial function, or quality of life in children with ISS" (Ross, 2004). In this study, the psychosocial adaptation and self esteem of the GH-treated youngsters were comparable to that of the placebo group at baseline. At no point did measures of self-esteem differ, but in the fourth year, parents reported significantly more behaviour

problems in the placebo-treated group. Nevertheless, no systematic relationship was observed between change in height and change in psychosocial adjustment. A recent review went on to conclude that "on average hormone treatment does not seem to improve psychosocial functioning" in children with ISS (Visser-van Balen et al 2006). Psychological evaluation has thus failed to provide clear evidence that there are psychological benefits of augmenting height with GH therapy.

Whilst accepting the clinical view that individual children with ISS might in special circumstances benefit from hormone therapy, it was noted that such circumstances were difficult to define adequately.

The CHMP, however, was made aware that demonstration of a treatment benefit beyond gain in height was not required for other non-GH-deficient indications.

2) The CHMP considered that a randomised, controlled clinical trial up to final height would have been needed to fully assess the effect size of GH treatment in this condition. In addition, only 40% of children in the pivotal study completed the study according to protocol, i.e. 60% stopped treatment prematurely. However, CHMP agreed that there are technical difficulties in conducting long-term trials in children including a placebo or untreated control group. In addition, despite the fact that adherence to the protocol was rather low, adult height was available in 70% of initially randomised children. Therefore, effect size was unlikely to be overestimated. The MAH provided reassurance that children did not stop treatment due to lack of efficacy.

The SAG discussed this issue as follows:
In the absence of such data (from randomised, controlled trials), a meta-analysis of the effect of GH in ISS should be taken into consideration (Finkelstein et al. 2002). This meta-analysis included 28 uncontrolled studies and only 10 controlled studies, only one of which (McCaughey et al. 1998) was a randomised controlled trial. Final height data were available from only 13 girls, 7 with GH treatment and 6 controls, the GH treated girls being on average 7.5cm taller than the controls after a mean duration of 6.2 years of therapy. A subsequent randomised controlled trial has been reported (Leschek EW et al. JCEM 2004) but here again, the numbers were small, and adult height was available from only 33 subjects randomised to GH or placebo at a mean age of 12.5 years). The achieved improvement in final height was only 3.7cm with GH treatment. To date, no other randomised controlled trials on GH treatment in ISS are available which include data on final height.

There was agreement that GH treatment is efficacious in promoting linear growth in ISS, as shown both in the pivotal study and elsewhere in the literature. The magnitude of the effect is controversial, however, and the claimed increment in height of about 6 cm questioned by some experts during the meeting.

Upon CHMP request, the MAH provided data from literature demonstrating that predicted final height, on average, was a reasonable estimate of true final height in patients with ISS. Therefore, the gain in final height of 6.5 cm in boys and 7.7 cm in girls comparable to the target population can be expected to be close to the true effect size.

3) The CHMP discussed the possibility of introducing a stopping criterion to avoid long-term GH treatment of children with a likely poor overall treatment response. In the absence of a correlation the MAH suggested, in analogy with the stopping criterion for the SGA indication, discontinuation of treatment if HVSDS is below +1 after the first year of GH therapy. However, the various correlation analyses provided by the MAH did not support this or other stopping criteria.

4) The Committee concluded that the clinical relevance of the observed height gain deserves a thorough discussion, particularly in the light of subjecting otherwise healthy children to long-term injections of a drug for which the short-term risk is considered low but for which the long-term risks are still being debated. The lack of a safety signal in the database provided by the MAH during this procedure was re-assuring, but further long-term safety data were considered necessary.

5) Considering that approval of the ISS indication would expose an increasing number of short but otherwise healthy children to long-term treatment with GH, availability of additional long-term safety data, particularly with regard to possible tumour promotion and diabetes risk, was considered important.

During the oral explanation held on 19th September 2007, the MAH made a presentation to the CHMP with regard to the use of NutropinAQ in the ISS indication, focusing on the efficacy results, the psychological aspect and the long-term benerit-risk. The CHMP reiterated their concerns with regards to the ISS indication itself.

3 PHARMACOVIGILANCE

3.1 Risk Management Plan

The MAH submitted a risk management plan. The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

3.2 Overall conclusion and Benefit-risk assessment

Whereas the effect of GH treatment on final height in children with severe ISS is only modest and in the absence of proof of a benefit regarding psychological wellbeing and social adjustment the benefit is considered insufficient to outweigh the potential long-term risks such as tumour-promotion or diabetes, the CHMP has recommended the refusal of the variation to the terms of the Marketing Authorisation. The proposal of a member state to restrict the indication of Nutropin Aq to severe ISS with a height below – 3 SDS, after excluding other causes of growth impairment, was discussed but did not change the conclusion of the CHMP of an unfavourable benefit-risk ratio.

Some members of CHMP did not agree with the CHMP's negative opinion recommending the refusal of the variation of the Marketing Authorisation for NutropinAq to include the indication of long-term treatment of children with severe ISS not explained by GHD or other medical conditions and with a predicted adult height at least 1 SDS below the target height. The reasons for divergent opinion were the following:

- the efficacy in terms of final height gain was considered reasonably well supported by data, sufficiently reliable and clinically relevant;
- no new safety signal(s) were detected from the large database in children with ISS and in case of a positive opinion, additional follow-up commitments proposed by the MAH would have been acceptable to collect further information on long term efficacy and safety with focus on tumor promotion and diabetes risk and potential long term effects on the use of Nutropin Aq in ISS.

Based on the review of the data on safety and efficacy, the CHMP considers that the variation application EMEA/H/C/000315/II/0024 for NutropinAq (somatropin), to include the long-term treatment of children with severe idiopathic short stature (ISS) not explained by growth hormone deficiency (GHD) or other medical conditions and with a predicted adult height at least 1 SDS below the target height is not approvable.