2 SYNOPSIS

Name of Sponsor/Company: IPSEN	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For national authority use only)*
Name of Finished Product: NutropinAq®		
Name of Active Ingredient(s): Somatropin		
Title of study: International Cooperative Growth Study (iNCGS) Post-Marketing Surveillance Program For NutropinAq® [Somatropin (rDNA Origin) Injection] Study number: 2-79-58035-005		
Investigators: There was no coordinating Investigator for this Registry study. A steering committee was however regularly consulted.		
Study centre(s): 166 participating sites in seven European countries: Germany, France, Spain, Italy, Romania, United Kingdom (UK) and Austria.		
Publication (reference): Not applicable.		
Studied period (years): Study initiation date: 03 October 2005 (original protocol approval date) Study completion date: 20 December 2016 (Last Subject Last Visit)	Phase of development: 4	
Objectives: The objective of this study was to collect long-term safety and effectiveness information on NutropinAq® during treatment of paediatric growth disorders for which Growth Hormone (GH) is indicated.		
Methodology: The iNCGS Registry is an international, multicentre, open-label, noninterventional, postmarketing surveillance study of NutropinAq®. As this is a noninterventional study, the decision to prescribe NutropinAq®, was to be taken prior to, and independently from, the decision to enrol the subject. Prescribing of NutropinAq® was to be made in accordance with routine clinical practice and applicable labelling recommendations in the centres concerned. The Investigators were free to choose the dose and administration schedule, within the terms of the respective local prescribing information, which were to be individualised for each subject. During the first visit (enrolment), the Investigator had to check the inclusion and exclusion criteria, and to obtain the Informed Consent Form fully signed. At the next visit (baseline), the study treatment was initiated. Subjects who had started the treatment before the initiation of the study in their country could also be enrolled. The study follow-up visits were thereafter conducted as per routine clinical practice (usually every 3-4 months), and included the treatment administration, with the subject assessments. Data were collected, as available,		

Name of Sponsor/Company: IPSEN	Individual Study Table Referring to Part of the Dossier	*(For national authority use only)*
Name of Finished Product: NutropinAq®		
Name of Active Ingredient(s): Somatropin	Volume: Page:	

until subjects reached adult age i.e. epiphyseal closure was achieved. No additional subject procedures or activities were mandated by this Registry.

The data were first collected locally using a software called iGT+ until 31 December 2014; then, from 2015 and on, the data were migrated to a modernized online data capture tool (electronic Case Report Form (eCRF)).

Number of patients (planned and analysed):

The iNCGS study aims at recruiting as many subjects as possible at the participating sites, to obtain a representative number of the treated population. As of 20 December 2016:

- Number of screened subjects: 3657 (The Screened Population included all eligible subjects i.e. meeting the inclusion/exclusion criteria and who could be asked to participate in the Registry).
- Number of enrolled subjects: 2792 (The Enrolled Population included all subjects with a documented written informed consent and with at least one collected data in the Registry).
- Number of subjects in the Registry Population: 2714 (The Registry Population included all enrolled subjects who completed at least one follow-up visit and who received at least one NutropinAq® injection).
- Number of subjects in the Safety Population: 3493 (The Safety Population included all subjects who received at least one NutropinAq® injection and with at least one follow-up visit or follow-up safety data).

Diagnosis and criteria for inclusion:

- Children of either sex who were initiated therapy or currently receiving therapy with NutropinAq® for the treatment of growth failure,
- Written informed consent signed by both parents or by the liable parent or by the legal guardian when applicable and by the child when applicable,
- Patients who were willing to comply with follow-up appointments throughout study participation.

Test product, dose and mode of administration:

The decision to prescribe NutropinAq® was made as per local clinical practice and labelling recommendations, prior to and independently from the decision to enrol the subject in this noninterventional study.

The drug was administered by subcutaneous injection.

Per NutropinAq® labelling:

Name of Sponsor/Company: IPSEN	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For national authority use only)*
Name of Finished Product: NutropinAq®		
Name of Active Ingredient(s): Somatropin		

- For children with growth failure due to inadequate endogenous GH secretion, a daily dose of 0.025–0.035 mg/kg of body weight was recommended;
- For children with growth failure associated with Turner syndrome (TS), a daily dose of up to 0.05 mg/kg of body weight was recommended;
- For prepubertal children with growth failure associated with chronic renal insufficiency (CRI) up to the time of renal transplantation, a daily dose of up to 0.05 mg/kg of body weight was recommended.

The NutropinAq Pen® allows the administration of a minimum dose of 0.1 mg to a maximum dose of 4.0 mg, in 0.1 mg increments.

Duration of treatment:

The recommended dose, administration schedule, and treatment duration were individualized for each subject, within the terms of the respective local prescribing information.

Criteria for evaluation:

Effectiveness endpoints:

- Height (cm and Standard Deviation Score (SDS)),
- Height velocity (cm/year),
- Predicted adult height (PAH) (cm),
- Final adult height (FAH) (cm).

Other endpoints:

- Body mass index (BMI) (kg/m² and SDS)
- Bone age (years),
- Tanner stage: pubic hair, breast development, testicular size,
- Exposure to GH.

Safety endpoints:

- Any serious adverse event (SAE),
- Any nonserious adverse event (AE) considered by the Investigator to be related to NutropinAq®.

Statistical methods:

Main analysis populations:

The assessment of effectiveness was based on the Registry Population and also by the following subgroups:

Name of Sponsor/Company: IPSEN	Individual Study Table Referring to Part of the Dossier	*(For national authority use only)*
Name of Finished Product: NutropinAq®		
Name of Active Ingredient(s): Somatropin	Volume: Page:	

- Treatment-naïve subjects overall and per aetiology (with growth hormone deficiency (GHD) (idiopathic and organic) and without GHD (TS, CRI and other);
- Treatment-naïve prepubertal subjects overall and per aetiology (with GHD (idiopathic and organic) and without GHD (TS, CRI and other)).

Effectiveness endpoints analysis

- Evaluation of changes from baseline

Raw values and changes from baseline were described at each timepoint for height in cm and SDS and for height velocity in cm/year. Height velocity was also described separately for boys and girls. Time course of height and height velocity were illustrated on a graph. Correlation between height velocity and height SDS at Year 1 and GH peak were displayed on a scatter plot with the Pearson correlation coefficient on treatment-naïve prepubertal GHD subjects and treatment-naïve subjects with isolated mild GH deficiency.

- Adult/near adult height

Adult/near adult height was described and mean difference (95% CI) between PAH (derived with Bayley-Pinneau method) and FAH were estimated. Height velocity at Year 1 and Year 2, change from baseline in height SDS at last follow-up and treatment duration were also described on the Completed Population by gender. These results were also conducted in treatment-naïve subjects.

- Multiple regression analysis

Multiple regression analysis was performed on the basis of follow-up visit data only on the following parameters:

- Change from baseline in height (SDS)
- Change from baseline in height velocity per treatment year (cm/year)
- Adult/near adult height (SDS)

This analysis was performed on treatment-naïve subjects treated for at least one year.

The multiple regressions were conducted in several steps (univariate analyses, correlation between preselected parameters, stepwise selection for multivariate analysis). The parameters were analysed at Year 1 (Year 2 ...) using an ANCOVA linear model including the following covariates: aetiology, pubertal status, parental heights, birth height, target height, height SDS at baseline, weight SDS at baseline, starting dose, mean dose during the first year (or two first years ...) of treatment, dose adaptation during the first year (or two first years ...), age at the first NutropinAq® intake.

Other endpoints analysis:

Other endpoints were analysed descriptively in the Registry Population.

Name of Sponsor/Company: IPSEN	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For national authority use only)*
Name of Finished Product: NutropinAq®		
Name of Active Ingredient(s): Somatropin		

Values and changes from baseline on BMI SDS and the ratio between chronological age and bone age were described at each timepoint overall and in the subgroups of treatment-naïve and treatment-naïve prepubertal subjects. Body Mass Index SDS was also described in TS and CRI subjects.

At each timepoint the status pubertal/prepubertal was described and shift tables from baseline were provided in the subgroup of treatment-naïve subjects.

Exposure to treatment was described in terms of treatment duration, number of treated patient-years, proportion of subjects who stopped the therapy and reasons for treatment discontinuation and proportion of subjects with a dose adaptation. The daily dose of NutropinAq® was also described at initiation, at each timepoint as continuous variable and in classes overall and per aetiology.

Safety endpoints analysis – The safety analyses included:

- Incidence of any Treatment Emergent AE (TEAE),
- Incidence of any TEAE considered by the Investigator to be related to NutropinAq®,
- Incidence of TEAEs leading to withdrawal,
- Incidence of any SAE.

Each type of AE was summarised with the number and proportion of subjects with at least one event classified by primary system organ class (SOC) and preferred term (PT). The number of occurrences was also presented. For each type of AE, intensity, causality and outcome were described.

Summary - conclusions:

Population:

From 03 October 2005 to 20 December 2016, 166 participating sites located in the seven following countries - Germany, France, Spain, Italy, Romania, UK and Austria - screened 3657 subjects. A total of 118 active sites included the 2792 subjects of the Enrolled Population.

The Registry Population included 2714 subjects. The main reason for exclusion of subjects from the Registry Population was the lack of follow-up visit (70 subjects, 89.7%). The Safety Population included 3493 subjects.

The disease aetiologies of the subjects enrolled in the Registry were consistent with the indications of NutropinAq®, with 2082 subjects (74.7%) presenting primarily with a GHD disease, of whom 1825 subjects had an idiopathic GHD. Among the 707 subjects without GHD (the primary aetiology was missing for three subjects), 498 subjects had "other" secondary aetiology, mainly Small for Gestational Age (SGA) (254 subjects); 199 subjects had a TS and 10 had a CRI.

Name of Sponsor/Company: IPSEN	Individual Study Table Referring to Part of the Dossier	*(For national authority use only)*
Name of Finished Product: NutropinAq®		
Name of Active Ingredient(s): Somatropin	Volume: Page:	

In the Enrolled Population, subjects with GHD and CRI were predominantly male (from 66.2% to 66.7%).

Growth hormone deficiency was generally diagnosed at a most advanced age in treatment-naïve subjects with GHD (median between 8 and 9 years old), while TS, CRI and other nonGHD condition were diagnosed at a youngest age, from 5 to 7 years old.

The difference between age at diagnosis and age at treatment initiation ranged from several months (in treatment-naïve subjects with GHD) to several years (in subjects with TS, CRI, other nonGHD).

Consistently with the product labelling recommendations, the lowest mean initial doses of NutropinAq® in the Enrolled Population, 0.030±0.008 mg/kg/day, were administered in subjects with GHD; higher mean initial doses, 0.043±0.009 mg/kg/day, or 0.042±0.010 mg/kg/day were administered to subjects with respectively TS or with CRI. During the treatment period, the average dose of NutropinAq® remained very close to the mean initial dose, irrespective of the aetiology.

According to the aetiology, the median treatment duration ranged from 32 months in subjects with organic GHD to 43.5 months in subjects with TS. At the end of this study, 235 subjects reached adult height or near adult height.

Effectiveness results:

In the Registry Population (N=2714), after one year of treatment:

- The mean change from baseline in height SDS was 0.60 (95% CI: [0.58;0.62], n=2125);
- The mean height velocity was 8.5 cm/year (95% CI: [8.4;8.6], n=2131);
- The mean change from baseline in height velocity was 3.2 cm/year (95% CI: [2.9;3.4], n=661).

In treatment-naïve subjects of the Registry Population (n=2314), after one year of treatment:

- The mean change from baseline in height SDS was 0.64 (95% CI: [0.61;0.66], n=1839);
- The mean height velocity was 8.8 cm/year (95% CI: [8.7;8.9], n=1843);
- The mean change from baseline in height velocity was 4.0 cm/year (95% CI: [3.8;4.3], n=523).

Multivariate analyses showed that in treatment-naïve subjects:

- The improvement in height SDS at Year 1 was better in subjects with a high starting dose, with a high target height, with a low height SDS at baseline whatever the aetiology and with a high birth height. These results were also observed at Year 3.

Name of Sponsor/Company: IPSEN	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For national authority use only)*
Name of Finished Product: NutropinAq®		
Name of Active Ingredient(s): Somatropin		

- The improvement in height SDS at Year 2 was better in subjects with a high starting dose, with a high target height, with a low height SDS at baseline whatever the aetiology and in prepubertal subjects.
- The improvement in height SDS at Year 4 was better in subjects with a high target height, with a low height SDS at baseline and in subjects with organic GHD.
- The height velocity at Year 1 was likely to be higher in subjects with a low age at the first NutropinAq® intake, with a high birth height, with a high target height, with a high starting dose whatever the aetiology.
- The height velocity at Year 2 was likely to be higher in subjects with a low age at the first NutropinAq® intake whatever gender or in subjects with organic GHD.
- The height velocity at Year 3 was likely to be higher in subjects with a high target height, with a high height velocity at Year 2 whatever the pubertal status or in subjects with organic GHD.
- The height velocity at Year 4 was likely to be higher in subjects with a high height velocity at Year 3, in boys and in subjects with a low age at the first NutropinAq® intake whatever the pubertal status.

The height SDS and height velocity analyses were also performed on the subgroups of treatment-naïve subjects with idiopathic GHD, organic GHD, TS or CRI or other nonGHD aetiology:

- The mean change from baseline in height SDS increased at each timepoint from Year 1 to Year 11, irrespective of the subgroup, in the exception of some subpopulation when the number of subjects was very low. The subgroup of subjects with organic GHD showed the best improvement in height SDS: from 0.71 (95% CI: [0.62;0.80], n=145) at Year 1 to 1.78 (95% CI: [1.45;2.12], n=35) at Year 5. The subgroup of subjects with TS showed the lowest/minimal improvement in height SDS: from 0.59 (95% CI: [0.53;0.65], n=133) at Year 1 to 1.11 (95% CI: [0.92;1.29], n=63) at Year 5.
- At Year 1, the mean height velocity was increased from baseline in all subgroups, and the highest mean height velocity was observed in subjects with organic GHD (9.3 cm/year; 95% CI: [8.8;9.7], n=147). From Year 2 to Year 5, height velocities decreased down to approximately 6 or 5 cm/year (depending on the subgroup), but were still higher than baseline, regardless of the subgroup.
- The highest mean change from baseline in height velocity occurred at Year 1, irrespective of the subgroup (around +3.5 to +4.9 cm/year). The subgroup of subjects with organic GHD generally showed the highest mean change from baseline in height

Name of Sponsor/Company: IPSEN	Individual Study Table Referring to Part of the Dossier	*(For national authority use only)*
Name of Finished Product: NutropinAq®		
Name of Active Ingredient(s): Somatropin	Volume: Page:	

velocity: from 4.9 cm/year (95% CI: [3.9;5.9], n=40) at Year 1 to 3.6 cm/year (95% CI: [1.8;5.3], n=15) at Year 3.

In all treatment-naïve subjects having reached the adult/near adult height (n=198), the mean height at last visit was 160.6±10.1 cm (153.9±7.7 cm for girls and 166.3±8.2 cm for boys). The mean height SDS at last follow-up was -1.3±1.0 (-1.4±1.1 for girls and -1.1±0.8 for boys) with an improvement from baseline in mean of 1.1±0.9 (1.1±1.0 for girls and 1.1±0.7 for boys). The mean height velocity at Year 1 was 8.1±2.2 cm/year (8.1±2.5 cm/year for girls and 8.1±1.9 cm/year for boys). The PAH was higher than adult/near adult height. The mean of the difference was overall 4.0±6.0 cm: 5.4±8.1 cm for boys and 2.8±2.8 cm for girls. Multivariate analyses showed that the adult/near adult height SDS seemed to be higher in subjects with a high height SDS at baseline.

Safety results:

Among the 3493 subjects of the Safety Population, a total of 1837 TEAEs were reported in 855 subjects (24.5%). The TEAEs were generally of mild to moderate intensity.

Nonserious TEAEs were considered as related to the study treatment by the Investigator in 610 subjects (17.5%). In most cases, the drug-related nonserious TEAEs that were reported with the highest frequencies were consistent with the known NutropinAq® safety profile (such as: injection site pain [2.7% of subjects], injection site haematoma [2.5%], headache [2.2%]; arthralgia [1.1%], scoliosis [0.9%], pain in extremity [0.5%], lipodystrophy, asthenia and gynaecomastia [0.4% each]), or with its known pharmacological effect (insulin-like growth factor increased [7.3% of subjects], insulin-like growth factor decreased [0.9%] or glycosylated haemoglobin increased [0.4%]).

Only 206 subjects (5.9%) experienced serious TEAEs. They were considered as related to the study treatment by the Investigator in 27 subjects (0.8%) and included scoliosis (four subjects) and epiphysiolysis (three subjects). Of note, in the SOC “Neoplasms benign, malignant and unspecified (including cysts and polyps)”, a total of 20 subjects (0.6%) experienced a serious neoplasm event in this Registry: 17 subjects during the treatment period and three subjects during the post-treatment period. The main serious neoplasm events reported were: craniopharyngioma (five subjects), astrocytoma (three subjects), medulloblastoma (three subjects) and cholesteatoma (two subjects). All the other serious neoplasm events were reported in seven subjects with one event/subject: teratoma, osteosarcoma, naevus, melanoma, ovarian germ cell teratoma, pituitary tumor, pituitary germinoma. Among the 20 subjects, 14 subjects had a prior history of neoplasm: craniopharyngioma in five subjects, astrocytoma in two subjects and medulloblastoma in four subjects. For four subjects, the recurrence was not confirmed and only a close Magnetic Resonance Imaging (MRI) monitoring was performed and reported.

Name of Sponsor/Company: IPSEN	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For national authority use only)*
Name of Finished Product: NutropinAq®		
Name of Active Ingredient(s): Somatropin		

Seven events had a fatal outcome: three events on treatment ("Streptococcal sepsis", "Medulloblastoma recurrent" and “Infection”) and the four others at least seven days after the last NutropinAq® injection ("Cardio-respiratory arrest", "Possible central respiratory dysfunction", “Haematemesis”, “Dyspnoea”). They were all considered as not related to the study treatment by the Investigator.

A total of 78 TEAEs leading to treatment discontinuation were reported in 61 subjects (1.7%), mainly injection site pain (16 events), scoliosis (seven events), Insulin-like Growth Factor-1 (IGF-I) increased (seven events), headache (four events), craniopharyngioma (two events) and hyperglycaemia (two events).

Overall conclusion:

In conclusion, the iNCGS study shows that under treatment with NutropinAq®, the mean height SDS as well as the mean height velocity were improved in all subjects. This improvement was observed in treatment-naïve subjects, in the subgroup of treatment-naïve prepubertal subjects and in treatment-naïve GHD subjects. The best improvement in growth rate was observed in the treatment-naïve subjects with organic GHD as well as in the subgroup of treatment-naïve prebubertal subjects with organic GHD.

In most cases, the drug-related nonserious TEAEs that were reported with the highest frequencies were consistent with the known NutropinAq® safety profile. Only 206 subjects (5.9%) experienced serious TEAEs, assessed as related to NutropinAq® in 27 subjects (0.8%). Of note, 20 subjects (0.6%) experienced a serious neoplasm event in this Registry but 14 of them had reported a prior history of neoplasm. Seven deaths assessed as not related to NutropinAq® were reported in the Registry.

The data observed in the iNCGS registry confirm that the benefit-risk status for NutropinAq remains favourable with no new safety signal in paediatric subjects with growth failure.

Date of report: 19 December 2017