Year-one effectiveness and overall safety of NutropinAq® for growth hormone deficiency (GHD) and other paediatric growth disorders: Completion of the International Cooperative Growth Study (iNCGS) European Registry

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Regis Coutant[1], Jordi Bosch Muñoz[2], Cristina Dumitrescu[3], Dirk Schnabel[4], Caroline Sert[5], Valerie Perrot[5] & Mehul Dattani[6]

[1]Diabetology, Paediatric Endocrinology, Centre Hospitalier Universitaire d'Angers, Angers, France; [2]Department of Paediatric Endocrinology, Hospital Arnau de Vilanova, LLeida, Spain; [3]Department of Paediatric Endocrinology, C.I. Parhon National Institute of Endocrinology, Bucharest, Romania; [4]Pediatric Endocrinology, Children's Hospital, Charité – University Medicine Berlin, Berlin, Germany; [5]Ipsen, Boulogne-Billancourt, France; [6]Genetics and Genomic Medicine Programme, UCL GOS Institute of Child Health and Great Ormond Street Hospital for Children, London, UK

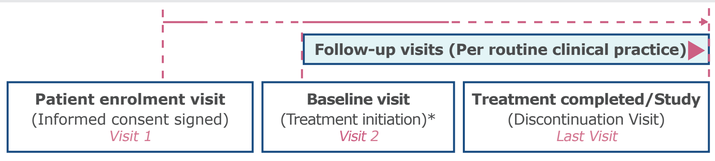
INTRODUCTION AND OBJECTIVES

- Growth Hormone Deficiency (GHD) in children is characterised by low growth velocity, sometimes after a period of normal growth, and short stature relative to the child's chronological age, sex and pubertal stage.[1]
- GHD is managed with growth hormone (GH) therapy,[2] with the aims of achieving optimal height development and expected adult height.[3]
- NutropinAq® (Ipsen Pharma, France) is a solution, administered daily by subcutaneous (SC) injection, containing 10 mg (30 International Units [IU]) of somatropin, a synthetic form of human GH produced by recombinant DNA technology with an identical sequence of 191 amino acids to endogenous human GH of pituitary origin.[4,5]
- In the paediatric population, NutropinAq® is indicated for:[4]
  - Long-term treatment of children with growth failure due to inadequate endogenous GH secretion: 0.025–0.035 mg/kg body weight daily SC.
  - Long-term treatment of girls from 2 years of age with growth failure associated with Turner syndrome: up to 0.05 mg/kg body weight daily SC.
  - Treatment of prepubertal children with growth failure associated with chronic renal insufficiency: up to 0.05 mg/kg body weight daily SC.
- The iNCGS (International Cooperative Growth Study) – an international multicentre, open-label, non-interventional study conducted in Europe – was initiated in 2005 to collect long-term safety and effectiveness data on NutropinAq® during treatment of indicated paediatric growth disorders (NCT00455728).
- Here we report year-1 effectiveness and safety data from the iNCGS registry.

METHODS

- Patient data were collected from 166 participating centres in seven European countries (Germany, France, Spain, Italy, UK, Austria, and Romania) between October 2005 and December 2016.
- Children with growth disorders, for which GH therapy was indicated, and who were initiating or already receiving therapy with NutropinAq®, were enrolled into the study and followed throughout their course of treatment (Figure 1).
- The decision to prescribe NutropinAq® was taken before and independently of the decision to enrol the patient.
  - Dosing was in accordance with the label and clinical practice, with the dose and schedule individualised to the patient based on the investigator's clinical judgement.

Figure 1. Study scheme for iNCGS



* Treatment could be initiated prior to the patient enrolment visit, and subsequently, baseline visit data could be collected retrospectively.

- Patients were assessed at their usual hospital visits in line with clinical practice at the treatment centre.
- The principal effectiveness measures were:
  - Height (cm) and Standard Deviation Score (SDS).
  - Height velocity (cm/year).
  - Predicted adult height (PAH; cm).
  - Final adult height (FAH; cm).
- Height was measured at each visit and SDS and height velocity calculated.
- Treatment dose and duration of treatment was recorded.
- Patients were to be withdrawn from study treatment and discontinue the study when their adult height – defined by closed epiphyses – was attained.
- Investigators reported non-serious related treatment-emergent adverse events (TEAEs) and serious AEs, regardless of relationship to study treatment.

Statistical analysis

- Statistical analysis was performed using Statistical Analysis System (SAS®) Version 9.4 (SAS Institute Incorporated, Cary, NC, USA).
- Descriptive statistics of patients characteristics, dosing and the principal efficacy and safety variables are presented.
- Height SDS and Height Velocity for five peak plasma growth hormone (GH) levels were compared by analysis of variance (ANOVA), with a 5% level of significance.

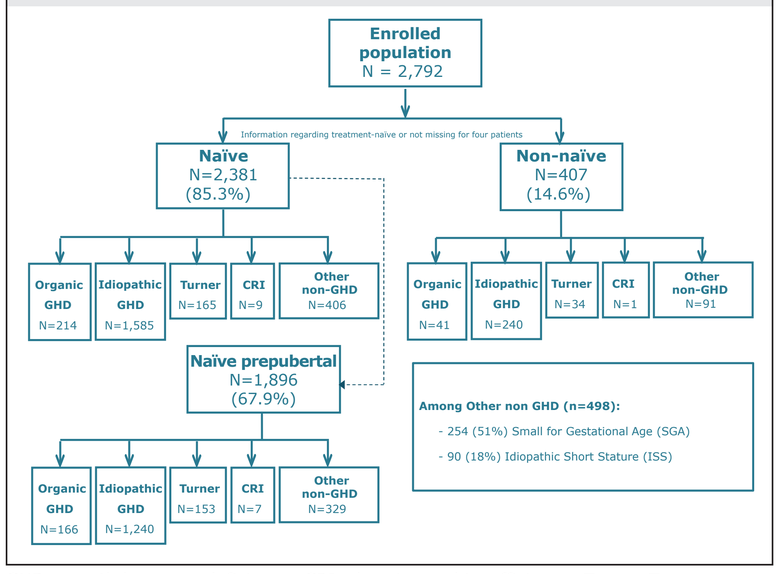
RESULTS

- A total of 3,657 patients were screened for the study, 864 were not enrolled due to lack of patient consent or non-availability of data.

Patient populations and disposition

- Enrolled population: 2,792 patients who were fully informed about the study, gave written informed consent to participate, and had data available (Figure 2).
- Registry population; 2,714 patients who were enrolled, completed at least one follow up visit and received at least one NutropinAq® injection.
- Safety population: 3,493 patients who received at least one NutropinAq® injection and with at least one follow-up visit, or follow-up safety data.

Figure 2. Patient disposition for enrolled population in iNCGS



GHD, growth hormone deficiency; CRI, chronic renal insufficiency; Turner, Turner syndrome

- Patients' baseline characteristics in the enrolled population are summarised in Table 1.

Table 1. Baseline characteristics – enrolled population

Characteristic	Treatment naïve patients (N=2,381)	Non-treatment naïve patients (N=407)	All patients (N=2,792)[a]
Gender			
n	2381	407	2789
Boys	1,435 (60.3%)	226 (55.5%)	1,662 (59.6%)
Girls	946 (39.7%)	181 (44.5%)	1,127 (40.4%)
Age at diagnosis (years)			
n	2,356	405	2,762
Mean (SD)	7.8 (4.0)	7.2 (4.4)	7.7 (4.1)
Age at the first NutropinAq® injection (years)			
n	2,376	407	2,784
Mean (SD)	9.2 (3.6)	11.0 (3.5)	9.5 (3.6)
Patients at first NutropinAq® injection in age classes			
n	2,376	407	2,784
<5 years	344 (14.5%)	28 (6.9%)	372 (13.4%)
From 5 to 10 years	977 (41.1%)	120 (29.5%)	1,097 (39.4%)
>10 years	1,055 (44.4%)	259 (63.6%)	1,315 (47.2%)
Bone age at first NutropinAq® injection (years)			
n	349	71	420
Mean (SD)	7.4 (3.4)	10.5 (3.2)	7.9 (3.6)
Ratio between chronological age and bone age (years)			
n	349	71	420
Mean (SD)	0.8 (0.2)	0.9 (0.1)	0.8 (0.1)
Height SDS at diagnosis			
n	1,408	221	1,630
Mean (SD)	-2.1 (1.1)	-1.9 (1.1)	-2.0 (1.1)
Height SDS at baseline			
n	2,306	372	2,679
Mean (SD)	-2.6 (0.9)	-1.7 (1.1)	-2.4 (1.0)
Height velocity at baseline (cm/year)			
n	660	182	843
Mean (SD)	4.7 (2.0)	7.1 (2.5)	5.2 (2.3)

[a]Treatment naïve, or non-naïve status not reported for four patients

Dosing and duration of exposure

- The starting dose of NutropinAq® varied by indication and followed the label recommendations for each indication (Table 2).
- The median duration of treatment was 3.2 years. Duration of treatment by aetiology is shown in Table 2.

Table 2. Exposure to NutropinAq® - enrolled population

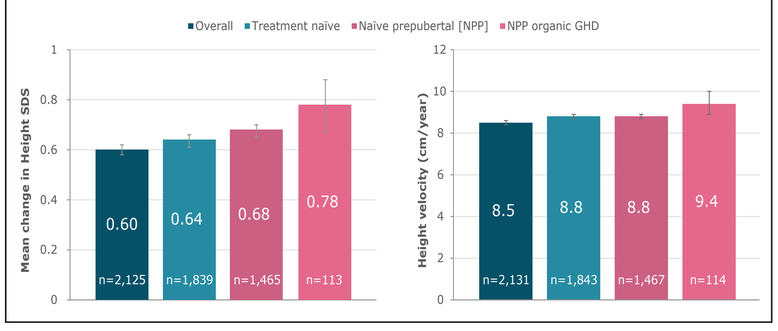
Enrolled population	Idiopathic GHD (n=1,825)	Organic GHD (n=255)	Turner syndrome (n=199)	Chronic renal insufficiency (n=10)	Other non-GHD (n=498)
Treatment duration (months)					
n	1,825	250	199	10	498
Mean (SD)	42.2 (26.5)	40.1 (29.3)	48.3 (29.0)	40.8 (35.4)	40.4 (26.9)
Initial dose (mg/kg/day)					
n	1,790	244	195	9	492
Mean (SD)	0.032 (0.007)	0.030 (0.008)	0.043 (0.009)	0.042 (0.010)	0.034 (0.009)

Effectiveness parameters at 1 year: height SDS, height velocity

- In the registry population, patients had a mean (SD) height SDS of 2.4 (1.0) and height velocity of 5.2 (2.4) cm/year at baseline. Both of these effectiveness variables improved after 1 year of treatment with NutropinAq® (Figures 3 and 4).

Figure 3. Changes in height SDS at 1 year – registry population

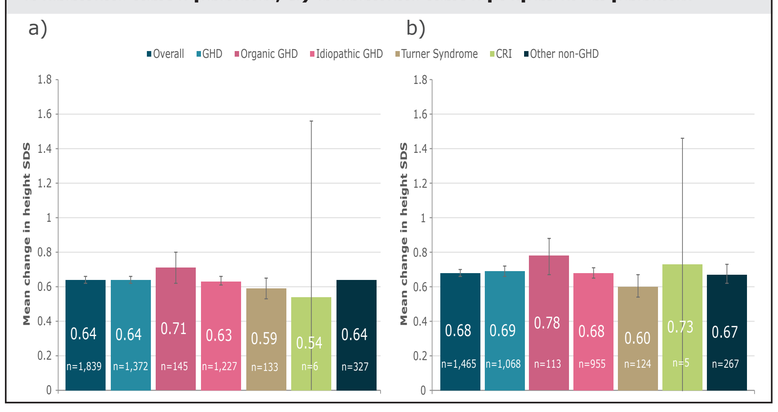
Figure 4. Height velocity at 1 year – registry population



Error bars represent 95% Confidence Intervals
GHD, growth hormone deficiency

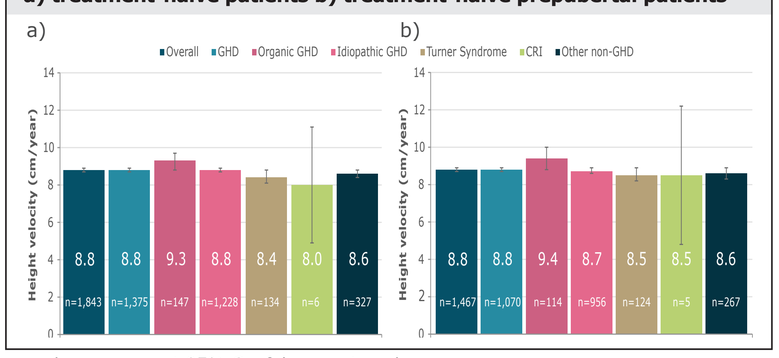
- Effectiveness parameters improved in all subgroups by disease aetiology, and were greatest in organic GHD (Figures 5 and 6).

Figure 5. Changes in height SDS at one year by aetiology: a) treatment-naïve patients; b) treatment-naïve prepubertal patients



Error bars represent 95% Confidence Intervals
GHD, growth hormone deficiency; CRI, chronic renal impairment

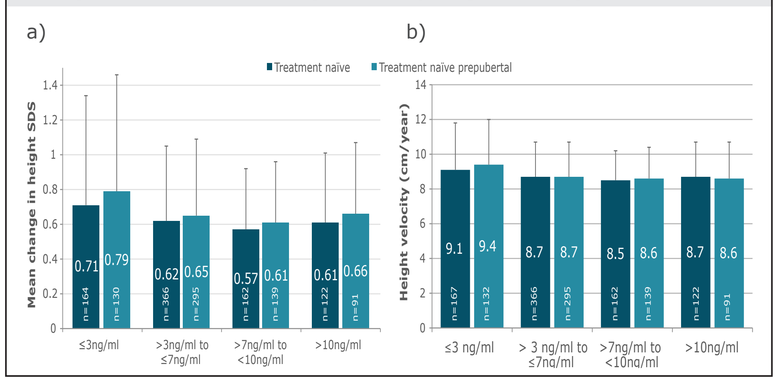
Figure 6. Height velocity at one year by aetiology: a) treatment-naïve patients b) treatment-naïve prepubertal patients



Error bars represent 95% Confidence Intervals
GHD, growth hormone deficiency; CRI, chronic renal impairment

- In both the treatment naïve and treatment naïve prepubertal populations of patients with GH deficiency, patients with a GH peak ≤3 ng/ml had higher change in height SDS at 1 year than patients with GH peak >3 ng/ml. A trend towards a higher height velocity in patients with a GH ≤3 ng/ml was also observed (Figure 7).
- ANOVA showed a significant difference between GH peak groups for change in height SDS in the treatment naïve (p=0.036) and treatment naïve prepubertal (p=0.011) populations, and in height velocity in the treatment naïve prepubertal population (p=0.005).

Figure 7: Effectiveness at one year by growth hormone peak in a) change from baseline in height SDS, b) height velocity



Error bars represent ± Standard Deviation

Safety

- A total of 610 patients (17.5%) in the safety population had at least one non-serious related TEAE.
  - Most frequently abnormal investigations (304 [8.7%]), including increased insulin-like growth factor (256 [7.3%]).
  - TEAEs leading to treatment discontinuation were reported in 61 patients (1.7%).
- 206 patients (5.9%) experienced at least one serious TEAE, and 30 of these TEAEs in 27 patients (0.8%) were considered to be related to NutropinAq®.
- Serious treatment-related TEAEs (≥3 events in any organ system) included:
  - Musculoskeletal and connective tissue disorder, 10 events in 9 patients (0.3%).
  - Neoplasm, 4 events (astrocytoma, cholesteatoma, craniopharyngioma, germ cell cancer) in 4 patients (0.1%). One patient with astrocytoma, and one with craniopharyngioma had prior histories of these neoplasms.
  - Nervous system disorder, 4 events in 4 patients (0.1%).
  - Eye disorders, 3 events in 3 patients (<0.1%).
  - Infections and infestations, 3 events in 3 patients (<0.1%).
- A neoplasm considered as a serious event occurred in 20 patients (0.6%).
  - 14 of these patients had a prior history of neoplasm.
- AEs leading to deaths occurred in seven patients during the study, all events were considered by the investigators as not related to study treatment.
  - During study period: streptococcal sepsis; infection; recurrent medulloblastoma.
  - After discontinuation of NutropinAq®: cardio-respiratory arrest; possible central respiratory dysfunction; haematemesis; dyspnoea.

Conclusions

- After 1 year of treatment with NutropinAq®, the mean height SDS as well as the mean height velocity improved in patients with growth failure whatever their prior treatment status and aetiology.
- This improvement was observed in treatment-naïve patients, in treatment-naïve prepubertal patients and in treatment-naïve GHD patients, despite a >1-year delay between diagnosis and start of treatment.
- These data confirm that the benefit-risk profile for NutropinAq® remains favourable in a real world setting, with no new safety concerns in children with growth failure treated within the recommended indication.

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Disclosures

RC has participated on advisory boards for and has received consulting fees from Ipsen, Pfizer, Novo Nordisk and Sandoz, has been a research investigator for Ipsen, Sandoz Merck and Pfizer, and a speaker for Lilly and Sandoz. JMB has received consulting fees from Ipsen, has been a research investigator for Ipsen, Lilly and Merck and a speaker for Lilly, Merck, Pfizer and Sandoz. CD has been a research investigator and speaker for Sandoz. DS has participated on advisory boards for Ipsen, Novo Nordisk, Merck, Sandoz and Pfizer, participated in corporate-sponsored research for Pfizer and Sandoz, has been a research investigator for Pfizer and speaker for Novo Nordisk and Merck. CS and VP are employees of Ipsen. MD has participated on advisory boards for Novo Nordisk and Ipsen and has received consulting fees from Ipsen, Sandoz and Pfizer.

Medical writing support

The authors thank Martin Gilmour PhD and Tim Latham BSc of ESP Bioscience, Crowthorne, UK for providing medical writing and editorial support, which was sponsored by Ipsen in accordance with Good Publication Practice guidelines.

Acknowledgements

The authors thank all patients involved in the study, as well as their caregivers, care team, investigators and research staff in participating institutions.

Presented at ESPE 2018 | Athens, Greece | 27–29 September 2018

This study was sponsored by Ipsen