International Cooperative Growth Study, NutropinAq® European Registry (iNCGS): countries specificities

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Introduction and objectives

- NutropinAq® [somatropin (rDNA origin) injection] is a human growth hormone (GH) indicated for the treatment of paediatric patients who have short stature or growth failure:
  - As a result of inadequate endogenous GH secretion
  - Associated with Turner syndrome (TS)
  - Associated with chronic renal insufficiency (CRI) up to the time of renal transplantation.[1]
- The iNCGS (International Cooperative Growth Study) is an international, multicentre, open-label, non-interventional post-marketing surveillance study in Europe.
  - The objective of the iNCGS is to collect long-term safety and effectiveness data on NutropinAq® during treatment of paediatric growth disorders for which GH is indicated.
- The iNCGS registry started at the end of 2005. It currently includes seven European countries with a European Marketing Authorisation for NutropinAq® (Germany, Austria, France, Spain, Italy, Romania and the UK).
- Here we report patient baseline characteristics and exposure to NutropinAq® for each participating country.

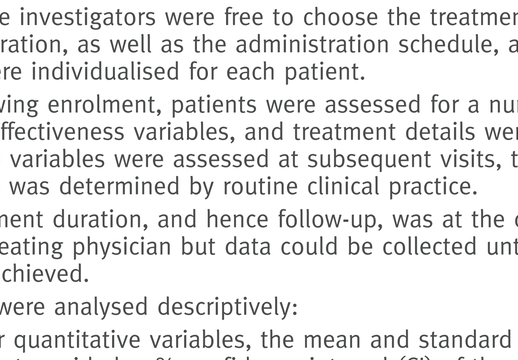
Methods

- The iNCGS registry is ongoing but data were collected for the current analysis from 3rd October 2005 to 31st December 2014.
  - Boys and girls with paediatric growth disorders (and who fulfilled the inclusion/exclusion criteria of the iNCGS registry), for which GH therapy has been decided by the physician, and who were initiating or already receiving therapy with NutropinAq® at the participating centres were included.
- This was a non-interventional study designed to document current clinical practice, thus:
  - The decision to prescribe NutropinAq® was taken before, and independently from, the decision to enrol the patient.
  - Prescribing of NutropinAq® was made in accordance with routine clinical practice.
  - The investigators were free to choose the treatment dose and duration, as well as the administration schedule, all of which were individualised for each patient.
- Following enrolment, patients were assessed for a number of safety and effectiveness variables, and treatment details were recorded. These variables were assessed at subsequent visits, the timing of which was determined by routine clinical practice.
- Treatment duration, and hence follow-up, was at the discretion of the treating physician but data could be collected until adult height was achieved.
- Data were analysed descriptively:
  - For quantitative variables, the mean and standard deviation (SD), the two-sided 95% confidence interval (CI) of the mean, the median, quartiles Q1 and Q3, the minimum and the maximum were recorded.
  - For qualitative variables, the frequency, percentage of each modality, and the two-sided 95% CI were calculated.

Results

- As of 31st December 2014, 3250 patients were screened at 160 participating centres.
- 249 patients were excluded, leaving an enrolled population of 3001 patients from 151 centres in seven countries (**Figure 1**).
- Patient characteristics at first dose of NutropinAq® are shown in (**Table 1**).

Figure 1. Enrolled patients by country



*Austria had one site that was pooled with Germany

Diagnosis and NutropinAq® treatment initiation

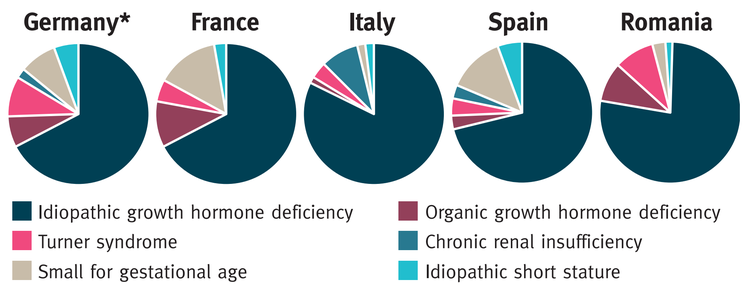
- Across all countries, the most frequent presentation was idiopathic growth hormone deficiency (IGHD) (**Figure 2**).

Table 1. Patient characteristics at first dose of NutropinAq® – enrolled population

	IGHD	Organic GHD	TS	CRI	SGA	ISS
Gender						
n	1948	205	194	58	287	120
Males, n(%)	1268 (65.1)	133 (64.9)	1 (0.5)*	40 (69.0)	158 (55.1)	77 (64.2)
Females, n(%)	680 (34.9)	72 (35.1)	193 (99.5)	18 (31.0)	129 (44.9)	43 (35.8)
Age, years						
n	1948	205	193	58	286	120
Mean (SD)	9.4 (3.6)	9.0 (4.0)	8.1 (3.7)	8.3 (4.8)	7.9 (3.3)	10.1 (3.6)
Bone age, years						
n	313	36	30	2	56	14
Mean (SD)	8.1 (3.6)	8.2 (4.2)	8.2 (3.7)	4.5 (3.5)	6.2 (3.4)	9.2 (3.5)
Height SDS						
n	1937	205	192	26	285	119
Mean (SD)	-2.4 (1.0)	-2.4 (1.3)	-2.5 (1.0)	-2.6 (1.3)	-2.6 (1.0)	-2.7 (1.2)
Height velocity, cm/year						
n	507	61	38	1	75	24
Mean (SD)	5.4 (2.5)	5.1 (2.4)	5.1 (2.2)	4.3	6.3 (3.5)	6.5 (5.1)

CRI, chronic renal insufficiency; GHD, growth hormone deficiency; IGHD, idiopathic growth hormone deficiency; ISS, idiopathic short stature; SD, standard deviation; SDS, standard deviation score; SGA, small for gestational age; TS, Turner syndrome. n: number of patients with available data.
* Aberrant data; TS is a genetic disorder that only affects females
Note data excludes n=189 (6.3%) of patients with "other" aetiologies which include central nervous system (CNS) damage (n=56), cancer (n=27), CNS cancer (n=62), chronic disease (n=19), dysmorphic syndrome (n=10), genetic cause (n=13), midline defect (n=2), multiple pituitary hormone deficit (n=10), Noonan syndrome (n=15), other (n=1), other hormonal syndromes (n=25), pituitary disease (n=32), and Russel-Silver syndrome (n=8). Patients could have more than one aetiology.

Figure 2. Disease aetiologies by country



*Austria had one site that was pooled with Germany. The data for UK (n=37 [1.2%]), were not taken into account for the analysis per country due to small sample size. The data for "other" aetiologies (n=189 [6.3%]) were also not included in this analysis.

- IGHD and idiopathic short stature (ISS) were diagnosed at an older age than TS, CRI and small for gestational age (SGA) (**Table 2**).
- Height at diagnosis did not differ greatly across the different aetiologies.
- The difference between age at diagnosis to age at first treatment with NutropinAq® indicated the time from diagnosis to treatment initiation and ranged from several months (IGHD, organic GHD and ISS) to several years (TS, CRI and SGA) (**Table 2**).
- Except in cases of TS, NutropinAq® was initiated at a slightly older age in France and Italy (mean [SD]: 10.0 [3.6]) compared with other countries (mean [SD]: 8.7 [3.6]) (**Table 2**).

Table 2. Age at diagnosis and at first NutropinAq® treatment

	IGHD	Organic GHD	TS	CRI	SGA	ISS
Germany - n	812	89	109/108	25/26	106	66
Age at diagnosis, years, Mean (SD)	8.7 (3.5)	8.7 (3.9)	5.7 (4.8)	4.2 (4.5)	5.2 (4.3)	9.2 (4.1)
Age at first NutropinAq® intake, years, Mean (SD)	8.8 (3.5)	9.4 (4.0)	8.2 (3.5)	7.1 (5.0)	7.6 (2.9)	9.7 (3.8)
France - n	573	85	41	3	125/124	24
Age at diagnosis, years, Mean (SD)	9.7 (3.8)	7.9 (4.1)	3.7 (4.5)	8.0 (6.9)	3.5 (4.6)	9.8 (3.2)
Age at first NutropinAq® intake, years, Mean (SD)	10.4 (3.6)	9.1 (3.8)	7.4 (4.1)	12.0 (4.4)	8.6 (3.5)	11.0 (2.9)
Italy - n	172	2	9	18	4	4
Age at diagnosis, years, Mean (SD)	10.0 (3.1)	7.5 (4.2)	4.6 (4.4)	4.8 (5.1)	12.6 (2.1)	12.1 (2.0)
Age at first NutropinAq® intake, years, Mean (SD)	10.1 (3.1)	8.0 (5.7)	8.4 (4.6)	9.9 (4.7)	12.3 (2.2)	11.8 (2.1)
Spain - n	261	11	15	10	47	23
Age at diagnosis, years, Mean (SD)	8.6 (3.6)	4.8 (3.9)	8.1 (4.3)	7.2 (4.0)	3.9 (3.8)	10.1 (3.5)
Age at first NutropinAq® intake, years, Mean (SD)	9.0 (3.7)	7.4 (4.5)	9.3 (3.6)	7.7 (3.7)	6.9 (2.9)	10.5 (3.5)
Romania - n	123	15	14	0	5	1
Age at diagnosis, years, Mean (SD)	8.1 (3.2)	7.0 (3.4)	7.6 (5.2)		5.7 (2.4)	7.9
Age at first NutropinAq® intake, years, Mean (SD)	8.1 (3.3)	6.7 (3.3)	9.4 (2.8)		5.4 (2.4)	12.0

CRI, chronic renal insufficiency; GHD, growth hormone deficiency; IGHD, idiopathic growth hormone deficiency; ISS, idiopathic short stature; SD, standard deviation; SGA, small for gestational age; TS, Turner syndrome. n: number of patients with available data. Where the n number is given as a fraction, the numerator applies to the age at diagnosis; the denominator applies to the age at first NutropinAq® intake.

Height standard deviation score

- Compared with the other countries in this study, in Germany and Romania there was a tendency for patients to have a lower height standard deviation score (SDS) (**Table 3**).
- Patients in France tended to have the greatest height SDS across most aetiologies.

Table 3. Height standard deviation score at first NutropinAq® treatment

	IGHD	Organic GHD	TS	CRI	SGA	ISS
Germany - n	809	89	107	8	105	66
Mean (SD)	-2.7 (0.9)	-2.8 (1.1)	-2.9 (0.8)	-2.6 (1.4)	-2.9 (1.2)	-3.0 (1.2)
France - n	571	85	41	2	124	24
Mean (SD)	-2.0 (0.8)	-1.7 (1.2)	-2.0 (1.1)	-2.6 (0.3)	-2.3 (0.9)	-2.6 (0.9)
Italy - n	170	2	9	5	4	4
Mean (SD)	-2.3 (0.9)	-3.2 (1.7)	-2.2 (0.8)	-3.8 (1.7)	-2.7 (0.5)	-2.5 (1.0)
Spain - n	258	11	15	10	47	22
Mean (SD)	-2.1 (1.0)	-2.7 (2.0)	-2.3 (1.4)	-2.2 (0.9)	-2.4 (0.9)	-1.8 (1.4)
Romania - n	122	15	14	0	5	1
Mean (SD)	-2.6 (1.0)	-3.1 (1.3)	-2.5 (1.0)		-3.1 (1.0)	-0.6

CRI, chronic renal insufficiency; GHD, growth hormone deficiency; IGHD, idiopathic growth hormone deficiency; ISS, idiopathic short stature; SD, standard deviation; SGA, small for gestational age; TS, Turner syndrome. n: number of patients with available data

NutropinAq® treatment

- In all countries, the mean treatment duration per patient tended to be between approximately 25 and 40 months (**Table 4**).
- Prescribed doses of NutropinAq® tended to be highest in France and lowest in Germany (**Table 4**).
  - IGHD patients had the same mean (SD) dose of 30 (5) µg/kg/day in Germany and Italy, and a slightly higher dose in France: 38 (8) µg/kg/day.
- Dose adjustments over time were more frequent in Germany, France and Italy compared with the other countries in this study

Table 4. NutropinAq® dose and treatment duration

	IGHD	Organic GHD	TS	CRI	SGA	ISS
Germany - n	811/812/812	89	109	8/24/26	105/106/106	66
Initial dose, µg/kg/day Mean (SD)	28 (6)	27 (6)	42 (8)	37 (12)	33 (6)	28 (5)
Average dose, µg/kg/day Mean (SD)	30 (5)	29 (5)	41 (7)	42 (12)	34 (6)	29 (5)
Treatment duration, months Mean (SD)	40.6 (25.6)	31.1 (27.7)	41.8 (29.0)	25.8 (19.1)	33.2 (26.2)	31.4 (22.8)
France - n	572/573/573	84/85/85	41	2/3/3	125	24
Initial dose, µg/kg/day Mean (SD)	37(7)	35 (7)	45 (9)	48 (3)	41 (10)	40 (8)
Average dose, µg/kg/day Mean (SD)	38 (8)	36 (8)	43 (7)	42 (3)	42 (9)	43 (10)
Treatment duration, months Mean (SD)	30.6 (21.3)	38.2 (27.7)	36.9 (25.1)	45.8 (29.4)	30.6 (19.5)	31.7 (21.0)
Italy - n	172	1/1/2	9	5/13/18	4	4
Initial dose, µg/kg/day Mean (SD)	31 (6)	41	39 (7)	46 (2)	31 (6)	32 (1)
Average dose, µg/kg/day Mean (SD)	30 (5)	37	35 (8)	44 (6)	34 (6)	28 (2)
Treatment duration, months Mean (SD)	37.3 (21.0)	28.1 (39.7)	38.9 (21.4)	17.4 (15.6)	34.0 (16.3)	29.4 (6.1)
Spain - n	259/261/261	11	15	10	47	23
Initial dose, µg/kg/day Mean (SD)	31 (5)	30 (4)	43 (6)	45 (22)	35 (7)	37 (7)
Average dose, µg/kg/day Mean (SD)	31 (5)	31 (3)	41 (6)	41 (15)	34 (7)	37 (6)
Treatment duration, months Mean (SD)	24.4 (19.3)	26.1 (22.4)	36.7 (20.2)	35.4 (26.1)	25.0 (22.5)	15.6 (15.0)
Romania - n	123	15	14	0	5	1
Initial dose, µg/kg/day Mean (SD)	30 (6)	31 (5)	41 (9)		37 (7)	13
Average dose, µg/kg/day Mean (SD)	31 (6)	32 (5)	43 (8)		36 (9)	28
Treatment duration, months Mean (SD)	34.3 (23.1)	26.6 (22.3)	31.3 (21.3)		17.1 (12.8)	9.1

CRI, chronic renal insufficiency; GHD, growth hormone deficiency; IGHD, idiopathic growth hormone deficiency; ISS, idiopathic short stature; SD, standard deviation; SGA, small for gestational age; TS, Turner syndrome n: number of patients with available data. Where multiple n numbers are given, the first applies to the initial dose; the second to the average dose; and the third to the treatment duration

Conclusions

- The present study shows IGHD as the main aetiology for which NutropinAq® treatment is received among the European countries included in this analysis.
- The prescribed doses of NutropinAq® tended to be highest in France and lowest in Germany across most aetiologies.
- There were no major differences in baseline characteristics between countries except patients appeared to have more severe growth retardation in Germany (lowest height SDS).
- Although mean age at diagnosis was as expected, mean age at treatment initiation was different between the aetiologies, reflecting differences in the delay between diagnosis and treatment initiation.

Reference

1. Ipsen Ltd. NutropinAq 10 mg/2 ml (30 IU) solution for injection. Summary of product characteristics. Available at: www.medicines.org.uk/emc/medicine/14244. Last updated 8 July 2013.

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Nick Brown

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