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Final results of NordiNet® International Outcome Study: key outcomes in paediatric patients

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Objective

To describe and report, by indication, patient distribution, key clinical effectiveness outcomes and safety data in children with growth hormone deficiency (GHD), born small for gestational age (SGA) or with Turner syndrome (TS), chronic renal disease (CRD), idiopathic short stature (ISS), Noonan syndrome (NS) or Prader–Willi syndrome (PWS) enrolled in the NordiNet® International Outcome Study (IOS).

Introduction

- Norditropin® (somatropin; Novo Nordisk A/S, Denmark) is indicated in many countries for the treatment of short stature in paediatric patients with GHD, born SGA or TS, with additional indications of CRD, ISS, NS or PWS in a few select countries.
- The collection of real-world data is considered important to evaluate and characterise real-life effectiveness and safety in a large patient population over a long follow-up period.
- NordiNet® IOS was a non-interventional study (2006–2016) that assessed the effectiveness and safety of Norditropin® as prescribed by treating physicians in a clinical setting.

Methods

- The design and methodology of NordiNet® IOS have been published previously.[1]
- Patient information was entered using a web-based system. In total, 17,995 paediatric patients were enrolled:
  - 17,711 included in the full analysis set (FAS: all patients exposed to growth hormone [GH] therapy that was initiated before age 18 years; used for safety evaluation).
  - 11,967 included in the effectiveness analysis set (EAS: patients <18 years who were GH-naïve at baseline visit, and had valid baseline height, age and dosing information).
- Patients with a syndrome with co-existing GHD were classified by the syndrome. If they were both born SGA and had GHD, they were classified as GHD.
- Effectiveness outcomes included:
  - Change from baseline in height standard deviation score (ΔHSDS).
  - Proportion (%) of patients with HSDS >–2.
  - Near-adult height standard deviation score (NAH SDS) (NAH: height at age >16 years [boys]/>15 years [girls] *and* height velocity <2 cm/year *or* height at >18 years).
- Safety events were reported as serious adverse reactions (SARs) and non-serious adverse reactions (NSARs). Serious adverse events (SAEs) judged unrelated to GH therapy were also reported.
  - Adverse reactions (NSARs/SARs) were classified by double causality assessment: if either the reporter or Novo Nordisk considered the relationship between a safety event and GH treatment as possible or probable, the event was classified as an adverse reaction.

Results

Patient disposition

- The demographics and characteristics of GH-naïve paediatric patients, by indication, are shown in **Table 1**.
- At treatment initiation:
  - Patients with PWS were the youngest (mean 4.7 years), followed by patients born SGA (mean 7.9 years), compared with the other indications (range: mean 8.3–10.1 years).
  - Patients born SGA were shortest (mean HSDS at baseline: –2.97) compared with the other indications (range: –2.83 to –1.94).
  - The mean baseline GH dose was lower for PWS (0.027 mg/kg/day) compared with the other indications (range: 0.031–0.043 mg/kg/day).
  - The mean duration of treatment follow-up was longest for patients with TS (4.3 years) compared with the other indications (range: 2.8–4.0 years).

Table 1 ♦ Demographics and characteristics of paediatric patients

Indication	*GHD*	*SGA*	*TS*	*CRD*	*ISS*	*NS*	*PWS*
FAS/ EAS, n	9967/ 7141	4274/ 3200	1374/ 936	290/ 200	485/ 317	154/ 106	132/ 67
Female, n (%)	2460 (34)	1463 (46)	936 (100)	75 (38)	136 (43)	30 (28)	28 (42)
Age at baseline, years	9.1 (4.1)	7.9 (3.4)	8.7 (3.8)	8.3 (4.4)	10.1 (3.5)	8.9 (3.8)	4.7 (5.0)
HSDS* at baseline	–2.55 (1.10)	–2.97 (0.91)	–2.66 (0.93)	–2.74 (1.17)	–2.82 (0.99)	–2.83 (1.13)	–1.94 (1.48)
IGF-I SDS† at baseline	–1.80 (1.53)	–0.76 (1.45)	–0.91 (1.44)	–0.74 (1.91)	–1.32 (1.63)	–1.49 (1.15)	–0.99 (1.70)
GH dose at baseline, mg/kg/day	0.031 (0.009)	0.037 (0.011)	0.043 (0.012)	0.039 (0.013)	0.033 (0.014)	0.037 (0.010)	0.027 (0.011)
GH dose during treatment, mg/kg/day	0.032 (0.008)	0.038 (0.009)	0.044 (0.009)	0.041 (0.011)	0.038 (0.014)	0.040 (0.009)	0.026 (0.008)
Treatment follow-up, years	3.8 (2.9)	3.6 (2.8)	4.3 (2.8)	2.8 (2.6)	3.3 (2.4)	3.4 (2.9)	4.0 (3.5)

Data are mean (standard deviation) for the EAS unless otherwise specified.*HSDS was calculated using age- and gender-specific national reference values. †Definition as per Brabant G *et al. Horm Res* 2003;60:53–60. CRD, chronic renal disease; EAS, effectiveness analysis set; FAS, full analysis set; GH, growth hormone; GHD, growth hormone deficiency; HSDS, height standard deviation score; IGF-I SDS, insulin growth factor-I standard deviation score; ISS, idiopathic short stature; NS, Noonan syndrome; PWS, Prader–Willi syndrome; SGA, small for gestational age; TS, Turner syndrome.

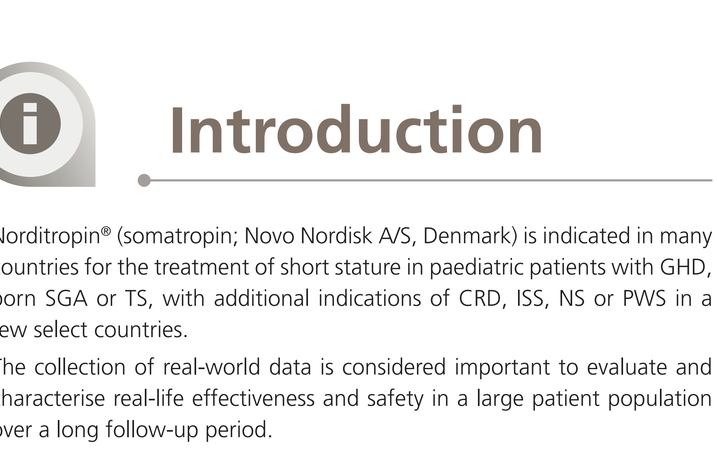
Effectiveness

- For every indication, the ΔHSDS from baseline increased with treatment duration, with the greatest yearly gains achieved in year 1 (**Figure 1**).
  - For TS, ΔHSDS was lower at 10 years than at 5 years. However, only a smaller subset of patients had 10 years of treatment, limiting the ability to draw definitive conclusions.[2,3]
- For every indication (with the exception of ISS), the proportion of patients with HSDS >–2 increased annually during GH treatment, until 3 years of treatment (**Figure 2**).
- NAH SDS are reported for GHD, SGA and TS (for other indications, only a small number of patients achieved NAH during the observation period).
  - The mean (standard deviation [SD]) NAH SDS was: GHD, –1.16 (1.22) (n=943); SGA, –1.97 (0.95) (n=190); TS, –2.08 (0.84) (n=189).
  - The mean (SD) change from baseline HSDS to NAH SDS was: GHD, 1.42 (1.19); SGA, 1.11 (0.81); TS, 0.83 (0.87).

Safety

- For each indication, the safety profile was consistent with data in the approved labelling for Norditropin®.
- No new safety signals were observed.
  - Overall, a total 421 adverse reactions were reported: 288 NSARs in 249 patients; 133 SARs in 90 patients. In addition, there were 352 SAEs not related to GH therapy in 224 patients.
- There were 11 deaths among paediatric patients: four with GHD, one with SGA, two with CRD, one with PWS and three with other/unspecified diagnoses.
  - Of these deaths, nine were considered unlikely to be related to GH treatment.
  - The deaths of two patients, following events assessed by the reporters as possibly related to GH treatment, are briefly described below:
    - A 16-year-old male in the GHD group, treated with GH from Sep 2003 to Aug 2011 (age at GH treatment start: 7.7 years). Medical history included: suprasellar cyst, hydrocephalus, short stature, congenital neurocutaneous melanosis and known hydrocephalus. In Aug 2011, he was increasingly tired, shaky and complained about abdominal pain; GH treatment was withdrawn. In Aug 2012 (1 year after the last GH injection), the patient was diagnosed with leptomeningeal melanocytosis and neurological symptoms due to leptomeningeal tumour. The patient died in May 2013.
    - A 20-year-old male, treated with GH due to GHD and CRD from Apr 2006 to an unknown date (age at GH treatment start age: 11.2 years). Medical history included: panhypopituitarism due to empty sella syndrome (since Jun 2006), GHD (since Apr 2006), perinatal asphyxia, CRD (since Jan 1995) with peritoneal dialysis (from Apr 2012) and epilepsy. In Jan 2015, he was admitted to the emergency department with reduced consciousness, with subsequent collapse and shock requiring endotracheal intubation. The patient died in Feb 2015. Adverse events near time of death were: brain oedema, cerebral haemorrhage, cerebral venous thrombosis, depressed level of consciousness, subdural haematoma and transverse sinus thrombosis.

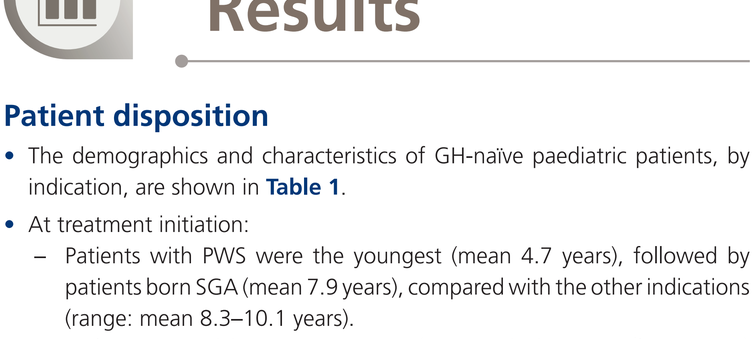
Figure 1 ♦ ΔHSDS from baseline in GH-naïve paediatric patients during GH treatment by indication



	GHD	SGA	TS	CRD	ISS	NS	PWS
Year 1	5173	2231	725	136	245	70	43
Year 2	4403	1882	642	94	190	56	30
Year 5	1916	897	344	31	65	25	17
Year 10	273	96	47	7	9	4	6

Data are mean (standard deviation) for the EAS. Table shows number of patients. When interpreting the results, note that for some indications, patient numbers were very low at 10 years.
CRD, chronic renal disease; EAS, effectiveness analysis set; GH, growth hormone; GHD, growth hormone deficiency; ISS, idiopathic short stature; NS, Noonan syndrome; PWS, Prader–Willi syndrome; SDS, standard deviation score; SGA, small for gestational age; TS, Turner syndrome; ΔHSDS, change in height standard deviation score.

Figure 2 ♦ Proportion (%) of GH-naïve paediatric patients with height SDS >–2 during GH treatment by indication



	GHD	SGA	TS	CRD	ISS	NS	PWS
Baseline	7141	3200	936	200	317	106	67
Year 1	5173	2231	725	136	245	70	43
Year 2	4403	1882	642	94	190	56	30
Year 3	3574	1538	540	69	139	40	28

Data are for the EAS. Table shows number of patients.
CRD, chronic renal disease; EAS, effectiveness analysis set; GH, growth hormone; GHD, growth hormone deficiency; ISS, idiopathic short stature; NS, Noonan syndrome; PWS, Prader–Willi syndrome; SGA, small for gestational age; TS, Turner syndrome.

Conclusions

- Real-world data from NordiNet® IOS demonstrated that treatment of paediatric patients with Norditropin® was associated with increased HSDS and an increased proportion of patients with height within the normal range.
- No new safety signals were revealed during the observation period.

References

1. Höybye C *et al. Clin Epidemiol* 2013;5:119–27; 2. van Pareren Y *et al. J Clin Endocrinol Metab* 2003;88:1119–25; 3. Wasniewska M *et al. Eur J Endocrinol* 2013;169:439–43.

Conflict of interest disclosure

MP, JB and TRR consulted for, and received honoraria, travel grants and unrestricted research grants from, Novo Nordisk. AP is an employee of Novo Nordisk Health Care AG. BTP is an employee of, and own stocks/shares in, Novo Nordisk A/S. LS has consulted for Ascendis, Novo Nordisk, Pfizer, Merck and Sandoz.

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