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Clinical Research Article

Comparative Outcomes of GH Treatment in Pediatric Idiopathic Short Stature and GH Deficiency

Moshe Phillip,[1,2] M. Jennifer Abuzzahab,[3] Alberto Pietropoli,[4] Jean-Marc Ferran,[5] Michael Højby,[6] Nicky Kelepouris,[7] Primož Kotnik,[8,9] Michel Polak,[10] and Lars Sävendahl[11]

[1]Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petah Tikva 4920235, Israel
[2]Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv 6997801, Israel
[3]Diabetes and Endocrine Center, Children's Minnesota, Saint Paul, MN 55102, USA
[4]Global Medical Affairs, Novo Nordisk Health Care AG Zurich 8058, Switzerland
[5]Data Science, Qualiance ApS, Copenhagen 1663, Denmark
[6]Clinical Drug Development, Novo Nordisk A/S, Søborg 2860, Denmark
[7]US Medical Affairs, Rare Endocrine Disorders, Novo Nordisk Inc, Plainsboro, NJ 08536, USA
[8]Department of Pediatrics, Medical Faculty, University of Ljubljana, Ljubljana 1000, Slovenia
[9]Department of Pediatric Endocrinology, Diabetes and Metabolism, University Children's Hospital Ljubljana, University Medical Center, Ljubljana 1000, Slovenia
[10]Pediatric Endocrinology, Gynecology and Diabetology, Hôpital Universitaire Necker Enfants Malades, Assistance Publique-Hôpitaux de Paris Université Paris Cité, INSERM U1016, Institut IMAGINE, Centre de Référence des Maladies Endocriniennes Rares de la Croissance et du Développement, Paris 75015, France
[11]Pediatric Endocrinology, Karolinska University Hospital and Department of Women's and Children's Health, Karolinska Institutet Solna 171 77, Sweden

Correspondence: Lars Sävendahl, MD, Pediatric Endocrinology, Karolinska University Hospital and Department of Women's and Children's Health, Karolinska Institutet, Biomedicum, kvarter A4 Solna 171 77, Sweden. Email: lars.savendahl@ki.se.
Authors who are members of the Endocrine Society: M. Jennifer Abuzzahab, Michael Højby.

Abstract

Context: GH treatment in children with idiopathic short stature (ISS) can be controversial, and analyses comparing responses to children with GH deficiency (GHD) are limited.

Objective: To compare the effectiveness and safety of GH treatment in children with ISS and GHD, including those reaching near adult height (NAH).

Methods: This post hoc analysis of the NordiNet International Outcome Study (2006-2016) and the American Norditropin Studies: Web-Enabled Research Program (2002-2016) included children with ISS or GHD who initiated treatment aged <18 years. The safety analysis set had birthdate and GH exposure information. The effectiveness analysis set was GH-naïve with valid baseline information. GH exposure, effectiveness, and safety outcomes were analyzed annually for ≤10 years.

Results: The safety analysis set included 3816 children with ISS and 22 858 with GHD. The effectiveness analysis set comprised 18 405 children (ISS: 2684; GHD: 15 721), 1856 of whom reached NAH (ISS: 230; GHD: 1626). Average dose of GH was higher for children with ISS vs children with GHD but mean duration of treatment was shorter. At NAH, height SD score (mean [SD]) was −1.21 (1.09) and −0.90 (1.20) for children with ISS and GHD, respectively, whereas change in height SD score (mean [SD]) from baseline to 10 years was 1.21 (0.86) and 1.45 (1.09). Incidence of adverse reactions was similar across indications, with no new safety signals.

Conclusion: GH treatment over 5 to 10 years effectively increased height in children with ISS and children with GHD, including those who reached NAH, with a favorable benefit-risk profile.

Key Words: idiopathic short stature, growth hormone deficiency, growth hormone response, growth hormone safety, somatropin

Abbreviations: ΔHSDS, change in height SD score; ANSWER, American Norditropin Studies: Web-Enabled Research; AR, adverse reaction; BA/CA, bone age/chronological age ratio; EAS, effectiveness analysis set; GHD, GH deficiency; HSDS, height SD score; HVSDS, height velocity SD score; IR, incidence rate; IRR, incidence rate ratio; ISS, idiopathic short stature; KIGS, Kabi/Pfizer International Growth Database; NAH, near adult height; NSAR, nonserious adverse reaction; PYE, patient-years of exposure; SAR, serious adverse reaction; SAS, safety analysis set; SDS, SD score.

Idiopathic short stature (ISS) is defined as short stature of unknown cause [1, 2]. A diagnosis of ISS is given when height is >2 SD scores (SDS) below the mean for a given age, sex, and population, after excluding underlying medical conditions or genetic differences that could contribute to short stature or slower growth [1, 3-5]. ISS accounts for a heterogeneous group of children who were normal size for gestational age at birth and have no evidence of systemic, endocrine, nutritional, or chromosomal abnormalities [4, 5]. Specifically, these children do not have a deficiency of GH [2].

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Evidence suggests that children with ISS can achieve close to average adult height following GH treatment [6-8]. According to US Food and Drug Administration guidelines, US children must have a height SDS (HSDS) ≥ 2.25 below the mean for treatment consideration [9]. A meta-analysis of results from 21 studies of children with ISS indicated that GH treatment can improve short-term linear growth and increase adult height compared with no GH treatment [7]. Furthermore, a systematic review of 14 randomized trials concluded that GH treatment in children with ISS can reduce the deficit in height as adults [8]. Although there is limited evidence from clinical trials assessing whether height-promoting interventions in ISS can potentially reduce the psychosocial burden [10], observations in other trials report positive changes in different measures related to quality of life [10-14]. Despite that, use of GH in children with ISS remains controversial because diagnosis is descriptive, and treatment response is variable because of the heterogeneity of underlying causes [15-17]. Furthermore, in some cases identified initially as ISS, a partial resistance to GH may be present because of acquired or genetic causes [11]. Use of GH in children with ISS requires accurate determination of the underlying abnormality in the GH/IGF axis and the predicted adult height and bone age of the patient [16].

Of GH-treated children, most data focus on GH deficiency (GHD), and the consensus is that GH treatment is effective in aiding children with GHD to achieve both short-term growth and adult height [18-20]. Nevertheless, there is disagreement as to whether patients with GHD respond equally or more favorably to GH than patients with ISS [21-23]. In particular, few studies have compared effectiveness and safety of long-term GH treatment in children diagnosed with GHD and ISS [24]. Although Norditropin is approved for treatment of children with GHD in Europe, the United States, and Japan, it is only approved to treat ISS in the United States and South Korea [25-28].

The aim of this analysis was to compare effectiveness and safety of treatment with Norditropin (somatropin), a daily recombinant GH, in children with ISS and GHD, including those who reached near adult height (NAH).

Materials and Methods

Study Design

This post hoc analysis used data from 2 complementary, noninterventional, observational studies, NordiNet International Outcome Study (NordiNet IOS; NCT00960128; 2006-2016) and the American Norditropin Studies: Web-Enabled Research (ANSWER) Program (NCT01009905; 2002-2016). The design and methodology of both studies have been previously reported [29, 30].

NordiNet IOS and the ANSWER Program were approved by the relevant ethics committees and conducted with informed consent from parents or legal guardians of pediatric patients. Pseudonymization of data was performed in accordance with the Declaration of Helsinki, regulatory requirements, and Guidelines for Good Pharmacoepidemiology Practices.

Study Population

Pediatric patients enrolled in NordiNet IOS or ANSWER, treated with Norditropin and diagnosed with ISS or GHD, as reported by their physician, were included in this analysis (Fig. 1). The safety analysis set (SAS) included patients with birthdate information and previous GH exposure, regardless of GH brand. Children in the SAS initiated Norditropin before 18 years of age and were treated until epiphyseal closure. Children who initiated any GH treatment before 18 years of age and Norditropin after the age of 18 years were also included, provided that Norditropin treatment did not continue after 20 years of age or after epiphyseal closure.

Effectiveness was analyzed in children in the SAS who had valid baseline height, age, and dosing information and were treatment-naïve at the baseline visit (effectiveness analysis set [EAS]). A further analysis set included children in the EAS who achieved NAH, defined by height velocity <2 cm/year during the last year and chronological age >15 years for females, >16 years for males, or when chronological age was >18 years.

Study Outcomes

The following effectiveness variables were calculated at baseline and annually, for up to 10 years of GH treatment in the EAS: GH exposure (mg/kg/day), height velocity SDS (HVSDS), HSDS, change in HSDS (ΔHSDS), IGF-I SDS, and bone age/chronological age ratio (BA/CA). IGF-I measurements were derived from local assays. Safety data were based on physicians' reporting of adverse events. Adverse reactions (ARs; adverse events deemed related to the product) were subdivided into serious adverse reactions (SARs) and nonserious adverse reactions (NSARs).

Statistical Analyses

Effectiveness outcomes were summarized using descriptive analyses (mean, SD, and p10/p90). Safety data were presented as incidence rates (IR) per 1000 patient-years of exposure (PYE) and as incidence rate ratios (IRR). Primary analyses included children grouped into ISS or GHD subgroups based on diagnosis reported by their physician.

Considering the large sample size included in this analysis and the difference in sample size between the 2 groups, *t*-tests were conducted to assess the statistical differences in means, and Cohen's d statistic was calculated to quantify the effect sizes [31, 32]. This was conducted on baseline characteristics with a mean difference and a clinical significance that can have an impact on the outcome, as multiple comparisons may increase the risk of type I error (false positive). These variables were age at treatment start, HSDS for bone age, and IGF-I SDS. For children who reached NAH, the statistical difference in HSDS was calculated.

Sensitivity analyses were carried out to validate the primary effectiveness data. As diagnoses of ISS and GHD are dependent on local guidance and evolve over time, sensitivity analyses were conducted using GH peak data with cutoffs at ≥7 ng/mL and <7 ng/mL, and at ≥10 ng/mL and <10 ng/mL to define ISS and GHD, respectively [33-35]. Further sensitivity analyses considered mean age of treatment initiation and mean duration of treatment.

Results

Study Population

The SAS included 26 674 children, of whom 3816 had a diagnosis of ISS and 22 858 had a diagnosis of GHD, as reported by their physician (Fig. 1). Of these children, 18 405 were included in

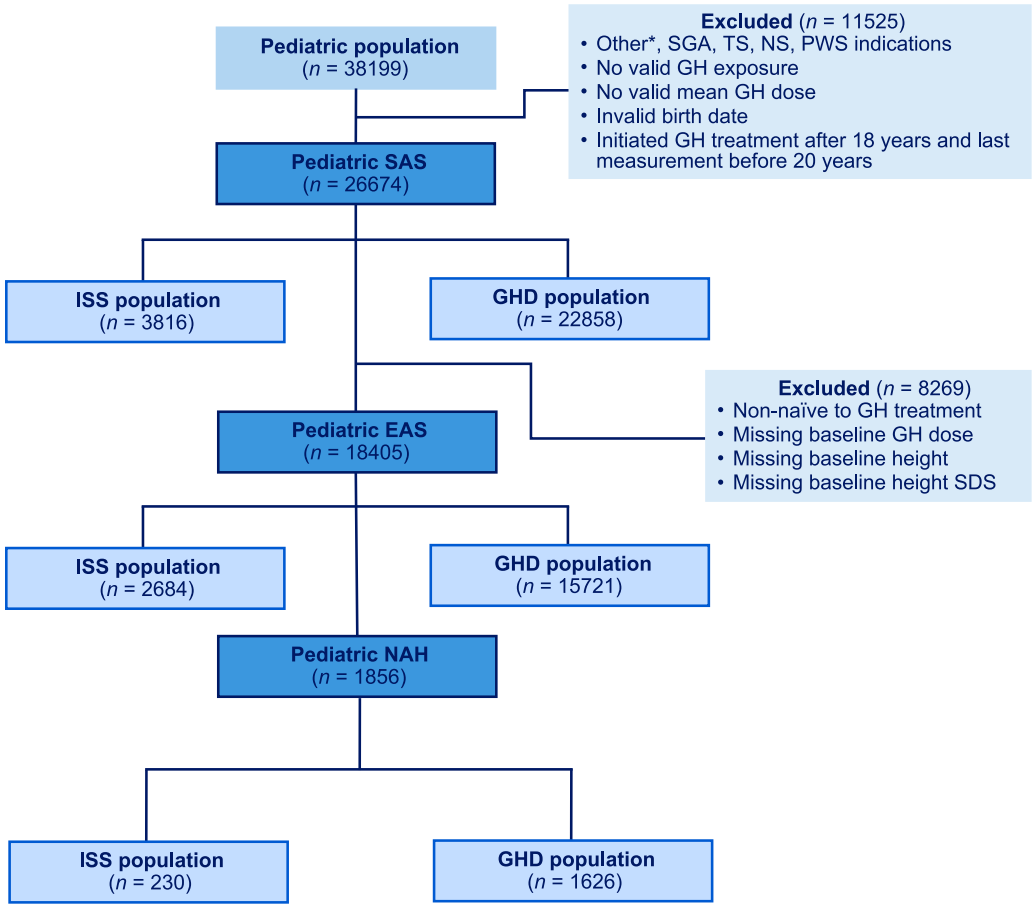

Figure 1. Disposition of patients with ISS and GHD included in the analyses.

Abbreviations: CRD, chronic renal disease; EAS, effectiveness analysis set; GHD, GH deficiency; ISS, idiopathic short stature; NAH, near adult height; NS, Noonan syndrome; PWS, Prader-Willi syndrome; SAS, safety analysis set; SDS, SD score; SGA, small for gestational age; TS, Turner syndrome. *Pediatric patients with a diagnosis other than GHD, SGA, TS, CRD, ISS, NS, and PWS.

the EAS (ISS: 2684; GHD: 15 721) and 1856 in the NAH population (ISS: 230; GHD: 1626). Of the total GHD diagnoses in the EAS, 12 490 (79.5%) and 3231 (20.6%) were deemed nonidiopathic GHD and idiopathic GHD, respectively. Baseline clinical characteristics of the EAS are presented in Table 1 and Table S1 [36]. The ISS group of the EAS started GH treatment at a mean (SD) age of 11.2 (3.2) years, which was later than the GHD group (10.2 [4.0] years). Mean (SD) difference in age at treatment start between the 2 groups was 1.03 (3.87, $P < .0001$, Cohen's d = 0.26). Mean (SD) difference in HSDS for bone age between the 2 groups was −0.52 (1.47, $P < .0001$, Cohen's d = −0.35). Mean (SD) difference in IGF-I SDS between the 2 groups was 0.48 (1.70, $P < .0001$, Cohen's d = 0.28).

Children who reached NAH were also older at treatment start (ISS: 13.4 [2.5] years; GHD: 12.9 [3.2] years) (for data per sex see Table S2 [36]). In the NAH population, female children with ISS and GHD started puberty at a similar age (ISS: 12.1 [1.9] years; GHD: 12.2 [2.0] years), as did male children (ISS: 13.7 [1.7] years; GHD: 13.9 [1.9] years). Baseline characteristics for children with and without baseline GH peak data were comparable (Table S3) [36].

GH Exposure

Throughout the 10 years of follow-up, mean (SD) GH dose exposure for children with ISS was consistently higher than for children with GHD (Fig. 2). The number of children treated with GH in the EAS decreased from baseline (ISS: 2684; GHD: 15 721) to 5 (ISS: 280; GHD: 3007) and 10 years (ISS: 18; GHD: 317) in both groups. Mean (SD) GH dose across the 10 years of treatment was 25% higher in children with ISS (0.050 [0.014] mg/kg/day) compared with children with GHD (0.040 [0.013] mg/kg/day). Mean [SD] duration of treatment was 34% longer for children with GHD (3.082 [2.544] years) than for those with ISS (2.307 [2.030] years).

There were fewer children in the NAH population, decreasing from baseline (ISS: 230; GHD: 1626) to 5 (ISS: 112; GHD: 815) and 10 years (ISS: 7; GHD: 155) in both groups. Mean (SD) GH doses in the NAH population were similar to in the EAS (ISS: 0.049 [0.013] mg/kg/day; GHD: 0.036 [0.014] mg/kg/day), whereas mean [SD] duration of treatment was longer (ISS: 4.16 [2.20] years; GHD: 4.68 [2.85] years).

Effectiveness

Growth response in EAS

GH treatment was associated with increase in mean [SD] HSDS from baseline (ISS: −2.28 [0.89]; GHD: −2.24 [1.08]) to 5 (ISS: −1.10 [1.01]; GHD: −0.86 [1.11]) and 10 years (ISS: −0.98 [1.52]; GHD: −0.56 [1.24]) in both groups (Fig. 3A). Distribution of HSDS levels progressed from most children having a HSDS <−2 at baseline, to most children

Table 1. Baseline characteristics of children with GHD and ISS in the EAS

	ISS (n = 2684)	GHD (n = 15 721)	Mean difference (SD) *P* value (Cohen's d statistic)
Male/female, n (%)	1813 (68)/871 (32)	11 066 (70)/4655 (30)	
Age at treatment start (year)	11.22 (3.24)	10.19 (3.97)	1.03 (3.9) *P* < .0001 (0.27)
BA/CA	0.89 (0.14)	0.84 (0.19)	
HSDS	−2.28 (0.89)	−2.24 (1.08)	
HSDS for bone age	−1.16 (1.15)	−0.64 (1.52)	−0.52 (1.5) *P* < .0001 (−0.35)
Target HSDS	−0.71 (0.93)	−0.52 (0.99)	
Target HSDS − HSDS	1.56 (1.15)	1.72 (1.26)	
GH peak (ng/mL)	15.64 (9.96)	5.44 (4.83)	
IGF-I SDS	−1.13 (1.7)	−1.61 (1.69)	0.48 (1.7) *P* < .0001 (0.28)
IGFBP-3 SDS	−1.00 (2.17)	−1.24 (1.83)	
Dose at baseline (mg/kg/day)	0.05 (0.01)	0.04 (0.01)	
GH treatment duration (year)	2.31 (2.03)	3.08 (2.54)	
Gestational age (weeks)	38.88 (2.65)	38.71 (2.74)	
Birth weight (g)	3020 (656)	3070 (682)	
Birth weight SDS	−0.50 (1.23)	−0.33 (1.25)	
Birth length (cm)	48.91 (3.42)	49.1 (3.79)	
Birth length SDS	−0.73 (1.50)	−0.51 (1.55)	
Height velocity (cm/year)	5.16 (2.08)	5.58 (2.86)	
HVSDS	−0.38 (1.67)	−0.61 (1.89)	

Data are mean (SD) unless otherwise stated. IGF-1 and IGFBP-3 measurements were derived from local assays.
Abbreviations: BA/CA, bone age to chronological age ratio; EAS, effectiveness analysis set; HD, GH deficiency; HSDS, height SD score; HVSDS, height velocity SD score; IGFBP-3, insulin-like factor binding protein-3; ISS, idiopathic short stature; N, number of children; SDS, SD score.

having HSDS ±2 after 1 year and throughout follow-up for both groups (Table 2). As with HSDS, mean [SD] ΔHSDS increased over follow-up in both groups from 1 year (ISS: 0.54 [0.43]; GHD: 0.66 [0.54]) through to 5 years (ISS: 1.40 [0.81]; GHD: 1.69 [0.10]) (Fig. 3B). In the ISS group, variability in growth response was observed after 6 years of treatment; mean (SD) ΔHSDS peaked at 2.04 (1.00) at 9 years and declined to 1.61 (0.89) at 10 years. Conversely, a continual increase until 10 years (mean 2.34 [SD 1.36]) was observed in the GHD group. Trends in HSDS and ΔHSDS from baseline throughout follow-up were similar in children with ISS and GHD, whether diagnosis was physician-determined or defined using GH peak data (Fig. S2) [36].

There was an increase in mean [SD] HVSDS from baseline to 1 year in children with ISS (−0.38 [1.67] to 1.80 [1.68]) and children with GHD (−0.61 [1.89], 2.29 [1.92]); levels remained >0 for the remainder of follow-up (Fig. 3C). IGF-I SDS (mean [SD]) increased from baseline to 1 year for both groups (ISS: −1.13 [1.71] to 0.80 [1.63]; GHD: −1.61 [1.69] to 0.60 [1.69]), remaining within the normal range (SDS ±2) throughout follow-up (Fig. 3D). Few children in both groups had IGF-I levels SDS <−2 after 1 year (<6%) and throughout follow-up (Table 2).

Near Adult Height

Evolution of change in HSDS, IGF-SDS, and HVSDS in the NAH population is shown in Fig. S3 [36]. Baseline HSDS (mean [SD]) in the NAH population was −2.43 (0.91) for children with ISS (target HSDS of −0.64) and −2.36 (1.16) for children with GHD (target HSDS of −0.50). At NAH, mean (SD) HSDS was −1.21 (1.09) and −0.90 (1.20) for children with ISS and GHD, respectively. Mean (SD) difference in HSDS between the 2 groups was −0.31 (1.2, *P* < .0001, Cohen's d = −0.26).

Mean (SD) ΔHSDS from baseline to 10 years was 1.21 (0.86) and 1.45 (1.09). Distribution of HSDS progressed from most children in the NAH group having a HSDS <−2 at baseline, to most children having HSDS ±2 after 1 year and throughout follow-up for both ISS and GHD groups (Table S4) [36]. Distribution of IGF-I SDS levels followed a similar pattern to HSDS for the GHD group, but for those with ISS, most children had IGF-I levels SDS ±2 at baseline (56.5%) and throughout follow-up. The only exception to this distribution occurred at 9 years, where the majority (75.0%) of children with ISS had IGF-I levels SDS ≥2 (Table S4) [36].

BA/CA

BA/CA (mean [SD]) for both ISS and GHD groups increased from baseline (0.89 [0.11] and 0.84 [0.14], respectively) but did not exceed 1 throughout the 10-year follow-up.

Effect of Age of Treatment Initiation and Treatment Duration on Growth Response

Children with ISS with ≥8 years' follow-up reached height SDS within the normal range (SDS ±2). Comparatively,

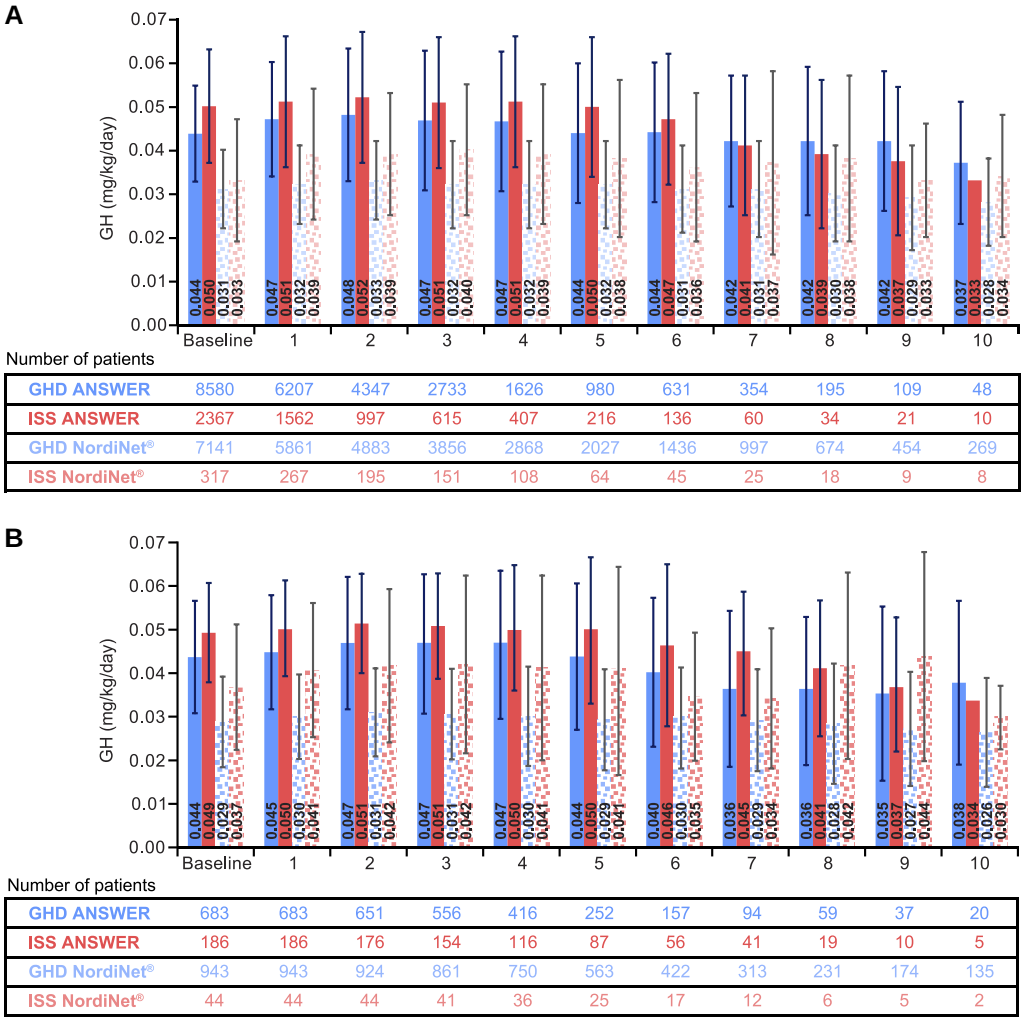

Figure 2. Average GH dose exposure for children with ISS and GHD. (A) EAS (SD); (B) NAH. Data are mean (SD).

Abbreviations: EAS, effectiveness analysis set; GHD, GH deficiency; ISS, idiopathic short stature; NAH, near adult height.

children with shorter treatment duration were more likely to have only reached height SDS <−2. In a sensitivity analysis of patients categorized by age of treatment start, children with ISS who started treatment before 3 years of age achieved a higher HSDS than those who initiated treatment at a later age, across all years of treatment (Fig. S4A) [36]. At year 8, the mean (SD) HSDS for children initiating treatment before 3 years of age was 0.1 (1.0), compared with −0.7 (1.4), −1.5 (1.2), and −0.9 (0.8) for those aged 3 to 6, 6 to 9, and >9 years, respectively. Between groups of patients who started treatment after 3 years of age (3-6, 6-9, and >9 years of age), no relevant difference was observed. Overall, children with GHD started treatment much earlier than children with ISS, with a greater proportion starting before 7 years old (Fig. S4B and S4C) [36].

Safety

The overall rates and frequencies of ARs across the 10-year follow-up were similar between groups. Total PYEs from which IRs were calculated were 9186.4 and 72 274.2 for ISS and GHD patients, respectively. The IR per 1000 PYE of overall ARs was 7.18 for children with ISS and 6.96 for children with GHD (IRR: 1.03; 95% CI, .50-2.12), the majority of which were NSARs (IR: 6.20 vs 5.23, respectively; IRR: 1.19; 95% CI, .61-2.30). For children with SARs, the overall IR was 0.98 and 1.73 for children with ISS and GHD, respectively (IRR: 0.57; 95% CI, .03-12.17). Across the 10-year follow-up, the frequencies of ARs/NSARs/SARs in the ISS and GHD groups followed similar patterns by the Medical Dictionary for Regulatory Activities system organ classes (Fig. S5) [36]. The most common types of disorders for ARs were muscular and connective tissue disorders (IR 2.94 for ISS and 2.05 for GHD), nervous system disorders (IR 2.18 for ISS and 2.01 for GHD), and general disorders and administration-site conditions (IR 0.76 for ISS and 1.08 for GHD). For these conditions, the IR of SARs was 0.54, 0.11, and 0 for children with ISS, and 0.40, 0.35, and 0.15 for children with GHD, respectively. Neoplasms benign, malignant, and unspecified (including cysts and polyps) were reported in 1 child with ISS (IR: SAR, 0.11) and 20 children with GHD (IR: SAR, 0.24; NSAR, 0.06). No deaths were reported among children with ISS and 8 deaths were reported among children with GHD; of these, 7 were deemed unlikely to be related to treatment. The death of 1 child from leptomeningeal melanocytosis, who had a medical history comprising supracellular cyst, hydrocephalus, and congenital neurocutaneous melanosis,

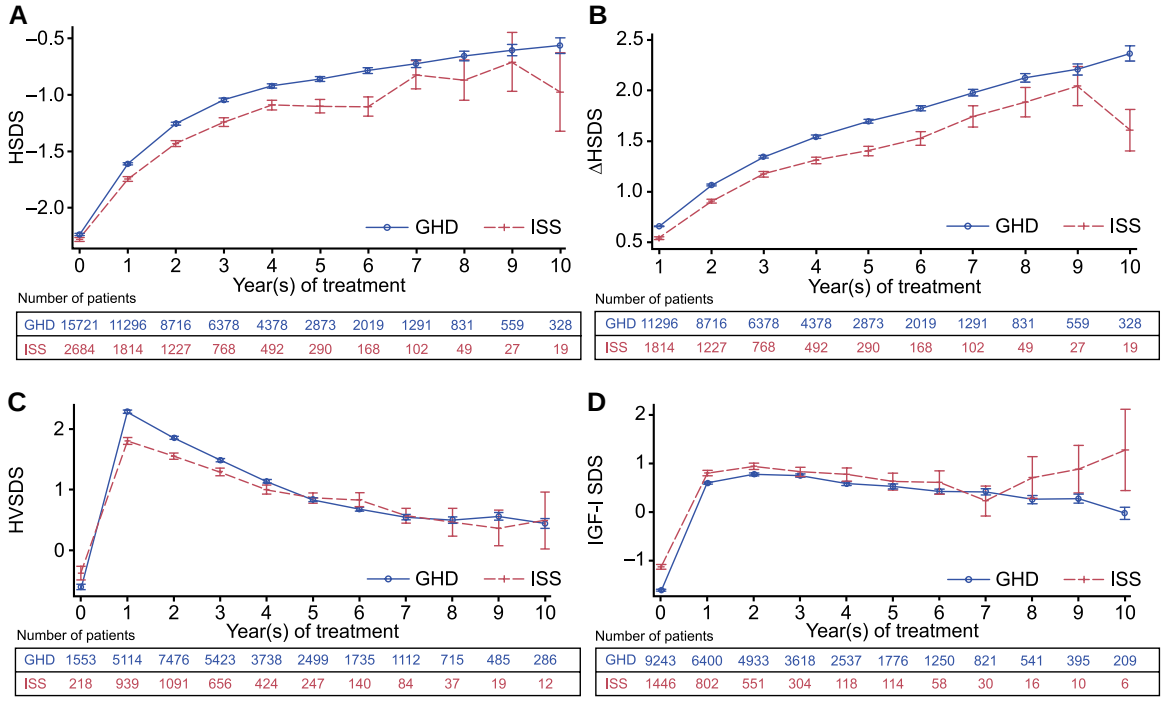

Figure 3. Growth outcomes from baseline to 10 years in children with GHD and ISS. (A) Height SDS; (B) change in height SDS; (C) height velocity SDS; (D) IGF-I SDS. Data are mean (StdErr).

Abbreviations: EAS, effectiveness analysis set; GHD, GH deficiency; HSDS, height SDS; ΔHSDS, change in HSDS; HVSDS, height velocity SDS; ISS, idiopathic short stature; SDS, SD score; StdErr, standard error. IGF-1 measurements were derived from local assays.

and was 7 years old at start of treatment and 16 years old on AR onset, was possibly related to treatment, according to investigator assessment.

Discussion

In this post hoc analysis, GH treatment effectively improved height outcomes in children with ISS and GHD over long-term follow-up, with IGF-I mean levels remaining within normal range and no observation of inappropriate advancement of BA/CA. These results included individuals who achieved NAH, where NAH was closer to target HSDS than baseline HSDS. The safety profile of GH treatment was tolerable and comparable in children with ISS and GHD.

Average GH dose for children with ISS was higher than for those with GHD across all treatment years, suggesting that children with ISS are less responsive to treatment because they are not deficient in endogenous GH [5]. Children in the United States received greater doses of GH across all years of treatment compared with those in Europe, highlighting regional prescribing differences. Likewise, initial treatment doses in the Kabi/Pfizer International Growth Database (KIGS) data, which included information from children with ISS, GHD, and others who were treated with recombinant human GH, were also higher in the United States [20].

Mean duration of treatment was longer for children with GHD compared to children with ISS, and children with GHD, on average, started treatment a year earlier. This is likely influenced by late diagnosis of ISS and insurance rejections for treatment for these patients (particularly in the United States). Indeed, the difference in age at treatment start between the 2 groups was statistically significant and showed a small effect size (Cohen's $d = 0.26$). Earlier GH treatment start has been shown to be a strong predictor of greater height outcomes [37, 38]. In the present analysis, children with ISS who started treatment before 3 years of age exhibited superior catch-up growth and greater improvement in HSDS compared with those who started treatment later. In addition, persistence of GH treatment of children with ISS for ≥8 years was associated with a greater improvement in height outcomes compared with children who had shorter treatment durations. Children who achieved NAH were approximately 2 years older at treatment start than those who had not yet completed growth; thus, it is possible that effectiveness results pertaining to the NAH population could underestimate the full potential of GH treatment. In addition, children with ISS had a shorter duration of GH treatment because they started treatment at an older age, which resulted in lesser height gains despite receiving a higher dose of GH. Nevertheless, these observations highlight the importance of early identification and early and continued GH treatment in children with ISS for the attainment of NAH, as well as height attainment in line with their genetic potential.

Trends in HSDS, ΔHSDS, and HVSDS from baseline to 10 years were similar between children with ISS and children with GHD, although outcomes were slightly greater for children with GHD. Although the difference in HSDS for children who reached NAH was statistically significant between the 2 groups, the effect size was small (Cohen's $d = -0.26$). Several anthropometric measures (weight, initial height, body mass index) and IGF-I have been shown to be predictive factors for growth in children with GHD [39]. Although the effect of these parameters was not investigated, the results of the present analysis align with previous studies comparing the effects of GH treatment in children with ISS and GHD, where similar effects on short-term growth response between groups were observed

Table 2. Distribution of HSDS and IGF-I SDS levels by year of treatment

	GHD			ISS		
	SDS < −2	SDS ±2	SDS ≥2	SDS <−2	SDS ±2	SDS ≥2
Height SDS, % of participants						
Baseline	60.66	39.26	0.08	65.91	34.09	0.00
1 year	32.68	67.09	0.24	35.28	64.72	0.00
2 years	21.05	78.65	0.30	24.12	75.63	0.24
3 years	15.66	83.74	0.60	20.18	79.56	0.26
4 years	13.80	85.52	0.69	14.02	85.98	0.00
5 years	13.44	85.76	0.80	15.52	84.48	0.00
6 years	12.78	86.23	0.99	17.26	82.74	0.00
7 years	12.08	86.52	1.39	14.71	84.31	0.98
8 years	12.27	86.16	1.56	12.24	87.76	0.00
9 years	10.20	88.91	0.89	11.11	85.19	3.70
10 years	14.33	83.84	1.83	21.05	78.95	0.00
IGF-I SDS, % of participants						
Baseline	42.39	54.58	3.03	32.37	62.66	4.98
1 year	5.95	74.03	20.02	4.61	72.69	22.69
2 years	5.31	71.86	22.83	3.45	68.42	28.13
3 years	6.25	70.90	22.86	4.93	71.71	23.36
4 years	6.62	73.28	20.10	5.85	68.62	25.53
5 years	6.70	73.48	19.82	8.77	70.18	21.05
6 years	8.80	72.40	18.80	10.34	65.52	24.14
7 years	8.28	73.57	18.15	10.00	76.67	13.33
8 years	10.91	70.98	18.11	12.50	68.75	18.75
9 years	9.37	75.19	15.44	0.00	60.00	40.00
10 years	12.44	76.08	11.48	0.00	50.00	40.00

IGF-1 measurements were derived from local assays.
Abbreviations: GHD, GH deficiency; HSDS, height SD score; ISS, idiopathic short stature; SDS, SD score.

[37, 40-42]. Specifically, analysis of data from KIGS demonstrated comparable ΔHSDS among children with ISS and congenital GHD in the first year of treatment. Consistent with the present study, GH response in prepubertal children with GHD was slightly more favorable than in those with ISS (ΔHSDS for GHD: 1.01; ISS: 0.55), as was the response in pubertal children, albeit smaller (ΔHSDS for GHD: 0.49; ISS: 0.39) [20]. Furthermore, in this study, treatment with GH was effective in the NAH population, with mean ΔHSDS >1 in both groups throughout follow-up. Comparatively, analysis of data from KIGS showed median gains in NAH SDS were >1 in children with ISS and GHD across follow-up [20]. In a systematic review, GH treatment was shown to significantly improve adult height of children with ISS vs untreated controls, with a ΔHSDS of 1.06 (0.30) and 0.18 (0.27), respectively ($P < .001$) [8]. This effect was enhanced in children who received higher doses of GH treatment vs lower doses [8]. Similar results were demonstrated following a meta-analysis of 21 studies investigating the use of GH in children with ISS [7]. Children who received recombinant human GH exhibited significantly higher height increment compared with untreated controls after 1 year and, in longer-term studies, after 2 years of treatment. The effect of GH on adult height attainment was also analyzed, demonstrating that treated children experienced significantly increased adult height compared with controls [7]. The present study builds on previous studies of the use of GH in children with ISS and GHD, offering evidence of the beneficial effects of GH on height outcomes for up to 10 years of treatment.

The difference in mean IGF-I SDS at baseline was statistically significant between the 2 groups but, the effect size was small (Cohen's d = 0.28). Importantly, mean (SD) IGF-I SDS increased >0 in the first year of follow-up (ISS: 0.80 [1.63]; GHD: 0.60 [1.69]) and did not drop below this afterwards across both indications. In addition, the number of children who exceeded the normal range of IGF-I was minimal. Children diagnosed with ISS may have varying degrees of IGF-I deficiency and, although this is usually less marked than in severe GHD or classical IGF-I deficiency, some children have IGF-I levels below −2 SDs of normal [43]. Children with lower IGF-I levels pretreatment can have significantly lower HSDS at baseline compared with those with normal IGF-I levels [44]. However, this can lead to greater increase in HSDS after 1 year of GH treatment.

Across all effectiveness outcomes, variability in response was observed in later years of treatment in children with ISS. The observed plateau in GH response among children with ISS between years 4 and 6 of treatment indicates that some, but not all, of the children with ISS may have ceased to respond to GH. In addition, those with ISS initiating treatment aged older than 3 years showed little height gain after 4 years of treatment. The variability in growth response

observed in children with ISS after 6 years of treatment in this study may be explained by the differing responses to GH documented in each etiology of ISS [45], and the lack of response among older children initiating treatment could be due to the adverse impact of delayed treatment start on height outcomes [37, 38]. However, because HVSDS did not drop below 0 either in children with ISS or GHD, it could be considered as a rationale for continuing treatment in children gaining HSDS within these populations. For children with ISS specifically, continuing GH treatment for 6 years at doses of 0.37 mg/kg/week has been shown to significantly increase height velocity compared with lower doses, with 94% of children reaching NAH [46]. The results of the present analysis provide a reasonable basis for continued treatment and appropriate dose escalation in children with ISS who respond to GH and are in line with previous guidance recommending that GH treatment in this population should continue until NAH attainment [5].

The safety profile of GH treatment was tolerable and similar across both indications. The incidence rate of ARs was low with few SARs, and no new safety signals were observed. Notably, IR of neoplasms was low for both groups. Although this has previously been regarded as an area of concern, there is insufficient clinical evidence in the present study to support an association of neoplasms or increased risk of cancer recurrence in patients with GH treatment [47].

This study was strengthened by using data from 2 large, international, observational studies. Children were followed over a long period in a real-world setting, which offered an inclusive picture of the use and effectiveness of GH treatment in clinical practice. Furthermore, the large population allowed for investigation of subgroups and infrequent events and strengthened the statistical power of the data.

As this was a longitudinal, observational study, changes in diagnostic and eligibility guidelines for GH treatment may have occurred during the study. There was also potential for confounding of results by local differences in diagnostics, laboratory analyses, and events reporting. In addition, the incorporation of multiple sites with distinct cultures and approaches in the management and ascertainment of variables used in this analysis, as well as selection biases relating to access to medication and physician-determined inclusion in the NordiNet IOS and ANSWER Program study, may have resulted in inconsistent data collection. Other limitations included potential underreporting of safety outcomes and lack of an untreated control group. Furthermore, the low number of children diagnosed with ISS, and hence included in this analysis compared with GHD, resulted in a depleted sample size, particularly after 6 years of follow-up. This may be due to misclassification of patients by physicians before inclusion in the study, exclusion of patients who did not meet all criteria for inclusion (no valid GH exposure information, no valid mean GH dose, invalid birthdate, or initiation of treatment after 18 years of age and last measurement before 20 years of age), or discontinuation of treatment from poor response after 6 years of treatment. Another possible reason is that Norditropin is only indicated for ISS in the United States and South Korea [26, 28], whereas it is approved for GHD in Europe, the United States, and Japan [25-27]; hence, the available treated patients with ISS are likely to be more restricted.

A specific limitation was incomplete reporting of variables, particularly GH peak test results. Because of this, children were assigned to the ISS or GHD groups based on physician-reported diagnosis. Criteria for diagnosis of these conditions can vary between countries, and it is also possible for children to be misdiagnosed; both factors may have led to incorrect grouping. Additionally, the GH provocative tests used to confirm GHD diagnosis and their recommended cutoffs differ between countries [48]. GH secretion significantly varies in the early years of development and those leading up to puberty [49]. High false-positive rates of GHD diagnosis through provocative testing have been identified in pre- and peripubertal children [50], and many children with idiopathic GHD (comprising >20% of children in this analysis) exhibit GH responses that imply a reversal of GHD after postpubertal retesting [51]. In the present study, the authors did not investigate the persistence of GHD in pubertal children at the end of GH treatment, nor was HSDS adjusted for pubertal status; however, sensitivity analyses of effectiveness data from children grouped by GH peak cutoff (7 and 10 ng/mL) confirmed that height outcomes did not differ regardless of how children were grouped. The present analysis also did not account for the influence of GHD etiology on GH response, nor did it investigate how differences in patient and parent perceptions of short stature vary between sexes, the latter being an important consideration when discussing and diagnosing ISS in a clinical setting [52]. Nevertheless, sharing the results from comprehensive databases like Nordinet IOS and ANSWER in studies such as the one described here enhances understanding of the impact of GH treatment on growth patterns in a broader population.

Conclusions

This was the first analysis to compare the long-term effectiveness and safety of GH treatment in children diagnosed with ISS and GHD. Results from the NordiNet IOS and the ANSWER Program show that GH treatment effectively increases height in children with ISS for up to 10 years, including those who reached NAH. The safety profile of Norditropin observed in patients with ISS was comparable to those with GHD, supporting a favorable benefit–risk profile of GH treatment in children diagnosed with ISS. These findings provide useful information on how and when to treat children with ISS and highlight the need for early and continued GH treatment in this population for attainment of NAH. However, further studies are needed to define a more homogeneous ISS population for the evaluation of GHT.

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Author Contributions

All authors made a significant contribution to the work reported, including 1 or more of conception, study design, execution, acquisition of data, analysis, and interpretation; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosures

M. Phillip reports being an advisory board member for AstraZeneca, Eli Lilly, Mannkind Medtronic Diabetes, Pfizer, Sanofi, DOMPE, LifeScan, Novo Nordisk, Insulet, ProventionBio, Merck, Ascensia, Bayer, Embecta, and Tandem; receiving consulting fees from Qulab Medical and ProventionBio; the institute he is heading receiving research grants from Eli Lilly, Medtronic Diabetes, Novo Nordisk, Pfizer, Sanofi, DreaMed Diabetes, NG Solutions, DOMPE, Lumos, Gwave, OPKO, ProventionBio, and AstraZeneca; and being a stock owner for DreaMed Diabetes and NG Solutions. M.J.A. reports that her institution has received research support from Ascendis, Lumos, Mannkind, Medtronic, Novo Nordisk, Rhythm, and Soleno; and she has, in the past 3 years, been a consultant for Ascendis, Endo Pharmaceuticals, Rhythm, and Novo Nordisk. A.P. is an employee of Novo Nordisk. J.-M.F. has worked with Novo Nordisk as an external statistician since August 2017 and has received consultancy fees from Novo Nordisk related to the analyses of the data. M.H. and N.K. are employees of and hold stock in Novo Nordisk. P.K. has received honoraria for consultancies and lectures for Novo Nordisk. M. Polak has participated in advisory boards for Ipsen, Novo Nordisk, and Pfizer; has received speaker fees from Novo Nordisk, Ipsen, and Merck; and has received research support from Novo Nordisk, Pfizer, Sandoz, Merck, and Sanofi, as well as French institutional grants (PHRC and ANR). L.S. has received lecture honoraria from Merck, Novo Nordisk, and Pfizer; travel support from Novo Nordisk; has participated in an adjudication committee for Aetherna-Icon; and has participated in advisory boards for Pfizer and Novo Nordisk.

Data Availability

Data collected for the study will be shared in data sets in a de-identified/anonymized format. Study protocol and redacted clinical study report will be available according to Novo Nordisk data-sharing commitments. The data will be available via access request proposal form and the access criteria can be found at novonordisk-trials.com. The data will be made available on a specialized SAS data platform. Data will be shared with bona fide researchers and for use as approved by the independent review board according to the IRB Charter.

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