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RESEARCH

Better growth outcomes in GH-deficient children treated younger than 2 years of age

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Abstract

Background: Limited data are available on the growth response to growth hormone (GH) treatment in very young children with GH deficiency (GHD). In the present analysis, we compared clinical outcomes after GH treatment in children with GHD aged <2 and ≥2 years at the start of GH treatment.

Methods: We analysed pooled data from two observational studies of paediatric patients who received Norditropin® treatment: NordiNet® IOS (NCT00960128) and the ANSWER Program (NCT01009905). Patients with GHD, who remained pre-pubertal after 1 year of treatment, were grouped by age at treatment start (<2 years; ≥2 years). The primary effectiveness outcome was change in height standard deviation score (SDS) after 1 and 10 years. We also investigated the frequency of non-serious adverse drug reactions (ADRs), serious ADRs and serious adverse events (SAEs).

Results: In total, 507 and 7,486 children initiated treatment at <2 and ≥2 years of age, respectively. Height SDS (mean change (SD) from baseline) improved after 1 year of treatment in both groups and was greater in children initiating treatment at <2 years than in those initiating treatment at ≥2 years (1.4 (1.2) and 0.75 (0.5), respectively); these findings were sustained after 10 years of treatment (3.2 (1.7) and 2.2 (1.3), respectively). SAEs were more frequent in children initiating treatment at <2 years vs ≥ 2 years (3.3 vs 0.67%, respectively).

Conclusions: Children aged <2 years at GH treatment initiation had better height outcomes, but more SAEs, after 1 and 10 years of GH treatment compared to children starting GH at age ≥2 years.

Trial registration: NordiNet® IOS, ClinicalTrials.gov NCT00960128; ANSWER Program, ClinicalTrials.gov NCT01009905.

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Plain language summary

Data from two large studies showed that children with growth hormone deficiency (GHD) who began treatment with Norditropin® under 2 years of age had better growth than those first treated at or above 2 years of age, but also had more side effects. This highlights the value of early diagnosis, treatment and close monitoring of children with GHD.

Keywords: growth factors; development/foetal nutrition; pituitary; paediatric endocrinology; growth hormone therapy; growth hormone deficiency; multiple pituitary hormone deficiency; clinical outcomes; real-world data

Introduction

GH deficiency (GHD) is characterised by reduced circulating GH, resulting in impaired growth and altered body composition and metabolism (1). Normal GH secretion varies across different age groups, and it is particularly challenging to identify GHD in very young children (<2 years) (2, 3, 4). For example, neonates with GHD may present with severe and persistent hypoglycaemia, dysmorphic features or prolonged jaundice rather than growth retardation (2, 3, 4, 5). It has been shown that, in the first year of life, children with congenital GHD may have a birth length within the normal range but a poor postnatal length velocity (6). An added challenge is in the interpretation of the GH biomarker insulin-like growth factor-I (IGF-I) in infants as concentrations are influenced by a range of factors, including premature birth, nutritional status, the presence of maternal diabetes and birth size (7, 8, 9). Levels may also vary depending on the assay used (10). Furthermore, GH stimulation tests are contraindicated in neonates due to the risk of adverse events (AEs) (11).

Recombinant human GH is approved for the treatment of GHD (12). Guidelines recommend treating children with GHD as soon as possible to promote normal adult height and to maintain an adequate body composition (5). Studies have shown that early diagnosis and treatment start are associated with better treatment response, but most were focused on children in their mid-childhood period (13, 14, 15) and very few focused on children aged <2 years (4, 16, 17). In an analysis of data from the KIGS registry, very young children (0–3 years) achieved greater gains in height per GH dose unit in comparison with children in mid-childhood (16). Another study showed that GH therapy in infancy can result in normal patterns of growth during childhood and the realisation of normal near-adult height (NAH) (17).

Despite these data, limited information is available on how very young children with GHD respond to GH treatment. The aim of this study was to compare the clinical outcomes and safety of GH treatment initiated in children with GHD aged <2 years at treatment start and pre-pubertal children starting treatment aged ≥2 years. The proportion of children <2 years with isolated GHD (IGHD) or multiple pituitary hormone deficiencies (MPHDs) at GH treatment start and clinical outcomes in these patients were also explored. This analysis used data from two large observational studies, the NordiNet® International Outcome Study IOS (NCT00960128) and the American Norditropin Studies: Web-Enabled Research (ANSWER) Program (NCT01009905).

Materials and methods

Study design

The NordiNet® IOS and the ANSWER Program were complementary, non-interventional, observational studies designed to assess clinical outcomes and safety of GH replacement therapy with Norditropin® (somatropin; Novo Nordisk A/S) in adults and paediatric populations following routine clinical practices (18). Both studies had similar designs, objectives and methods and used the same electronic, web-based platform (NordiNet®/NovoNet®) to collect the data (19). Detailed methodology and design of the studies have been previously published (19, 20).

NordiNet® IOS was conducted from April 2006 to December 2016 and involved 469 clinics across 19 countries in Europe and the Middle East (19). The ANSWER Program was ongoing between June 2002 and September 2016 across 207 clinics in the United States (19). The number of paediatric patients enrolled was 17,995 in NordiNet® IOS and 20,204 in the ANSWER Program (18). Both studies were approved by the relevant ethics committees and conducted with written consent from patients, and pseudonymisation of all data was performed in accordance with the Declaration of Helsinki, regulatory requirements and Guidelines for Good Pharmacoepidemiology Practices.

Study population

The study population comprised paediatric patients with a diagnosis of GHD, as reported by their physician, who

were prescribed Norditropin®. Patients were divided into two groups based on the baseline age at treatment initiation: <2 years and pre-pubertal ≥2 years. Children aged <2 years were further sub-categorised into <2 years with IGHD and <2 years with MPHDs, as reported by their physician. Children were considered pre-pubertal when aged <8 years for girls and <9 years for boys or, if pubertal status was documented, Tanner stage I.

The effectiveness analysis set (EAS) comprised all patients who were treatment-naïve at baseline with valid baseline information and who remained pre-pubertal after 1 year of treatment. The safety analysis set (SAS) included all patients who received ≥1 GH injection.

Study outcomes

The main objective of this analysis was to compare the clinical outcomes (primary effectiveness outcome: change in height standard deviation score (SDS) at 1 and 10 years after the start of GH treatment) and safety profiles of GH replacement therapy after 1 and 10 years of treatment in children aged <2 and ≥2 years at GH treatment start. At 10 years of treatment, some children were pubertal. A secondary objective was to compare the proportion of children aged <2 years with IGHD or MPHDs at GH treatment start and the clinical outcomes in these children.

The following variables were calculated at baseline and after 1 and 10 years of GH treatment: height SDS, GH dose (mg/kg/day), height velocity (HV) SDS, the proportion of patients with height SDS within the normal range (between −2 and +2), NAH SDS, body mass index (BMI) SDS and IGF-I SDS.

Dose adjustments were at the discretion of the treating physician. Missing GH doses were imputed using the last observation carried forward/interpolation of weight for the calculation of relative GH dose. BMI was calculated in kg/m^2, from height and weight measured at the treating physician's office. NAH was defined as the height achieved when HV was <2 cm/year and the chronological age was >16 years for boys or >15 years for girls, or when the participant's chronological age was >18 years. IGF-I measurements were not conducted at a central laboratory, and reference values from Brabant *et al.* (21) were used to calculate IGF-I SDS. GH peaks from stimulation testing were not recorded in all patients.

Height SDS, height SDS for bone age and target height SDS were calculated based on the corresponding national standards for patients from the NordiNet® IOS study or the United States Centers for Disease Control standards for patients from the ANSWER Program. The target height was calculated using the following formulae:

$$\text{Target height for boys} = \frac{(\text{father's height} + \text{mother's height} + 13)}{2}$$

$$\text{Target height for girls} = \frac{(\text{father's height} + \text{mother's height} - 13)}{2}$$

HV SDS was calculated based on the European Union references (22) for all patients from the NordiNet® IOS study and for patients <6 years old from the ANSWER Program. The United States standards (23) were used for children aged ≥6 years in the ANSWER Program.

The frequency of non-serious adverse drug reactions (NSARs), serious adverse drug reactions (SARs) and serious AEs (SAEs) was recorded. AEs of interest (hypoglycaemia, elevated liver enzymes, and jaundice) were reported in patients with MPHDs.

Statistical analyses

Baseline was defined as the first treatment with Norditropin® after enrolment in NordiNet® IOS or ANSWER and was therefore synonymous with treatment start. Baseline characteristics were reported as mean (SD), where appropriate. Clinical outcomes were described as change from baseline to years 1 and 10 of GH treatment. Safety variables were expressed as the number and proportion of patients. Where data were not normally distributed, variables were presented as median values. A Satterthwaite test was used if the condition of normality was met; otherwise, the Mann–Whitney U test (two-sided Wilcoxon two-sample test with Hodges–Lehmann estimation) was used. A P value < 0.05 was considered significant. The characteristics that were tested for significance were BMI SDS, GH peak, length/height SDS and IGF-I SDS.

Results

Study population

This study included 23,212 children with GHD. Of these, 7,993 comprised the EAS and 22,858 comprised the SAS. In the EAS, the number of children aged <2 years at treatment start was 507 (325 from the NordiNet® IOS and 182 from the ANSWER Program) and the number of children aged ≥2 years was 7,486 (4,119 from the NordiNet® IOS and 3,367 from the ANSWER Program) (Fig. 1) In total, 4,390 (54.9%) children in the EAS were European and 54 (0.68%) children were from the Middle East. By age group, the number of children aged <2 and ≥2 years from Europe was 324 (7.4%) and 4,066 (92.6%), respectively. Most children from the Middle East were aged ≥2 years (n = 53 (98.1%)); only one child was aged <2 years.

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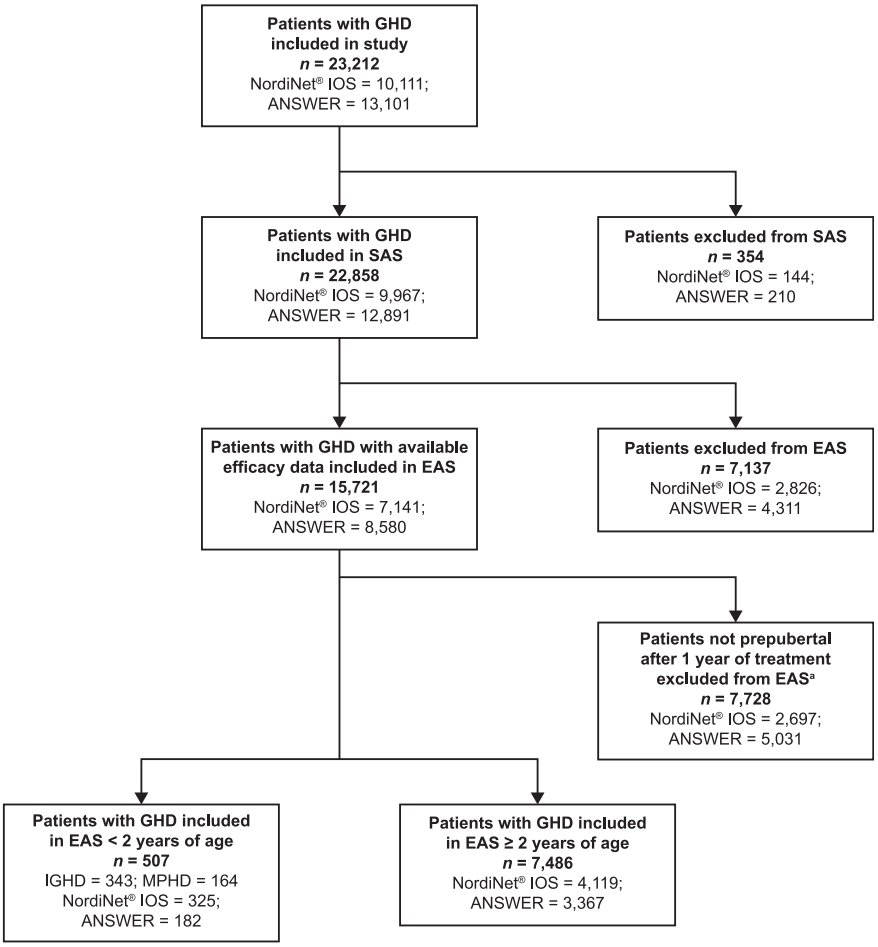

Figure 1

Flowchart showing patient disposition in the study. [a]Patients did not meet inclusion criteria of being GH treatment-naïve at baseline and remaining pre-pubertal after 1 year of treatment. EAS, effectiveness analysis set; GHD, growth hormone deficiency; IOS, International Outcome Study; SAS, safety analysis set.

The mean birth weight SDS was greater in children aged <2 years (−0.34) than in those aged ≥2 years (−0.41). However, the mean birth length SDS was lower in children aged <2 years (−0.87) compared with those aged ≥2 years (−0.62) (Table 1; (22, 23, 24)). A similar proportion of patients had birth weight SDS <−2 SDS in both groups; 8.52% (39/458) and 7.86% (500/6,360) in children aged <2 and ≥2 years, respectively. In children aged <2 years, 19.78% (73/369) had birth length SDS <−2 SDS compared to 14.36% (720/5,014) in children aged ≥2 years.

At baseline, children aged <2 years had a similar length/height SDS to those diagnosed with GHD ≥2 years. Children <2 years of age had a lower GH peak after GH stimulation testing than children ≥2 years of age ($P < 0.0001$). GH dose was similar between age groups. The mean IGF-I SDS was below zero in both groups; however, it was higher in children <2 years versus ≥2 years of age ($P = 0.0058$), although this difference may not be clinically significant (Table 1).

Within the <2 years age group, 343 children had IGHD and 164 had MPHDs. The proportion of children with MPHDs was 32.3% in children aged <2 years and 6.3% in children aged ≥2 years (Fig. 2). MPHDs identified at baseline included adrenocorticotropic hormone (ACTH) deficiency, diabetes insipidus, GHD, luteinizing hormone/follicle-stimulating hormone (LH/FSH) deficiency and thyroid-stimulating hormone deficiency.

At baseline, out of 507 children aged <2 years, 37.5% underwent cranial imaging, of which 72.6% had abnormal readings (Table 2). Out of 7,486 children aged ≥2 years, 35.0% underwent cranial imaging, of which 24.4% had abnormal results. The most common tumour types in children aged ≥2 years were craniopharyngioma ($n = 9$), Rathke's pouch cyst ($n = 9$) and medulloblastoma ($n = 6$); no pattern was observed among children aged <2 years. The pituitary gland was the most common tumour localisation for both age groups ($n = 4$ and $n = 27$ in children aged <2 years and ≥2 years, respectively). The most common congenital abnormalities were septo-optic dysplasia ($n = 13$) in children aged <2 years and ectopic neurohypophysis ($n = 29$) and septo-optic dysplasia ($n = 24$) in children aged ≥2 years.

Concomitant medications

The number (%) of patients in both groups taking concomitant medication was as follows: 2,628 (11.5%)

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Table 1 Baseline demographics and clinical characteristics of study participants in the effectiveness analysis set, according to the age at GH treatment initiation.

	Age <2 years				Age ≥2 years	
	IGHD		MPHD			
	n	Mean (SD)[a]	*n*	Mean (SD)[a]	*n*	Mean (SD)[a]
Total	343		164		7,486	
Proportion of males, %	210	41.4	93	18.3	5,148	68.8
Age at treatment start, years	343	1.2 (0.7)	164	0.9 (0.6)	7,486	7.9 (3.1)
Bone age/chronological age	55	0.9 (1.1)	21	0.6 (0.3)	3,367	0.78 (0.20)
Length/height SDS[b,c]	343	−2.6 (1.8)	164	−2.4 (1.8)	7,486	−2.5 (1.0)
BMI SDS[c]	176	−0.3 (1.4)	146	−0.075 (1.7)	7,469	−0.21 (1.3)
Length/height SDS for bone age[b]	32	−0.7 (2.9)	15	−0.6 (3.5)	2,022	−0.42 (1.7)
Target height SDS[b]	267	−0.2 (1.1)	129	−0.2 (0.9)	6,730	−0.58 (1.0)
Median GH peak, ng/mL[d]	126	3.43	66	2.30	3,583	4.88
GH dose, mg/kg/day	343	0.036 (0.012)	164	0.035 (0.017)	7,486	0.036 (0.011)
IGF-I SDS[e]	174	−1.3 (1.1)	79	−1.5 (0.9)	4,369	−1.5 (1.6)
IGFBP-3 SDS	77	−1.2 (1.3)	44	−1.4 (1.4)	2,120	−1.3 (1.7)
Birth weight, g	314	2,986.4 (691.8)	159	3,137.0 (662.1)	6,790	3,002.4 (710.9)
Birth weight SDS[f]	304	−0.38 (1.25)	154	−0.27 (1.06)	6,360	−0.41 (1.25)
Birth length, cm	258	48.0 (4.0)	123	49.2 (3.0)	5,285	48.7 (4.0)
Birth length SDS[f]	248	−0.97 (1.72)	121	−0.65 (1.44)	5,014	−0.62 (1.51)
Mid-parental height, cm	268	170.7 (11.3)	129	172.1 (8.7)	6,757	169.8 (11.2)
Length/height velocity, cm/year	31	14.2 (4.6)	14	13.2 (5.9)	934	5.3 (2.2)
Length/height velocity SDS[g]	31	0.4 (1.5)	14	−0.014 (1.9)	933	−0.99 (1.9)

BMI, body mass index; GH, growth hormone; IGF-I, insulin-like growth factor-I; IGFBP-3, insulin-like growth factor binding protein 3; IGHD, isolated growth hormone deficiency; IOS, International Outcome Study; MPHD, multiple pituitary hormone deficiency; SD, standard deviation; SDS, standard deviation score.

[a]Values are mean (SD) unless otherwise specified. [b]Calculated based on the corresponding national standards for patients from the NordiNet® IOS study or the US Centers for Disease Control standards for patients from the ANSWER Program. [c]No significant difference at baseline. [d]The data for GH peak are not normally distributed. The medians are reported instead of the means. The difference is statistically significant with $P < 0.0001$ from the two-sided Wilcoxon two-sample test with Hodges–Lehmann estimation of the median difference of −1.50. GH peak test results were not used to classify patients in this study – instead, prior diagnoses from treating physicians were used. [e]Significant difference, $P = 0.0058$ with the Satterthwaite test. This difference may not be clinically significant. [f]Birth length and birth weight SDS were calculated using Usher 1969 gestational age-specific references (24). [g]Calculated based on the EU references (22) for patients from the NordiNet® IOS study and the ANSWER Program aged <6 years and the US references (23) for children aged >6 years in the ANSWER Program.

were taking levothyroxine/levothyroxine sodium (<2 years: 269 (30.5%); ≥2 years: 2,359 (10.7%)), 1,066 (4.7%) were taking hydrocortisone (<2 years: 219 (24.8%); ≥2 years: 847 (3.9%)), 502 (2.2%) were taking desmopressin (<2 years: 45 (5.1%); ≥2 years: 457 (2.1%)), and 429 (1.9%) were taking testosterone (<2 years: 27 (3.1%); ≥2 years: 402 (1.8%)). Some patients were also treated with stimulants: 1,073 (4.7%) were taking methylphenidate (<2 years: 15 (1.7%); ≥2 years: 1,058 (4.8%)) and 520 (2.3%) were taking amphetamine (<2 years: 11 (1.2%); ≥2 years: 509 (2.3%)).

GH exposure

The mean (SD) GH doses at baseline, 1 year and 10 years for children aged <2 and ≥2 years are reported in Table 3. For children aged <2 years with IGHD (n = 343), the GH dose at baseline was 0.036 (0.012), and for children aged <2 years with MPHDs (n = 164), it was 0.035 (0.017). After 1 year of treatment for children aged <2 years with IGHD (n = 275) and MPHDs (n = 132), the GH dose was 0.036 (0.011) and 0.033 (0.012), respectively.

Clinical outcomes

GH treatment was associated with an increase in length/height SDS in both groups after 1 year. The mean (SD) change from baseline was 1.4 (1.2) in children aged <2 years (n = 354) and 0.75 (0.5) in children aged ≥2 years (n = 5,304) at treatment start. After 10 years of GH treatment, the length/height SDS gain was 3.2 (1.7) for children aged <2 years (n = 51) and 2.2 (1.3) for children aged ≥2 years (n = 259) at treatment start (Fig. 3A).

At 1 year of GH treatment, the mean (SD) length/height SDS was within the normal range for both groups but statistically different: −1.2 (1.5) for children aged <2 years (n = 360) and −1.8 (1.0) for children aged ≥2 years (n = 5,396); P value < 0.0001. Similarly, at 10 years of GH treatment, the mean (SD) height/length SDS was within the normal range, but the difference between the two groups was statistically significant: 0.17 (1.3) for children aged <2 years (n = 54) and −0.72 (1.2) for children aged ≥2 years (n = 265); P value < 0.0001 (Fig. 3B).

The proportion of children aged <2 years at treatment start with the mean height SDS <−2 decreased from 62.7%

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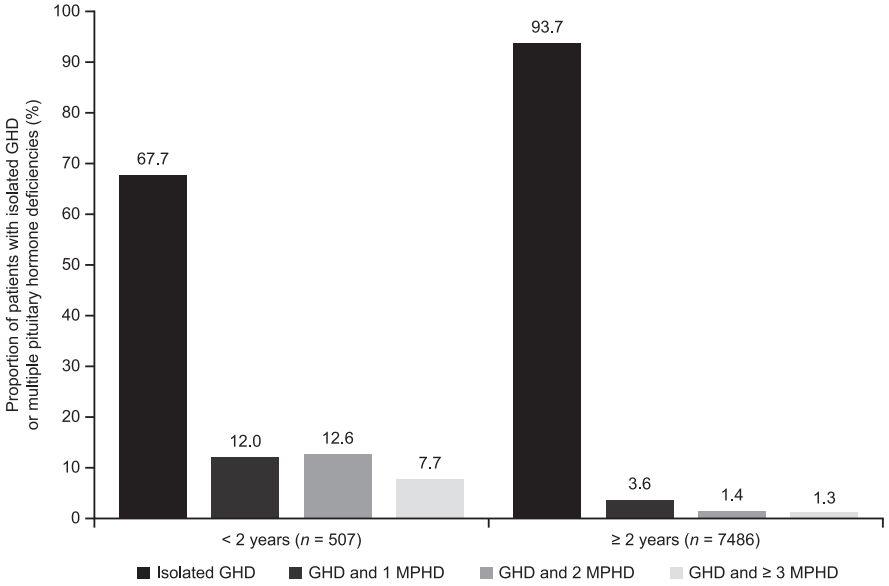

Figure 2

Proportion of patients with IGHD or MPHD, according to the age at GH treatment initiation. GH, growth hormone; IGHD, isolated growth hormone deficiency; MPHD, multiple pituitary hormone deficiency.

at baseline (n = 318) to 26.3 and 3.9% after 1 year (n = 93) and 10 years (n = 2) of treatment, respectively.

For children aged <2 years with IGHD (n = 246) and MPHDs (n = 108), the mean (SD) length/height SDS at 1 year of treatment was −1.3 (1.5) and −0.9 (1.5), respectively. At 10 years of treatment, the mean (SD) height SDS was 0.08 (1.3) and 0.26 (1.4) for children aged <2 years with IGHD (n = 26) and MPHDs (n = 25), respectively (Fig. 4). At NAH, the mean (SD) height SDS was −1.84 (0.9) for children aged <2 years with IGHD (n = 3) and 0.4 (2.3) for children aged <2 years with MPHDs (n = 6).

The mean (SD) change in BMI SDS from baseline after 1 year of treatment was similar for both groups: 0.01 (1.38) in children aged <2 years (n = 221) and −0.02 (0.69) in children aged ≥2 years (n = 5,295); P > 0.05. After 10 years of treatment, change in BMI SDS from baseline was more pronounced for children aged <2 years: 0.54 (1.63) in children aged <2 years (n = 43) and −0.1 (1.18) in children aged ≥2 years (n = 256); P = 0.0170; Satterthwaite test.

Table 2 Cranial imaging at baseline of study participants in the effectiveness analysis set according to the age at GH treatment initiation.

	Age <2 years (n = 507)	Age ≥2 years (n = 7,486)
Cranial imaging type, *n* (%)		
No imaging	317 (62.5)	4,867 (65.0)
Any imaging	190 (37.5)	2,619 (35.0)
Abnormal MRI	134 (26.4)	617 (8.2)
Normal MRI	49 (9.7)	1,916 (25.6)
Abnormal CT/Other	4 (0.8)	23 (0.3)
Normal CT/Other	3 (0.6)	63 (0.8)

CT, computed tomography; MRI, magnetic resonance imaging.

Safety outcomes

All patients in the EAS were included in the SAS. IGF-I SDS values were above 0 after 1 year of treatment and were maintained after 10 years of treatment in both groups. The mean (SD) change from baseline in IGF-I SDS to year 1 was 2.1 (1.39) in the group aged <2 years (n = 125) and 1.9 (1.55) in the group aged ≥2 years (n = 2,125), with no statistically significant difference between the two groups (Fig. 5). The mean (SD) change from baseline after 1 year for children aged <2 years with IGHD (n = 90) and MPHDs (n = 35) was 2.04 (1.30) and 2.07 (1.60), respectively. At 10 years, this was maintained in children with IGHD at 2.02 (2.22; n = 12) and a small difference was seen in those with MPHDs at 1.67 (1.60; n = 10).

NSARs were registered in 0.57% of children aged <2 years and in 1.3% of children aged ≥2 years at treatment start. SARs were slightly higher in children aged <2 years (0.79%) versus ≥2 years (0.38%). The most frequent SARs in children aged <2 years were epiphysiolysis (two events reported in two patients at 4.3 and

Table 3 GH exposure at baseline and after 1 and 10 years of treatment, in patients aged <2 and ≥2 years at treatment initiation.

	<2 years Mean (SD)	≥2 years Mean (SD)
GH dose, mg/kg/day		
Baseline	0.036 (0.014)	0.036 (0.011)
At 1 year	0.035 (0.011)	0.037 (0.011)
At 10 years	0.029 (0.009)	0.030 (0.012)

GH, growth hormone; SD, standard deviation.

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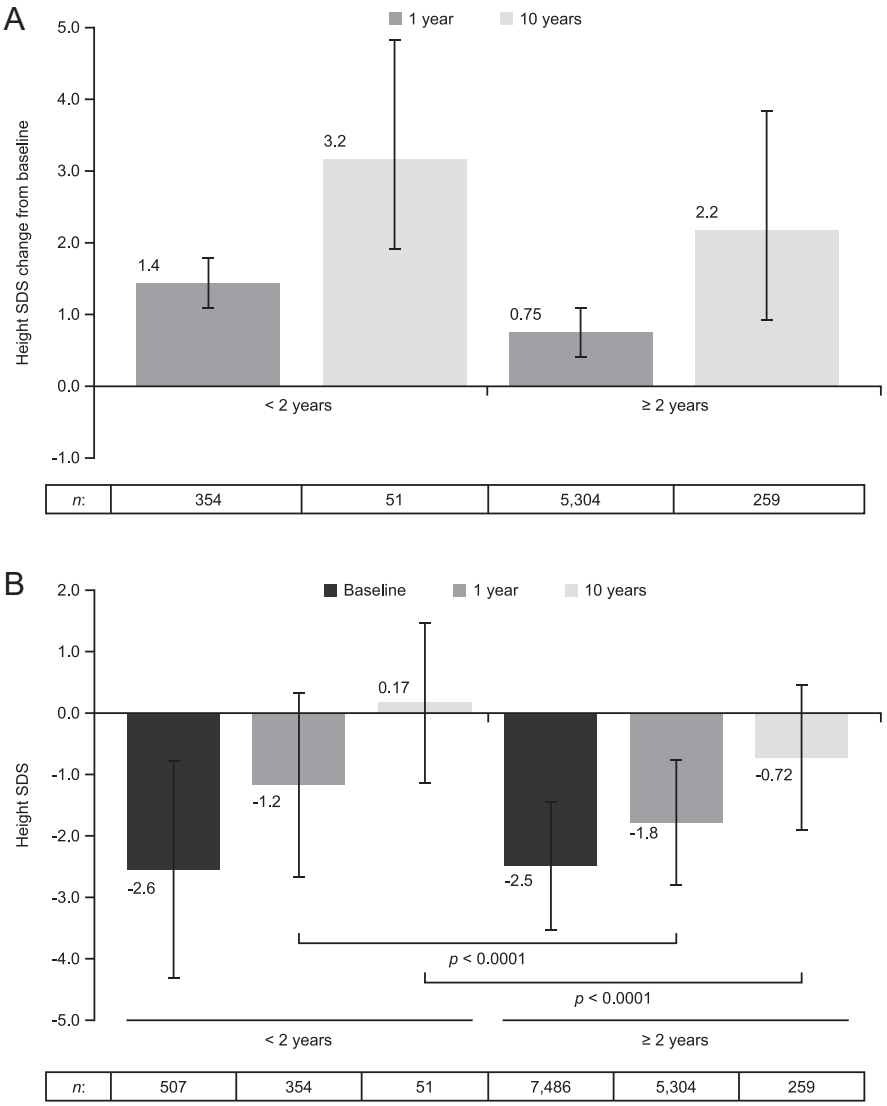

Figure 3

Length/height SDS according to the age at treatment initiation: (A) change in length/height SDS from baseline after 1 and 10 years of GH treatment and (B) length/height SDS at baseline and after 1 and 10 years of GH treatment. GH, growth hormone; *n*, number of patients; SDS, standard deviation score.

9.8 years of age, respectively; details not provided), restlessness (two events reported in one patient), screaming (two events reported in one patient) and sleep disorder (two events reported in one patient). In children aged ≥2 years at treatment start, the most frequent SARs were raised intracranial pressure (11 events reported in ten patients), headache (eight events reported in eight patients), epiphysiolysis (five events reported in five patients), scoliosis (four events reported in three patients) and hyperglycaemia (four events reported in three patients). SAEs occurred in 3.3% of children aged <2 years and in 0.67% of children ≥2 years at treatment start. AEs (NSARs, SARs and SAEs) occurring in each age group are summarised in Table 4.

Regarding AEs of interest in children with MPHDs, hypoglycaemia was observed in three patients, hypoglycaemic seizure in one patient, and vomiting in one patient. These AEs were observed in patients aged <2 years at treatment start and all were deemed unlikely to be related to treatment. In one patient aged ≥2 years at treatment start, focal nodular hyperplasia in the liver was reported after 1 year of treatment, which was deemed possibly related to the treatment.

Four deaths were reported and deemed unlikely to be related to the treatment. Details have been previously published (18).

Discussion

This analysis of pooled data from two large international databases showed that children aged <2 years experienced superior height outcomes after 10 years of

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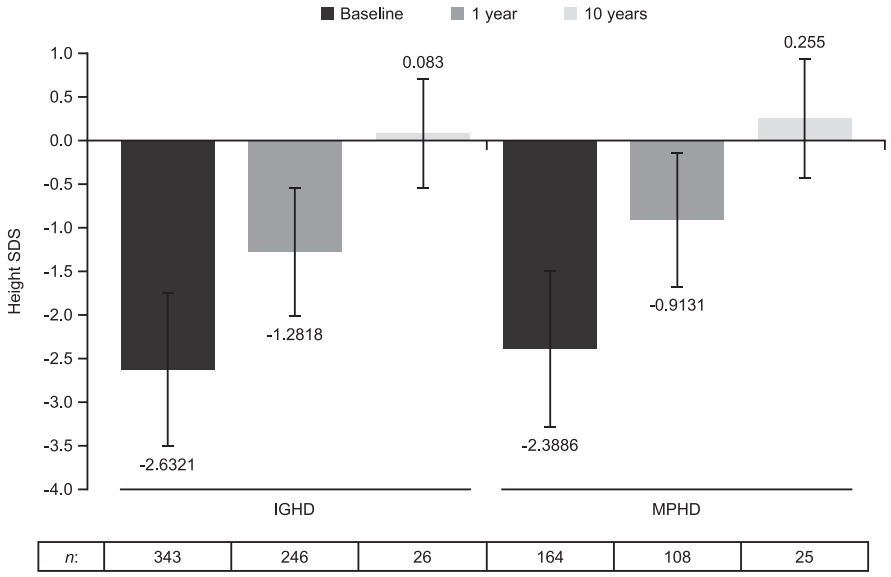

Figure 4

Height SDS at baseline and after 1 year and 10 years of GH treatment in patients aged <2 years at treatment initiation, according to IGHD or MPHD diagnosis. GH, growth hormone; IGHD, isolated growth hormone deficiency; MPHD, multiple pituitary hormone deficiency; SDS, standard deviation score.

GH treatment, compared with children who started GH at, or later than, 2 years of age. There was no significant difference in change from baseline in IGF-I SDS between groups, and no unexpected safety signals were observed.

GHD was the main diagnosis in the registries (followed by born small for gestational age and idiopathic short stature), and it represented a higher proportion of patients registered in the ANSWER Program than in the NordiNet® IOS study (18). In this analysis, more than 50% of patients in both groups were males. Male predominance was also observed in other observational studies of children with GHD (18, 25), and it was noted that the tendency to refer more boys than girls is more common after the age of 3 years (18).

In an analysis of children with GHD from France, the mean age at diagnosis in very young children (treated before 1 year of age) was lower for boys than for girls, potentially due to the presentation of clinical features in boys (micropenis or cryptorchidism), leading to an earlier diagnosis (26).

A higher prevalence of additional pituitary deficiencies was observed in younger children (32.3%, younger children and 6.3%, older children). These observations are in line with earlier results showing that GHD develops early in patients with hypothalamic–pituitary disorders and is common among these patients, and that manifestation is more severe in younger children (4, 16, 27). An analysis of 774 children with GHD from

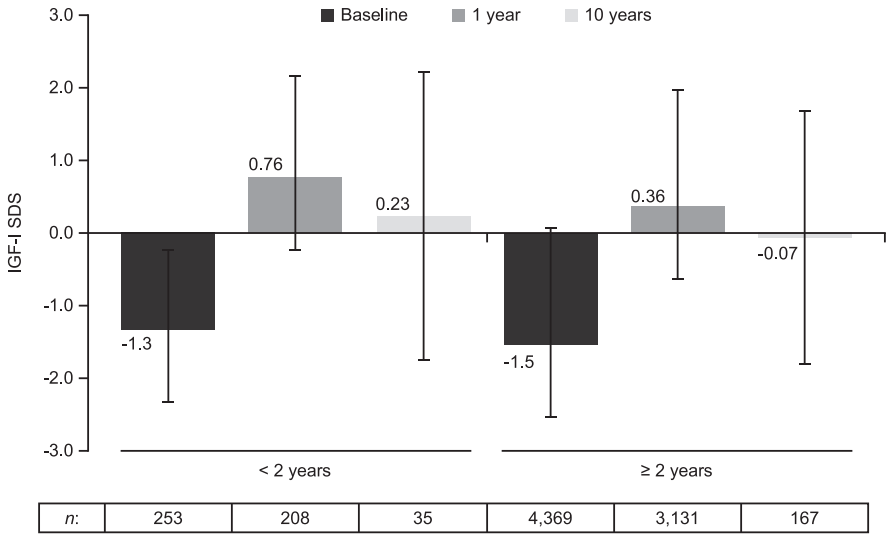

Figure 5

IGF-I SDS at baseline and after 1 year and 10 years of GH treatment, according to the age at treatment initiation. GH, growth hormone; IGF-I, insulin-like growth factor-I; SDS, standard deviation score.

Table 4 Summary of AEs (NSARs, SARs, and SAEs) by system organ class in children included in the NordiNet® IOS and ANSWER Program studies, according to the age at growth hormone treatment initiation.

		Age <2 years				Age ≥2 years	
		n = 882*					
		IGHD (*n* = 592)		MPHD (*n* = 290)		*n* = 21,976*	
System organ class	Total events, *n*	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)
Nervous system disorders	208	2	2 (0.34)	**7**	**5 (1.72)****	199	163 (0.74)
Seizure	31	2	2 (0.34)	3	3 (1.03)	26	14 (0.06)
Febrile convulsion	2	–	–	1	1 (0.34)	1	1 (<0.01)
Generalised tonic–clonic seizure	4	–	–	1	1 (0.34)	3	2 (<0.01)
Hypoglycaemic seizure	2	–	–	2	2 (0.69)	–	–
Musculoskeletal and connective tissue disorders	155	2	2 (0.34)	**3**	**3 (1.03)**	150	126 (0.57)
Epiphysiolysis	9	–	–	2	2 (0.69)	7	7 (0.03)
Myalgia	16	–	–	1	1 (0.34)	15	15 (0.06)
General disorders and administration-site conditions	98	3	3 (0.51)	**8**	**6 (2.07)**	87	79 (0.36)
Hyperthermia	3	–	–	3	2 (0.69)	–	–
Hypothermia	1	–	–	1	1 (0.34)	–	–
Pyrexia	3	1	1 (0.17)	1	1 (0.34)	2	2 (<0.01)
Injection site atrophy	4	–	–	1	1 (0.34)	3	3 (0.01)
Oedema	8	–	–	1	1 (0.34)	7	6 (0.03)
Infections and infestations	55	3	3 (0.51)	**16**	**12 (4.14)**	36	28 (0.13)
Gastroenteritis	7	1	1 (0.17)	4	4 (1.38)	2	2 (<0.01)
Gastroenteritis norovirus	1	–	–	1	1 (0.34)	–	–
Gastroenteritis rotavirus	1	–	–	1	1 (0.34)	–	–
Gastroenteritis viral	2	–	–	1	1 (0.34)	1	1 (<0.01)
Cellulitis orbital	1	–	–	1	1 (0.34)	–	–
Infection	2	–	–	1	1 (0.34)	1	1 (<0.01)
Influenza	1	–	–	1	1 (0.34)	–	–
Meningitis pneumococcal	1	–	–	1	1 (0.34)	–	–
Otitis media	2	–	–	1	1 (0.34)	1	1 (<0.01)
Pneumonia	9	–	–	1	1 (0.34)	8	7 (0.03)
Pyelonephritis	1	–	–	1	1 (0.34)	–	–
Respiratory syncytial virus bronchitis	1	–	–	1	1 (0.34)	–	–
Viral upper respiratory tract infection	2	–	–	1	1 (0.34)	1	1 (<0.01)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	50	1	1 (0.17)	0	0	49	43 (0.20)
Gastrointestinal disorders	32	2	1 (0.17)	**5**	**5 (1.72)**	25	20 (0.09)
Abdominal pain	2	–	–	1	1 (0.34)	1	1 (<0.01)
Inguinal hernia	2	–	–	1	1 (0.34)	1	1 (<0.01)
Stomatitis	1	–	–	1	1 (0.34)	–	–
Vomiting	10	1	1 (0.17)	2	2 (0.69)	7	7 (0.03)
Metabolism and nutrition disorders	32	0	0	**4**	**4 (1.38)**	28	25 (0.11)
Hypoglycaemia	3	–	–	3	3 (1.03)	–	–
Lack of satiety	1	–	–	1	1 (0.34)	–	–
Injury, poisoning, and procedural complications	27	1	1 (0.17)	1	1 (0.34)	25	20 (0.09)
Skin and subcutaneous tissue disorders	23	0	0	2	2 (0.69)	21	20 (0.09)
Psychiatric disorders	19	6	1 (0.17)	0	0	13	11 (0.05)
Investigations	17	1	1 (0.17)	3	3 (1.03)	13	11 (0.05)
Respiratory, thoracic, and mediastinal disorders	13	1	1 (0.17)	1	1 (0.34)	11	9 (0.04)
Endocrine disorders	11	1	1 (0.17)	0	0	10	9 (0.04)
Surgical and medical procedures	11	1	1 (0.17)	2	1 (0.34)	8	8 (0.04)
Congenital, familial, and genetic disorders	9	0	0	1	1 (0.34)	8	7 (0.03)
Eye disorders	8	0	0 (0)	0	0 (0)	8	8 (0.04)
Renal and urinary disorders	8	0	0 (0)	1	1 (0.34)	7	7 (0.03)
Cardiac disorders	5	0	0 (0)	1	1 (0.34)	4	4 (0.02)
Hepatobiliary disorders	4	1	1 (0.17)	0	0	3	3 (0.01)
Reproductive system and breast disorders	4	0	0 (0)	0	0 (0)	4	4 (0.02)
Immune system disorders	3	0	0 (0)	0	0 (0)	3	3 (0.01)
Vascular disorders	3	0	0 (0)	0	0 (0)	3	3 (0.01)
Blood and lymphatic system disorders	2	0	0 (0)	0	0 (0)	2	2 (0.01)

(Continued)

Table 4 Continued.

System organ class	Total events, *n*	Age <2 years *n* = 882* IGHD (*n* = 592) Events, *n*	Age <2 years *n* = 882* IGHD (*n* = 592) Patients, *n* (%)	Age <2 years *n* = 882* MPHD (*n* = 290) Events, *n*	Age <2 years *n* = 882* MPHD (*n* = 290) Patients, *n* (%)	Age ≥2 years *n* = 21,976* Events, *n*	Age ≥2 years *n* = 21,976* Patients, *n* (%)
Ear and labyrinth disorders	2	0	0 (0)	0	0 (0)	2	2 (0.01)
Social circumstances	1	0	0 (0)	0	0 (0)	1	1 (0.01)

IGHD, isolated growth hormone deficiency; IOS, International Outcome Study; MPHD, multiple pituitary hormone deficiency; NSARs, non-serious adverse reactions; SAEs, serious adverse events; SARs, serious adverse reactions; SAS, safety analysis set.
The breakdown of specific NSARs, SAEs and SARs occurring in >1.0% of participants are presented.
*Patients in each group for the SAS. **Bold type highlights findings for main system organ classes with listed subcategories for children with MPHD.

the KIGS database showed that 38% of patients aged 0–3 years had MPHDs versus 14% of those aged 7–8 years (16). Similarly, in a cohort of 59 children with GHD treated before 1 year of age, a high frequency of clinical manifestations associated with pituitary dysfunction was observed (jaundice and hypoglycaemia) (4). In another study population of 67 children with pituitary stalk interruption syndrome, neonates showed a more severe hormonal and radiological phenotype compared with children referred for growth retardation, and progressive endocrine impairment was documented throughout childhood in those with growth retardation (27). These results stress the importance of periodic testing for additional deficits in infants at diagnosis and during follow-up (3, 26).

GH therapy was associated with rapid and sustained catch-up growth in both groups. After 1 year of GH treatment, the mean length/height SDS was within the normal range (−2 to +2) in both groups. Although length/height SDS and GH dose were similar between the two groups at baseline, the increase in length/height SDS from baseline to 1 year in younger children was almost twice that in older children and over one-third more than that in older children after 10 years of GH therapy. After 10 years of treatment, children who began treatment with GH < 2 years of age had better growth outcomes compared to children who started GH ≥ 2 years of age. One explanation for this observation could be that a more pronounced deficiency of GH in infants leads to a correct diagnosis of GHD, whereas suspected GHD in pre-pubertal children aged ≥2 years could be mistaken due to delayed maturation. This would also be in line with the higher proportion of patients aged <2 years with abnormal MRI findings (26.4%) compared with children aged ≥2 years (8.2%). However, this cannot be confirmed without GH peak test results for those participants for whom these were missing.

Another explanation may be the use of concomitant testosterone and certain medications (particularly hydrocortisone), which have been shown to independently affect growth (28, 29). These were used more frequently in children aged <2 years than those aged ≥2 years (testosterone: 3.1 vs 1.8%; hydrocortisone: 24.8 vs 3.9%) and may have affected height outcomes in the younger group. Furthermore, children who initiated GH treatment later during childhood, up to 1 year before puberty, had a shorter period of pre-pubertal growth ahead; thus, GH treatment may have had less of an impact on clinical outcomes in these children. A study found that a longer duration of GH treatment before the onset of puberty was associated with improved height outcomes; however, there was no significant difference in achieving target height between children who started treatment before or after puberty onset. In addition, children who started treatment after puberty onset had greater pubertal height gain, suggesting that they may have not yet started catch-up growth (30).

Rapid catch-up growth in very young children with GHD has been described previously (4, 16, 26). In one study, after 1 year of treatment in patients with IGHD, an increase in height SDS of 1.7 was observed for children aged 0–3 years, while an increase of 0.6 was observed for children aged 7–8 years (16). In another report, children with GHD treated before 1 year of age achieved an approximately 1.5 increase in height SDS after 1 year of treatment (4). These findings suggest that treating children at an earlier age can restore normal growth velocity and infancy–childhood spurt (31). However, it is important to note that, in the general population, the natural growth velocity is higher within the first 3 years of age than during later childhood (32). The rapid catch-up growth seen in the younger children after 1 year of GH treatment may in part reflect the higher growth velocity.

In the current study, outcomes were similar between children with MPHDs and IGHD. This stands in contrast to a previous analysis where children with MPHDs achieved a statistically greater gain in height SDS compared with children with IGHD after 1 year of treatment; both groups were between 0 and 3 years old

(33). In addition to the potential difference in the age distribution between children with IGHD and MPHDs, in that study, all children received a higher dose (0.042 mg/kg/day) than in the current analysis (0.035 or 0.036 mg/kg/day) (33).

In this study, IGF-I SDS values increased after 1 year of treatment and remained within the normal range for most patients in both groups. Children <2 years experienced a higher increase of IGF-I levels after 1 year of treatment, but the increases were in accordance with the GH dose and catch-up growth reported in the study. It is recommended that IGF-I concentrations are carefully monitored in children with GHD (26), and guidelines recommend titrating the GH dose to achieve IGF-I levels within the age-adjusted reference range (5).

The safety data were consistent with the approved labelling for Norditropin® and previous studies of GH treatment in children (34, 35, 36). NSARs were more frequent in older children, whereas SARs were more frequent in younger children. AEs of interest occurred in six children with MPHDs. This could be related to MPHDs, as young children with MPHDs are particularly vulnerable to hypoglycaemia if they have both GHD and ACTH deficiency.

The main limitations of this study are associated with its observational design, such as the potential selection bias, lack of central laboratory analysis, and incomplete reporting of variables (particularly GH peak test results). Diagnoses of IGHD or MPHDs were as reported by the physicians, and hence, some participants may have been misdiagnosed. At baseline, younger children appeared to have had more severe GHD than the older age group. This is important as severe GHD has been shown to be a negative predictor of GH response, regardless of age (37, 38, 39). However, GH peak test data were only collected for 192 children aged <2 years, thus conclusions on the severity of GHD cannot be made with certainty. Missing data limit the interpretation of results and make it difficult to draw conclusions; however, this reflects the real-world nature of the analysis. Recent evidence suggests that the IGF-I/insulin-like growth factor binding protein 3 molar ratio, a rough proxy for unbound (freely circulating) IGF-I, could be a useful marker for the diagnosis of GHD in children who do not have disorders that can affect IGF-I levels (40). This could be of particular use in those individuals without a GH stimulation test, or who do not have an optimal response. Other limitations include the differential number of patients by age group (507 in children aged <2 years vs 7,486 in those aged ≥2 years at treatment initiation) and any potential unmeasured confounders (e.g. genetic factors, nutritional status, socioeconomic factors and treatment adherence) that may have influenced growth but were not accounted for in the study.

Despite these limitations, this is the first study analysing the long-term safety and effectiveness of GH treatment in children with GHD aged <2 years using real-life data from the NordiNet® IOS and ANSWER Program. The findings of this study provide data on the comparison between very young children with IGHD and MPHDs, an area with very limited data availability. In this context, observational studies allow the evaluation of effectiveness and safety parameters in very young children with GHD.

To conclude, children with early GHD onset had evidence of more severe GHD and a higher prevalence of MPHDs and abnormal MRI findings. It is important that physicians who diagnose GHD in very young children are aware of the occurrence of additional pituitary deficiencies, which may be clinically silent in this young age group. GH therapy in this age group was associated with rapid and sustained catch-up growth, showing improved height outcomes after 10 years of GH treatment compared with children who started GH later than 2 years of age. No new safety concerns were observed. The results of this study reinforce the importance of early diagnosis and treatment to achieve adult height in children with GHD.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-25-0493.

Declaration of interest

TRR has received consulting fees, payment or honoraria for lectures/presentations from BioMarin, Merck and Novo Nordisk. PK has consulted for Novo Nordisk and Pfizer. BSM has consulted for Amgen, Ascendis Pharma, BioMarin, EMD Serono, Endo Pharmaceuticals, Novo Nordisk, Pfizer, Provention Bio, Sanofi and Tolmar and received research support from Alexion, AbbVie, Aeterna Zentaris, Foresee Pharmaceuticals, Lumos Pharma, Lysogene, Novo Nordisk, OPKO Health, Pfizer, Prevail Therapeutics and Sangamo Therapeutics. NK is an employee of Novo Nordisk and holds stocks in Novo Nordisk and Pfizer. AHO is an employee of and shareholder in Novo Nordisk. AP is an employee of Novo Nordisk. MP has received advisory board fees from Ipsen, Novo Nordisk and Pfizer France and research support from Ipsen, Novo Nordisk, Pfizer, Sandoz, Merck, Sanofi and French Public Research funds (ANR and PHRC) and speaker fees from Novo Nordisk, Ipsen and Pfizer. JB has received honoraria for presentations at meetings sponsored by Novo Nordisk, received sponsorship to attend scientific meetings by Novo Nordisk, and received payment for membership of the Publication Steering Committee of the International Outcomes Study, sponsored by Novo Nordisk; received honoraria for presentations at a meeting sponsored by Sandoz; and received honoraria for presentations at meeting sponsored by Ipsen.

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Statement of ethics

Approval was obtained from relevant ethics committees, written informed consent was obtained, and all data were anonymised. A list of Independent Ethics Committees/Institutional Review Boards for the ANSWER Program is provided in Supplementary Table 1 (see the section on supplementary materials given at the end of the article) and a list of clinics for NordiNet® IOS is provided in Supplementary Table 2. This study was conducted in accordance with the Declaration of Helsinki and was approved by the local Institutional Ethics Committee/Institutional Review Board and the local regulatory authorities at each study centre and data privacy agencies as required. NordiNet® IOS and ANSWER were conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practice.

Patients provided informed consent before any study-related activities. For paediatric patients, the parent(s) or a legally authorised representative granted consent. Children who reached adult height and discontinued GH had the option of continuing in the study during a transition period of up to 2 years (and being monitored during this period without being treated with Norditropin®). According to local rules, at the start of this transition period, patients aged ≥18 years were expected to sign a separate transition informed consent form if the patient continued to stay under follow-up in the NordiNet® IOS in the respective paediatric clinics. For children <18 years, the parent(s) or legal guardian was to take this responsibility. If a later date reassessment of the patient indicated that the patient satisfied the diagnostic criteria of adult GHD, then he/she would have the option of re-initiating Norditropin®. The informed consent process using the study's main informed consent form was to be completed before re-initiation of Norditropin®. If applicable, written informed consent was obtained from female partners in case of reporting data on pregnancy.

Author contribution statement

TRR helped with conceptualisation, data curation, investigation, methodology, project administration, supervision, validation, writing of the original draft, review and editing. PK helped with conceptualisation, writing of the original draft, review and editing. BSM helped with funding acquisition, review and editing. NK helped with conceptualisation, formal analysis, writing of the original draft, review and editing. AHO helped with methodology, writing of the original draft, review and editing. AP took part in conceptualisation, data curation, funding acquisition, supervision, review and editing. MP helped with conceptualisation, investigation, methodology, review and editing. JB took part in conceptualisation, investigation, methodology, review and editing.

Data availability

The data that support the findings of this study are not publicly available because they contain information that could compromise the privacy of research participants but are available from the corresponding author upon reasonable request.

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