Growth hormone treatment of Canadian children: results from the GeNeSIS surveillance program

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Abstract

BACKGROUND: Country-specific data on outcomes of recombinant human growth hormone (GH) treatment are lacking, so we present such data for GH-treated children in Canada.

METHODS: We describe characteristics and outcomes of 850 GH-treated children (mean baseline age 8.5 years) constituting the Canadian cohort of the multinational observational Genetics and Neuroendocrinology of Short-stature International Study (GeNeSIS; Clinical Trial Registry Number: NCT01088412) of pediatric patients. Diagnosis associated with short stature was as determined by the investigator. Auxological data were evaluated yearly until near-adult height (NAH). Adverse events were assessed in all GH-treated patients.

RESULTS: The diagnosis ascribed as the cause of short stature was GH deficiency (GHD) in 61.9% of cases, predominantly organic (OGHD) rather than idiopathic (IGHD), particularly congenital pituitary abnormalities and intracranial tumors. All diagnostic groups with sufficient patients for analysis had increased height velocity standard deviation score (SDS) and height SDS during GH treatment. For patients who reached NAH (n=293), mean height SDS was within normal range for approximately 80% of patients with OGHD (n=131) or IGHD (n=50), 50% of patients with idiopathic short stature (n=10) and 46% of patients with Turner syndrome (n=79). Eleven deaths were reported, seven in patients with OGHD. Serious adverse events considered GH-related (n=19) were isolated except for medulloblastoma recurrence (n=2) and adenoidal hypertrophy (n=2).

INTERPRETATION: GH treatment was effective and had a good safety profile in Canadian children. Compared with the USA and total GeNeSIS cohorts, GH doses were lower and a greater proportion of treated Canadian children had OGHD.

Introduction

Children with short stature and/or low growth velocity may benefit from growth hormone (GH) treatment to increase adult height [1]. Recombinant human GH was initially approved for GH deficiency (GHD), which remains the main indication. GHD can be due to congenital or acquired causes [2,3]. Pediatric GH therapy has been approved in many countries for additional conditions, including Turner syndrome, small for gestational age (SGA), Prader-Willi syndrome, chronic renal insufficiency, short stature homeobox (*SHOX*)-containing gene deficiency, Noonan syndrome and idiopathic short stature (ISS) [1,4–11].

For approved indications and doses, GH therapy is generally believed to be safe [12-14]. Large international databases of GH-treated patients, including the Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS), have been used to examine long-term outcomes and safety in 'real-world' settings [15-21]. Canada has a long history in helping establish GH safety and effectiveness, through clinical trials and surveillance programs [4,22-24] beginning in the 1960s and continuing until 2015 with the GeNeSIS program.

While multinational surveillance studies, such as GeNeSIS, provide global information, GH treatment uptake and outcomes may differ across and between countries. Such differences may involve approved indications and doses, age chosen for treatment initiation, funding sources for treatment, and patient characteristics that can influence the outcomes. Country-specific data on outcomes of GH therapy have currently been reported to only a limited extent [19,25-28]. The objective of the current report was to evaluate outcomes of GH treatment in pediatric patients in Canada, comparing findings with those from the US and the overall global population, using data collected in GeNeSIS.

Methods

Patient population

The prospective, multinational, open-label, post-marketing surveillance program GeNeSIS was designed to examine safety and effectiveness of GH (somatropin; Humatrope®, Eli Lilly and Company, Indianapolis, USA) administered in children. Data were collected according to the ethical principles of the Declaration of Helsinki, and the protocol was approved by appropriate local ethics review committees. Written informed consent for data collection, processing and publication was provided by a parent/legal guardian according to national laws and regulations; the child also provided assent when appropriate.

The observational nature of GeNeSIS meant that all diagnoses and measurements were as reported by the attending physician. GHD and ISS were defined using current guidelines [14,29]. Diagnoses and treatments were to be performed according to standard pediatric endocrinology practice, and all treatment decisions were at the discretion of the participating investigator. Patients enrolled in GeNeSIS and who received GH treatment could be either GH-naïve at entry or already treated with GH. Patients presenting with closed epiphyses were excluded, although patients who had epiphyseal closure during participation could continue in the study. Patients were enrolled at 14 centers in Canada. The present report examined data from the start of the study in April 1999 until study closure in September 2015.

Study evaluations

The 2000 US National Center for Health Statistics standards [30] were used to calculate height standard deviation score (SDS) for all countries in GeNeSIS, except Japan. Pre-specified age- and gender-matched reference data [31] were used for height velocity SDS. Target height was based on the sex-adjusted average of parental heights where available;

pubertal stage was recorded according to the Tanner classification [32,33]. Near-adult height (NAH) was defined as the patient having reached one of the following criteria: closed epiphyses, height velocity <2 cm/year or bone age >14 years for girls or >16 years for boys.

Adverse events were evaluated, with the investigator assessing the relationship of each event to GH treatment (possibly/probably or not related). Serious adverse events (SAEs) were classified according to Canadian guidelines [34]. Treatment-emergent adverse events (TEAEs) were defined as events that first occurred or worsened in severity after the start of GH treatment and, thus, were evaluated only in GH-treated patients with at least one post-baseline visit. Adverse events were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA), version 18.1.

Data analysis and statistics

The observational nature of the study meant that various data were missing for some patients. Each analysis used the maximum available data, and patient numbers therefore varied between specific analyses. Changes in auxological parameters during treatment were evaluated for the following patient subgroups: (1) GH-naïve at entry with both baseline and 1-year height SDS data (n=274); (2) GH-naïve at entry with yearly height measurements for at least 4 years (n=165); and (3) reached NAH during the study and were either GH-naïve or already GH treated at entry to GeNeSIS (n=293). Data are presented as means with 95% confidence interval (CI) for continuous variables, and as frequency and percentage for categorical variables. Outcomes across different diagnostic groups could be compared by examination of the overlap of 95% CI. Statistical analyses were conducted using SAS® 9.1.

Results

Patient characteristics

In total, 848 GH-treated Canadian children (53.7% male, 46.3% female) had data evaluable for effectiveness analyses; two further patients were only included in safety analyses. At GeNeSIS entry, 528 (62.3%) were receiving GH and 320 (37.7%) were GH-naïve. Ethnic origin was Caucasian for 90.1% of patients with relevant information; however, ethnicity data were not provided for 59.8% of patients. The most frequent primary diagnosis was GHD (61.9%; Table 1), with the majority reported to be due to organic causes (379/526 [72.1%]). Among the 379 patients with organic GHD (OGHD), 184 had congenital pituitary development abnormalities and 102 had an intracranial tumor. After GHD, the next largest diagnostic category identified was Turner syndrome (18.4%). The diagnoses for the US GeNeSIS patients are shown for comparison. The proportions of children with idiopathic GHD (IGHD) or ISS were higher in the USA than in Canada, whereas the proportion with Turner syndrome appeared lower in the USA. The proportions of males with GHD (OGHD or IGHD) were similar in Canada and the global population, whereas GH-treated patients with ISS or born SGA appeared more likely to be male in Canada than globally (data not shown).

Overall mean age at start of GH treatment was 8.5 years (range 0.01–18.2 years). For diagnostic groups most frequently reported (Supplemental Table 1), mean age at GH start was highest for patients with ISS. Patients with OGHD had a lower mean age at GH start than patients with IGHD. Age at GH start was ≥10 years for 47.5% and 64.6% of patients with OGHD and IGHD, respectively, and for 57.1% of patients with Turner syndrome and 78.9% of patients with ISS. At baseline, the majority of both female (85.8%) and male (79.9%) patients were prepubertal, with similar percentages across diagnostic groups, except for ISS,

in which 60.0% of females and 48.0% of males had started puberty. Gender data for the US (not shown) and the entire GeNeSIS cohort were similar.

Mean peak GH in GH stimulation tests was <5 µg/l for both OGHD and IGHD (Supplemental Table 1), whereas results for patients with ISS were higher, as expected (mean peak GH 24.1 µg/l). Stimulated peak GH levels in Canadian children with GHD were lower than those in the global cohorts.

Mean dose at GH start was highest for patients with Turner syndrome (0.29 [95% CI 0.28 to 0.29] mg/kg/week), and lowest for patients with OGHD (0.18 [95% CI 0.18 to 0.19] mg/kg/week). Canadian mean GH doses were lower than those used in the USA (data not shown) and the global cohort (Supplemental Table 1).

Reported mean duration of GH treatment was 6.6 (95% CI 6.3 to 6.9) years overall, and was longest for patients with OGHD (8.0, 95% CI 7.5 to 8.4 years) and shortest for those with ISS (2.7, 95% CI 2.2 to 3.2 years; not all data shown). Duration of GH treatment was >4 years for 556 patients (65.4%).

Height data during growth hormone therapy

Auxological data at baseline and 1 year for patients naïve to GH treatment at study entry are summarized in Table 2 for Canada (2a) and the global database (2b). For Canadian patients overall, mean height velocity SDS increased from −1.19 (95% CI −1.43 to −0.94) at baseline to 1.97 (95% CI 1.69 to 2.26) at 1 year. All diagnostic groups had a mean gain in height SDS at 1 year, with the least gain in those with ISS (0.33 [95% CI 0.21 to 0.45]) and the greatest gain in patients with IGHD (0.60 [95% CI 0.46 to 0.73]).

Mean height SDS and height velocity SDS over the first 4 years of GH treatment are shown in Figure 1. For each diagnostic group, mean height velocity SDS increased in the first year and declined over subsequent years, as expected.

Auxological parameters for all patients who reached NAH are shown in Table 3a and 3b, and mean gain in height SDS is shown in Figure 2. NAH SDS was > −2 for the majority of patients with OGHD and IGHD but for only about half of the patients with Turner syndrome or ISS. Mean age at baseline was lower and mean therapy duration to NAH was longer for patients with OGHD than for those with IGHD; however, this did not result in a greater mean change from baseline for height SDS (Figure 2).

Safety outcomes

Of 850 GH-treated Canadian children included in the overall safety analysis (Table 4), 11 were reported to have died during the study; patient characteristics and cause of death are shown in Supplemental Table 2. The majority of deaths (n=7 [64%]) were in patients with OGHD. Death was considered possibly related to GH treatment by the investigator for three patients, for whom the primary diagnosis was medulloblastoma (n=2) or anaplastic astrocytoma (n=1) and cause of death was tumor recurrence in each case.

SAEs were reported for 97 patients, with events in 19 patients considered related to GH treatment by the investigator (2.2% of the total safety population; see the footnote to Table 4). The GH-related SAEs were isolated events in individual patients, except for the aforementioned medulloblastoma recurrence in two patients (both with OGHD) and adenoidal hypertrophy in two patients (one with OGHD and one with Turner syndrome).

Among 833 GH-treated patients with at least one post-baseline visit, 587 (70.5%) had at least one TEAE reported (Table 4). TEAEs were reported more frequently for patients with OGHD than for those with IGHD or other diagnoses. The most frequently reported TEAEs for Canadian patients overall were headache and secondary (central) hypothyroidism, consistent with the known GH safety profile and an inherent risk of hypothyroidism due to the underlying diagnosis. TEAEs classified by the investigator as possibly GH-related occurred in 87 patients overall (10.4% of the study population).

Interpretation

The results of GeNeSIS indicated a positive treatment effect on height gain, both during the first 1–4 years of GH therapy and at NAH, and a reassuring safety profile both within Canada and globally. Among the 30 countries involved in GeNeSIS, Canada was the sixth largest contributor of patients, with 850 GH-treated patients (3.8%) out of approximately 22,000 globally. Currently approved pediatric indications in Canada are GHD (approved in 1987), Turner syndrome (1997), SGA (2006), ISS (2006) and SHOX deficiency (2008); chronic renal insufficiency is an approved indication for some GH formulations (1996) but not for the GH primarily used in GeNeSIS.

The majority of patients had GHD (Canada 61.9% vs. global 62.9% vs. USA 52.9%). However, the proportions with OGHD (44.6% of all diagnoses vs. global 13.3% vs. USA 10.9%) versus IGHD (17.3% vs. 49.4% vs. 41.7%) reflected a higher frequency of inclusion in Canada of patients with abnormal pituitary development and intracranial tumor. The proportion of patients with Turner syndrome in Canada was also higher than globally and in the USA (18.4% vs. 8.4% vs. 7.5%), which may, in part, have been attributable to enrollment in GeNeSIS of patients from a large Canadian clinical trial [4]. In addition, fewer patients in Canada than in the USA had ISS or were born SGA. This likely indicates a more conservative approach of endocrine specialists in Canada to administering GH to children with non-GHD conditions, with the exception of Turner syndrome. Also, ISS and SGA are privately funded in many provinces in Canada, whereas GHD is fully reimbursed by provincial programs.

Patients showed increased height velocity SDS within the first year, with a positive mean value maintained over the first 3–4 years of GH treatment, resulting in an increase in height SDS over time. Across all indications, growth response in the Canadian cohort was lower

than that seen in the global data. Differences in GH response may be, in part, attributable to our more conservative approach to treatment dosages compared with the global, and particularly the US, populations. The stimulated peak GH was higher in the global vs. the Canadian IGHD group. This could reflect inclusion of milder or transient forms of GHD in the global cohort compared with a more severely affected group of patients in Canada. The GH stimulation test result considered to indicate GHD is lower in Canada than in the USA.

Patients with Turner syndrome in Canada remained shorter than the global cohort at NAH, and percentages with NAH SDS within the normal range were lower than globally, consistent with past research showing NAH to be influenced by age at GH start, GH dose and concomitant estrogen treatment [6,35-37]. However, compared with global rates, patients with Turner syndrome in Canada had a similar height SDS gain from baseline to NAH of 0.96. This gain was consistent with the results from the Canadian randomized clinical trial and other studies of GH treatment in Turner syndrome [4,5,38]. The tendency of Canadian physicians to treat shorter patients with Turner syndrome may reflect parent/patient healthcare priorities, as previously published [37], although the impact of provincial funding decisions may also play a role.

TEAEs were reported more frequently for Canadian patients than for the global population (Canada 70.5% vs. global 30.1%), suggesting that physicians in Canada may be more vigilant in reporting adverse events than physicians in other countries. Indeed, the Canadian cohort was the second largest contributor of adverse events to the global database, surpassed only by the Netherlands, a country with an established national registry. Among the 850 patients in GeNeSIS in Canada, with mean treatment duration 6.6 years, 11 patients (1.3%) were reported to have died (standardized mortality rate of 3.0 [95% CI 1.5 to 5.4]). This was a higher frequency of death than reported in 21,106 patients in the global cohort with follow-up in study and known gender, who were GH-treated for a mean of 5.0 years (42 deaths [0.2%])

[21]. The Canadian cohort included a higher proportion of patients with OGHD (particularly with a history of intracranial tumor) than the global cohort. Of the 11 reported deaths, seven were children with a primary diagnosis of OGHD; four of the seven died because of cancer recurrence, and one patient previously treated with cranial irradiation died because of a second cancer. Analyses from various studies have indicated an increased risk of mortality in patients previously treated for a malignancy, irrespective of GH treatment [21,39-42]. Results from the Childhood Cancer Survivor Study (CCSS) indicate no association of death or tumor recurrence with GH treatment [42], supporting the assessment that these deaths were unlikely to be GH-related. Nevertheless, three of the deaths (2 recurrences of medulloblastoma and 1 anaplastic astrocytoma recurrence) were recorded by the investigators as being possibly related to GH treatment.

A previous analysis of GeNeSIS found no increased risk for primary cancers during study participation in patients with no previous cancer history when compared with general population cancer registries [16]. Similarly, the US Pediatric Endocrine Society Drug and Therapeutics Committee found no association between GH treatment and the risk of *de novo* cancer development in children with no prior history of or known predisposition to cancer [44].

Analyses from the large Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) cohort demonstrated an increased risk of mortality from a number of second malignancies in patients whose original diagnosis was cancer [45], with no clear raised risk in patients with growth failure without other major disease. Initial reports from the CCSS indicated that GH-treatment was associated with a higher relative risk for second neoplasms [39,45]. However, a recent analysis of the CCSS, with an extended period of follow-up, found no direct evidence to support an increased risk of second neoplasms of the central nervous system in GH-treated patients, who clearly have risk factors other than GH for

development of subsequent neoplasms [42]. Our observational study cannot resolve this question but the balance of evidence suggests that the risk of malignancy relates to the underlying condition rather than GH treatment.

Limitations

This analysis of Canadian data from GeNeSIS is limited in that the study was open-label and observational; however, the data reflect the "real-world" clinical setting of GH treatment for a large patient cohort.

Conclusion

This study of pediatric patients in Canada, who received GH treatment in an observational setting, showed that the major indication for GH treatment in Canada is OGHD. Overall effectiveness and safety results from the GH-treated Canadian cohort were generally consistent with those from other clinical trials and international surveillance databases. Approximately 80% of patients with OGHD or IGHD achieved a NAH within the normal range despite use of a lower dose of GH than the global GeNeSIS population, with smaller proportions achieving NAH within normal range for non-GHD conditions. The 11 reported deaths generally reflected the serious underlying etiology of GHD. While the current approach to GH treatment in Canada is more conservative than some other global practices, it appears efficacious and safe, but—as per international guidelines—continued monitoring of patients previously treated with GH is recommended [13].

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Competing interests: Cheri Deal has been involved with Phase 3 and/or Phase 4 studies with Eli Lilly and Company, Serono, Versartis, OPKO; invited lectureships sponsored by Novo-Nordisk, Eli Lilly and Company, Pfizer, EMD Serono, Merck-Serono; ad hoc consulting with EMD Serono, Novo-Nordisk, Merck-Serono, Versartis, OPKO, Zafgen; Grant for Growth

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Figure 1: Height velocity standard deviation score (SDS; open squares) and height SDS (closed circles) over the first 4 years of growth hormone (GH) treatment for patients in Canada (solid lines) and the global population (broken lines) with data for each year and who were GH treatment-naïve at study entry, for all patients and for evaluable diagnostic groups. Values show means with 95% confidence intervals. SDS corresponds to the following height percentiles on a standard height of age growth curve: −3SDS = 0.2%; −2SDS = 2.3%; −1SDS = 16%; 0SDS = 50%; +2SDS = 97.7%; +3 SDS = 99.8%. Data from patients with idiopathic short stature are not shown because of the small number of patients in this diagnostic group in Canada with relevant data (n=9).

Figure 2: Change in height standard deviation score (SDS) from baseline to near-adult height for all growth hormone (GH)-treated patients and by diagnostic group in Canada (solid bars) and the global population (striped bars). Note: GHD = growth hormone deficiency. SDS correspond to the following height percentiles on a standard height of age growth curve: −3SDS = 0.2%; −2SDS = 2.3%; −1SDS = 16%; 0SDS = 50%; +2SDS = 97.7%; +3SDS = 99.8%. Data from patients with idiopathic short stature are not shown because of the small number of patients in this diagnostic group in Canada with relevant data (n=10).

Fig 1a

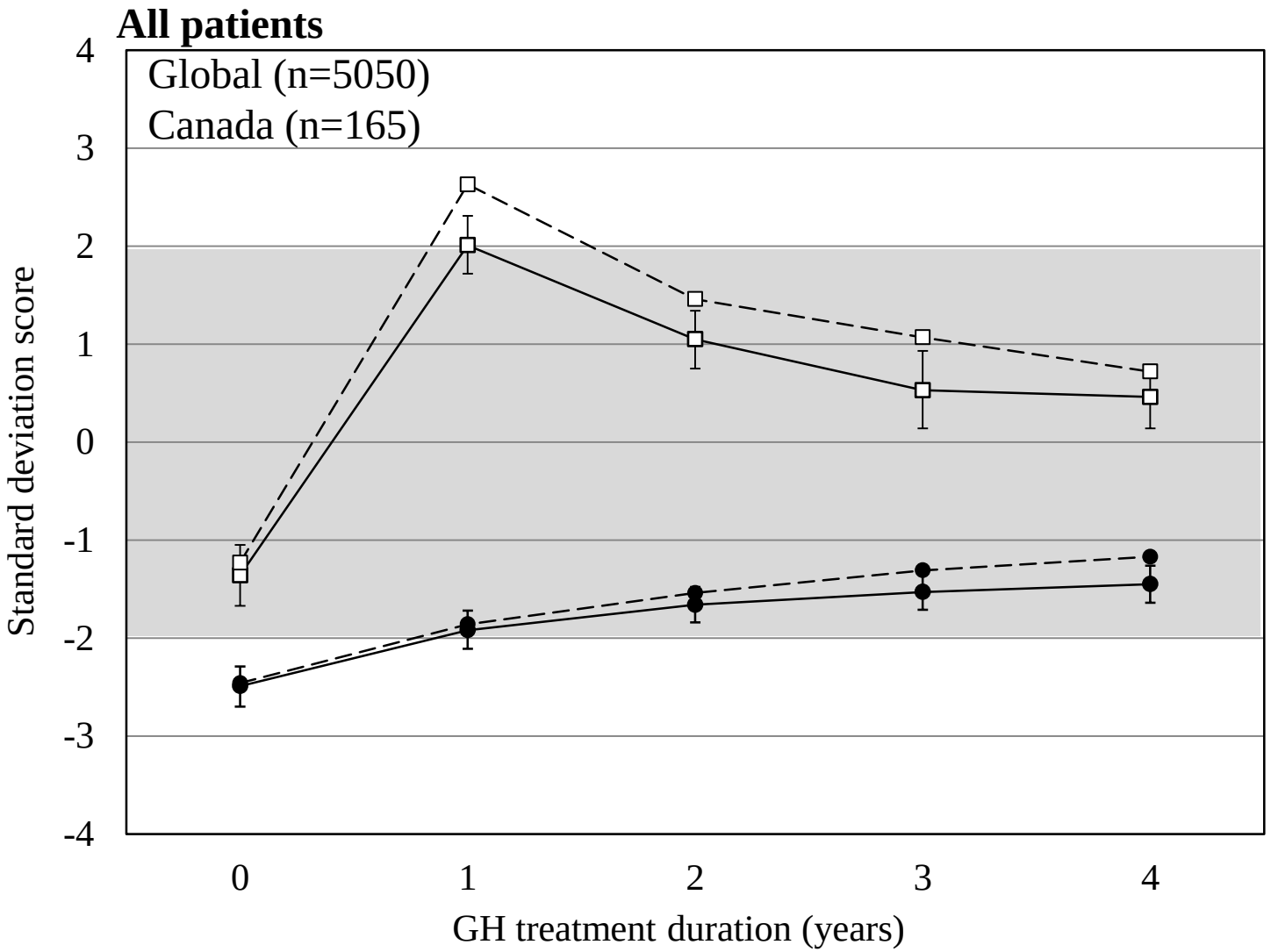


Fig 1b

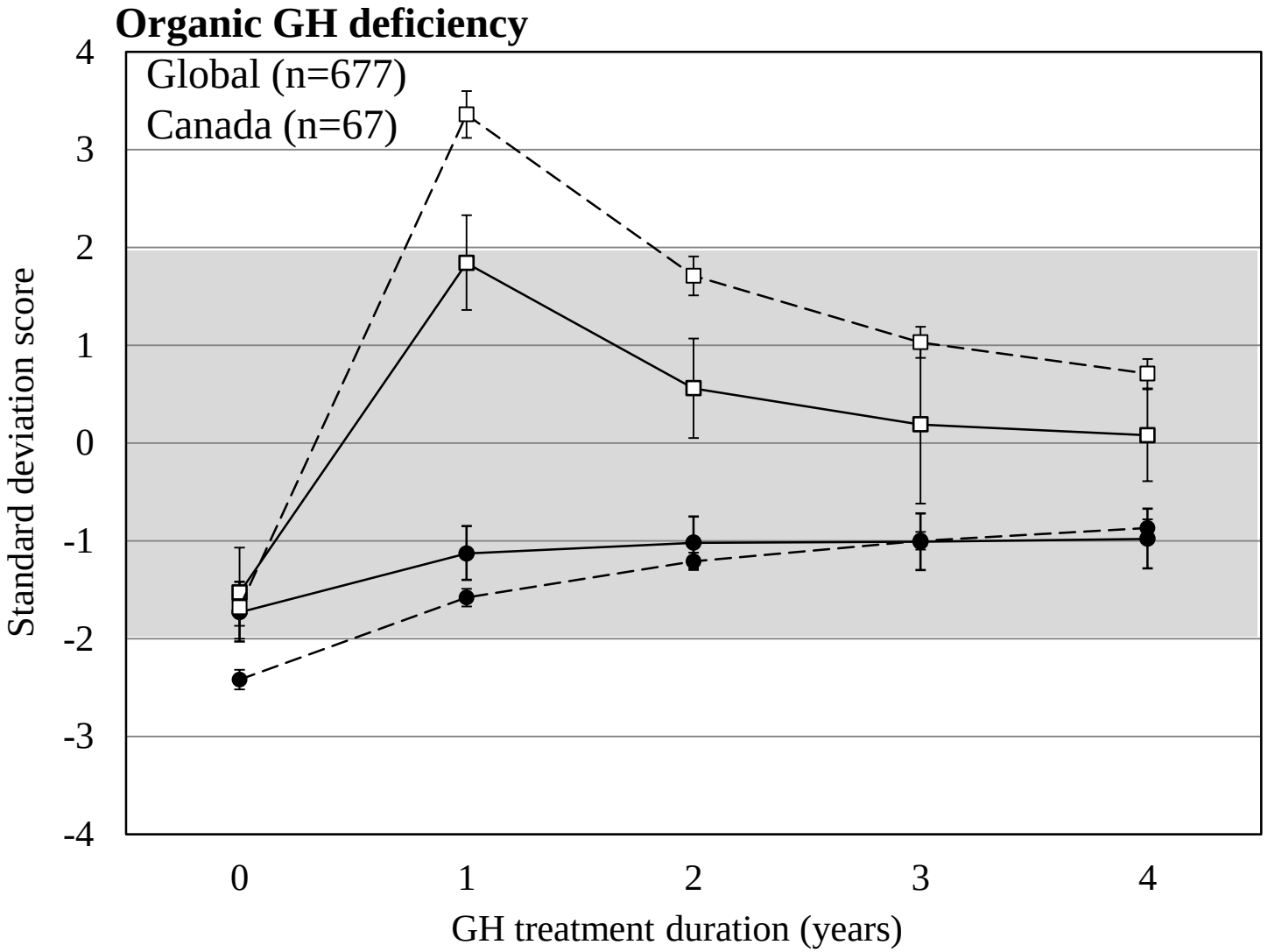


Fig 1c

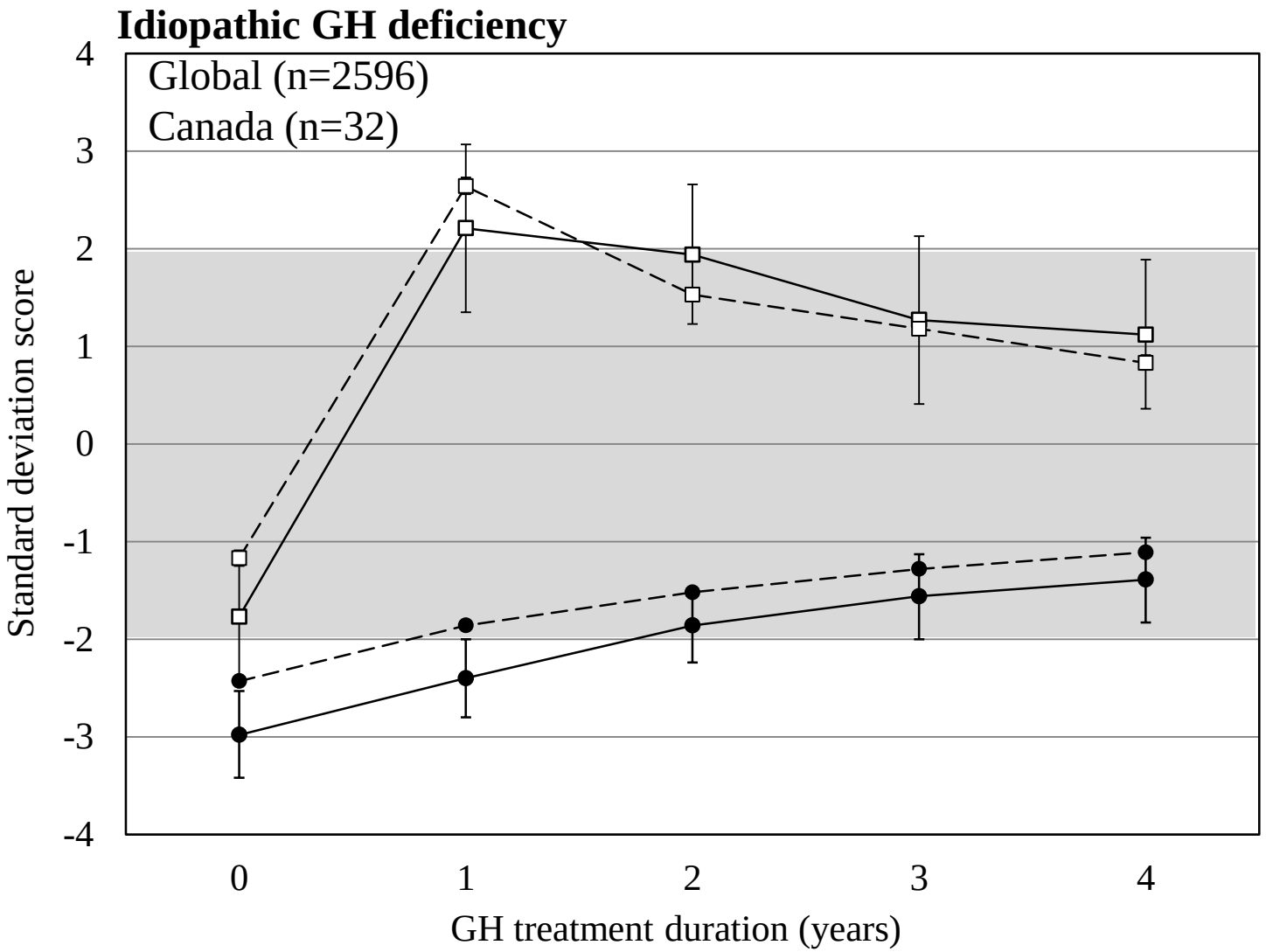


Fig 1d

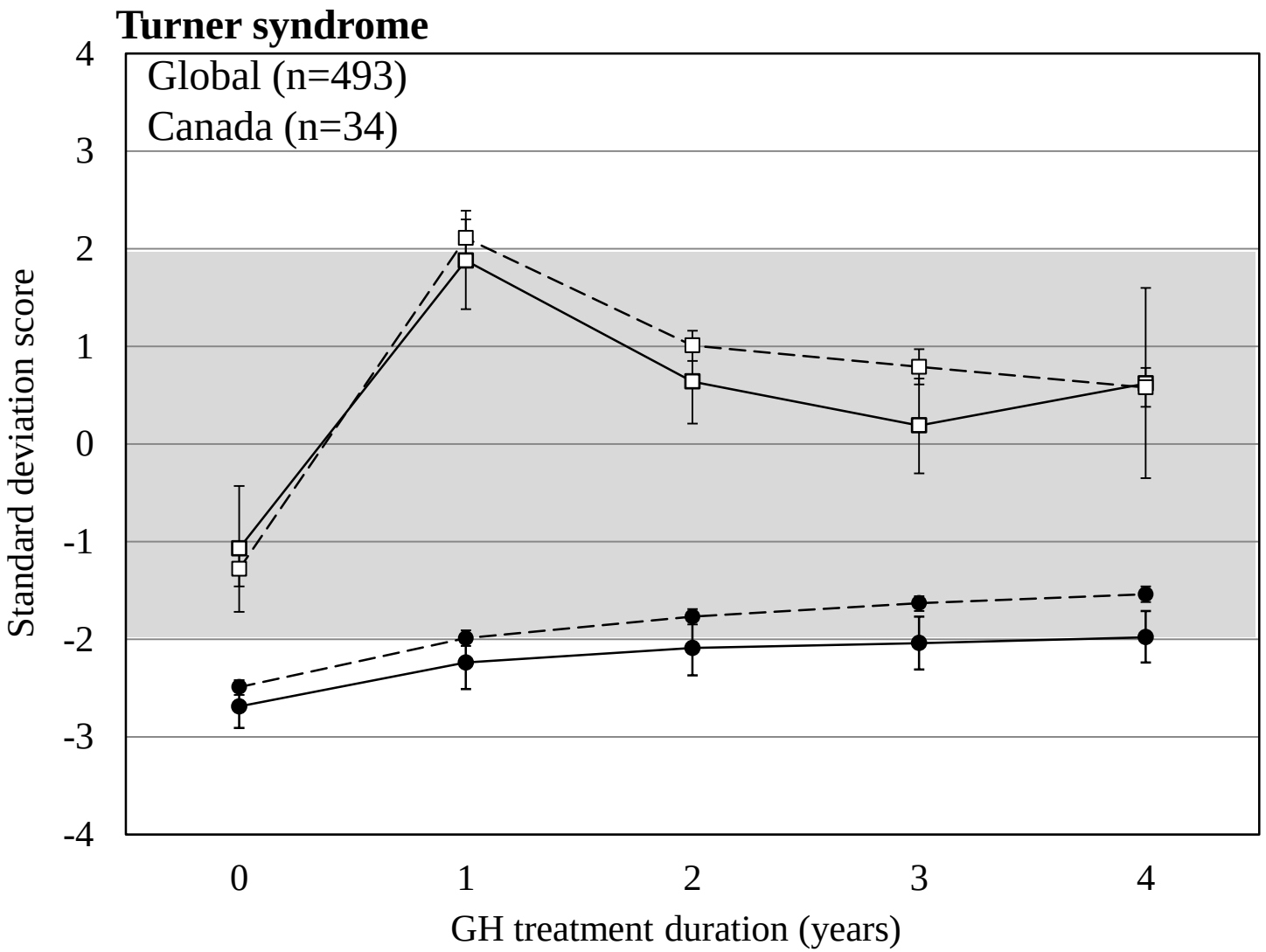
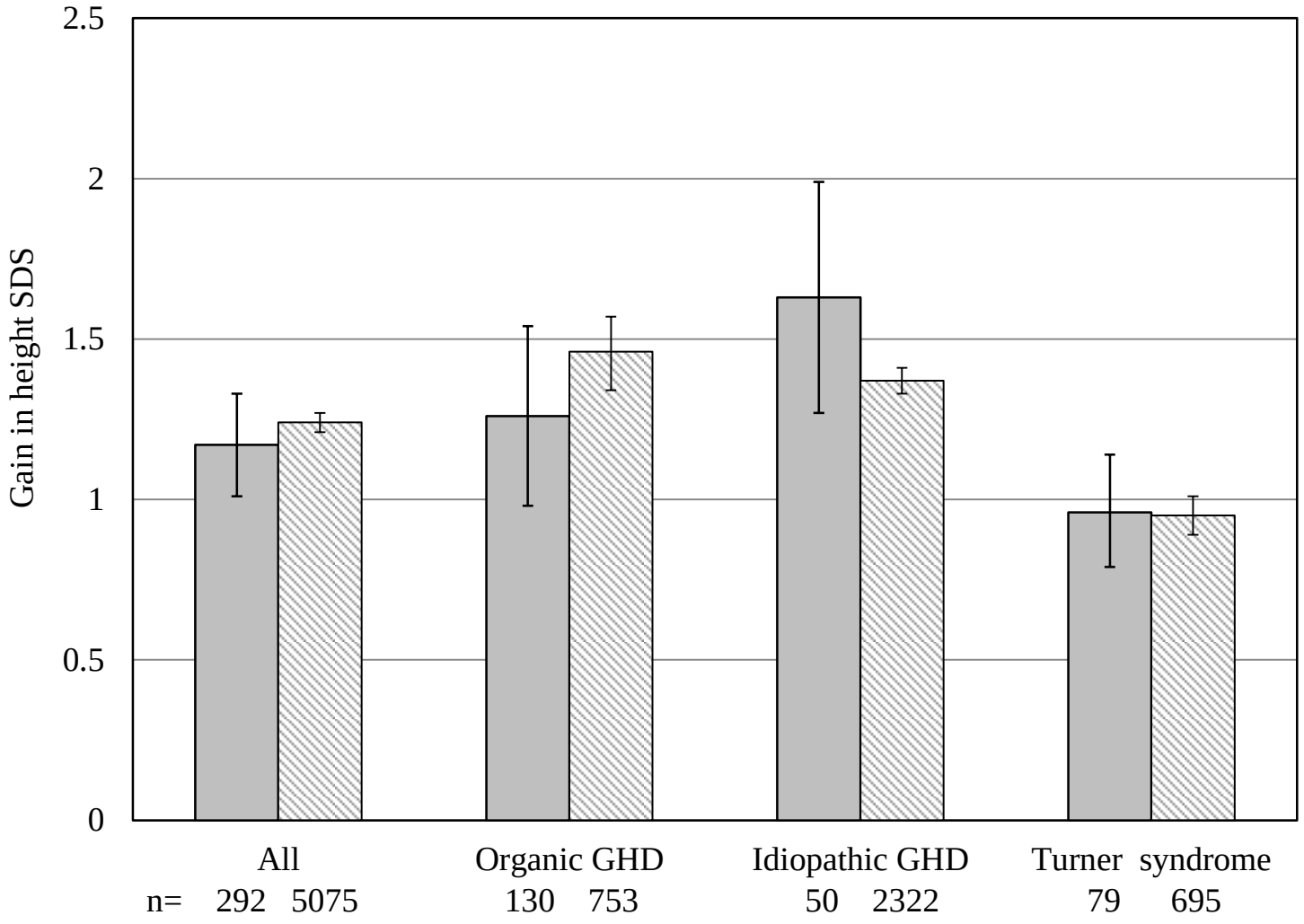


Fig 2



Canada = solid; Global = striped

Table 1: Reported primary diagnosis in 850 children in Canada and 9806 children in the USA treated with growth hormone for short stature[a]

Primary diagnosis	Canada n (%[b])	USA n (%[b])
GH deficiency (GHD)	526 (61.9)	5184 (52.9)
Idiopathic	147 (17.3)	4088 (41.7)
Classic	133 (15.6)	3198 (32.6)
Neurosecretory dysfunction	4 (0.5)	533 (5.4)
Organic	379 (44.6)	1065 (10.9)
Congenital	243 (28.6)	665 (6.8)
Abnormal pituitary development	184 (21.6)[c]	522 (5.3)
Clinical syndromes	35 (4.1)[d]	57 (0.6)
Genetic defect	6 (0.7)	16 (0.2)
Other CNS malformations	10 (1.2)	53 (0.5)
Acquired	136 (16.0)	400 (4.1)
Intracranial tumor	102 (12.0)[e]	273 (2.8)
Cranial irradiation	13 (1.5)[f]	23 (0.2)
CNS trauma/infection	2 (0.2)	16 (0.2)
Histiocytosis	2 (0.2)	17 (0.2)
Other	14 (1.6)	71 (0.7)
Other defects of GH axis (e.g. bioinactive GH)	0 (0.0)	31 (0.3)
SHOX deficiency-associated syndromes	162 (19.1)	804 (8.2)
Turner syndrome	156 (18.4)	737 (7.5)
Mixed gonadal dysgenesis	3 (0.4)	6 (0.1)
Léri-Weill syndrome	2 (0.2)	21 (0.2)
SHOX deficiency – other	1 (0.1)	40 (0.4)
Other causes of short stature or reduced linear growth	61 (7.2)	540 (5.5)
Genetic defect	43 (5.1)	273 (2.8)
Other	18 (2.1)[h]	267 (2.7)
Idiopathic short stature	38 (4.5)[i]	2594 (26.5)[j]
Small for gestational age	19 (2.2)	353 (3.6)
Skeletal dysplasia	2 (0.2)	19 (0.2)
No GHD[g]	19 (2.2)	52 (0.5)
Prader-Willi syndrome	16 (1.9)	33 (0.3)
Other	3 (0.4)	19 (0.2)

Note: CNS = central nervous system, GH = growth hormone, GHD = growth hormone deficiency, SHOX = short stature homeobox.

Investigator-provided diagnoses were assigned to a pre-defined hierarchical diagnostic tree to classify the primary cause of short stature and establish appropriate diagnostic groups; however, more detailed levels of diagnosis were not always provided (so n of subdiagnoses may not always sum to n of main diagnostic groups).

[a]Diagnosis was unknown for 23 children in Canada and 229 in the USA.

[b]Percentage of total number of patients in country cohort.

[c]Includes patients with primary diagnoses of ectopic posterior pituitary (76), septo-optic dysplasia (67), pituitary hypoplasia (18), pituitary aplasia (10), pituitary stalk defect (8).

[d]Includes patients with primary diagnoses of Prader-Willi syndrome (30), mid-line palatial defect (3), other (2).

[e]Includes patients with primary diagnoses of medulloblastoma (43), craniopharyngioma (26), glioma (9), astrocytoma (7), germinoma (4), primitive neuroectodermal (2), ependymoma (1), pituitary adenoma (1), unspecified (9).

[f]Treatment for leukemia (12), medulloblastoma (1).

[g]A small number of patients, indicated as not having GHD by the investigator, were enrolled with complex diagnoses that, following the structure of the case report form diagnostic module, would routinely be recorded under GHD; assignment of no GHD status to these cases means that in general they were not included in efficacy analyses of the main GeNeSIS diagnostic groups but were included in safety-related analyses.

[h]Includes patients with primary diagnoses of Noonan syndrome (4), chronic renal failure (2), glucocorticoid therapy (2), rheumatoid arthritis (1), inflammatory bowel disease (1), other unspecified (8).

[i]Includes children with primary diagnoses of constitutional delay of growth and familial short stature (7).

[j]Includes children with primary diagnoses of constitutional delay of growth and familial short stature (43)

Table 2: Patient characteristics and auxological data at baseline and after 1 year of growth hormone treatment, by primary diagnostic category (patients naïve to growth hormone treatment at study entry and with baseline and 1-year height measurement available)

a) Canada

	OGHD n=89	IGHD n=57	Turner syndrome n=44	Idiopathic short stature n=25	Small for gestational age n=5
Baseline					
Males (%)	61%	67%	–	84%	80%
Age (years)	8.9 (7.8 to 10.0)	11.3 (10.2 to 12.4)	9.6 (8.5 to 10.6)	12.9 (11.8 to 14.0)	6.3 (3.7 to 9.0)
Height SDS	−1.87 (−2.13 to −1.60)	−2.58 (−2.91 to −2.25)	−2.76 (−2.97 to −2.55)	−2.57 (−2.96 to −2.18)	−4.02 (−5.40 to −2.65)
Height velocity (cm/year)	5.17 (4.12 to 6.22)	4.22 (3.39 to 5.04)	4.96 (4.24 to 5.67)	4.58 (3.78 to 5.37)	6.32 (3.15 to 9.49)
Height velocity SDS	−1.65 (−2.05 to −1.24)	−1.55 (−2.04 to −1.05)	−1.01 (−1.54 to −0.47)	−0.61 (−1.58 to 0.35)	0.31 (−4.70 to 5.32)
Target height SDS	0.25 (0.03 to 0.47)	−0.37 (−0.64 to −0.10)	0.18 (−0.04 to 0.40)	−0.44 (−0.72 to −0.15)	−0.62 (−1.26 to 0.03)
Target height SDS deficit[a]	−2.19 (−2.54 to −1.84)	−2.22 (−2.62 to −1.83)	−2.92 (−3.18 to −2.66)	−2.13 (−2.55 to −1.72)	−3.41 (−5.16 to −1.65)
Stimulated peak GH (µg/l)	4.3 (2.4 to 6.1)	4.4 (3.6 to 5.3)	NA	25.0 (17.2 to 32.8)	NA
GH dose (mg/kg/week)	0.18 (0.17 to 0.19)	0.18 (0.17 to 0.19)	0.29 (0.28 to 0.30)	0.22 (0.19 to 0.25)	0.22 (0.15 to 0.29)
Year 1					
Height SDS	−1.30 (−1.54 to −1.05)	−1.97 (−2.29 to −1.65)	−2.28 (−2.54 to −2.03)	−2.24 (−2.64 to −1.83)	−3.45 (−4.75 to −2.15)
Height velocity (cm/year)	9.30 (8.28 to 10.33)	8.79 (8.14 to 9.44)	7.84 (7.28 to 8.40)	7.31 (6.33 to 8.28)	7.24 (5.59 to 8.90)
Height velocity SDS	1.72 (1.31 to 2.13)	2.20 (1.58 to 2.81)	2.54 (1.54 to 3.53)	1.47 (0.76 to 2.17)	1.49 (−0.12 to 3.10)
Height SDS gain	0.59 (0.43 to 0.76)	0.60 (0.46 to 0.73)	0.50 (0.38 to 0.61)	0.33 (0.21 to 0.45)	0.57 (0.14 to 1.00)
Target height SDS deficit[a]	−1.60 (−1.93 to −1.27)	−1.61 (−1.99 to −1.24)	−2.44 (−2.72 to −2.16)	−1.80 (−2.23 to −1.36)	−2.83 (−4.46 to −1.20)
GH dose (mg/kg/week)	0.19 (0.18 to 0.20)	0.19 (0.18 to 0.20)	0.30 (0.29 to 0.31)	0.24 (0.21 to 0.27)	0.27 (0.21 to 0.33)

b) All countries combined (including Canada)

	OGHD n=1210	IGHD n=5974	Turner syndrome n=886	Idiopathic short stature n=1353	Small for gestational age n=756

Baseline					
Males (%)	63%	67%	–	71%	54%
Age (years)	8.8 (8.5 to 9.1)	10.3 (10.2 to 10.4)	9.2 (9.0 to 9.4)	11.5 (11.3 to 11.6)	8.6 (8.3 to 8.8)
Height SDS	−2.42 (−2.50 to −2.34)	−2.39 (−2.41 to −2.37)	−2.56 (−2.62 to −2.50)	−2.36 (−2.40 to −2.32)	−2.62 (−2.68 to −2.56)
Height velocity (cm/year)	4.54 (4.32 to 4.75)	4.70 (4.64 to 4.77)	4.86 (4.66 to 5.06)	4.81 (4.65 to 4.96)	5.22 (5.02 to 5.41)
Height velocity SDS	−1.56 (−1.70 to −1.42)	−0.99 (−1.04 to −0.93)	−1.11 (−1.26 to −0.96)	−0.72 (−0.84 to −0.60)	−0.84 (−0.99 to −0.69)
Target height SDS	−0.06 (−0.11 to 0.00)	−0.55 (−0.57 to −0.53)	0.07 (0.01 to 0.13)	−0.54 (−0.59 to −0.50)	−0.64 (−0.70 to −0.58)
Target height SDS deficit[a]	−2.42 (−2.50 to −2.33)	−1.84 (−1.86 to −1.81)	−2.62 (−2.69 to −2.55)	−1.82 (−1.87 to −1.76)	−1.98 (−2.07 to −1.90)
Stimulated peak GH (µg/l)	4.5 (4.1 to 4.8)	8.2 (8.0 to 8.4)	N/A	16.9 (16.3 to 17.4)	14.1 (13.1 to 15.1)
GH dose (mg/kg/week)	0.22 (0.21 to 0.22)	0.23 (0.23 to 0.24)	0.31 (0.31 to 0.32)	0.32 (0.32 to 0.33)	0.27 (0.27 to 0.28)
Year 1					
Height SDS	−1.65 (−1.72 to −1.58)	−1.85 (−1.87 to −1.83)	−2.10 (−2.16 to −2.04)	−1.87 (−1.91 to −1.82)	−2.05 (−2.11 to −2.00)
Height velocity (cm/year)	9.76 (9.54 to 9.98)	8.79 (8.73 to 8.85)	7.83 (7.70 to 7.97)	8.63 (8.51 to 8.76)	8.52 (8.37 to 8.68)
Height velocity SDS	3.21 (3.02 to 3.40)	2.48 (2.42 to 2.54)	2.26 (2.07 to 2.45)	2.38 (2.26 to 2.50)	2.34 (2.19 to 2.49)
Height SDS gain	0.78 (0.74 to 0.82)	0.56 (0.55 to 0.57)	0.48 (0.46 to 0.51)	0.52 (0.50 to 0.54)	0.58 (0.55 to 0.61)
Target height SDS deficit[a]	−1.63 (−1.70 to −1.55)	−1.29 (−1.32 to −1.27)	−2.16 (−2.23 to −2.09)	−1.31 (−1.37 to −1.26)	−1.41 (−1.49 to −1.33)
GH dose (mg/kg/week)	0.23 (0.22 to 0.23)	0.25 (0.25 to 0.25)	0.32 (0.32 to 0.33)	0.35 (0.35 to 0.36)	0.29 (0.29 to 0.30)

Note: GH = growth hormone, IGHD = idiopathic growth hormone deficiency, OGHD = organic growth hormone deficiency, NA = data available for <60% of patients, SDS = standard deviation score.
Data show mean (95% confidence interval); patient numbers are for those with height SDS at baseline and 1 year, but not all patients had all other information.
[a]Height SDS minus target height SDS.

Table 3: Characteristics and auxological data at baseline and at near-adult height for patients with idiopathic growth hormone deficiency, organic growth hormone deficiency or Turner syndrome, who were either growth hormone treated or growth hormone naïve at study entry

a) Canada

	All patients (n=293)[a]	OGHD (n=131)[b]	IGHD (n=50)[c]	Turner syndrome (n=79)	Idiopathic short stature (n=10)[d]
Baseline					
Age	10.2 (9.8 to 10.6)	9.2 (8.5 to 9.9)	11.4 (10.4 to 12.5)	10.3 (9.8 to 10.9)	12.8 (11.3 to 14.4)
Height SDS	−2.62 (−2.78 to −2.46)	−2.29 (−2.57 to −2.00)	−2.70 (−3.06 to −2.33)	−2.99 (−3.15 to −2.83)	−2.52 (−3.25 to −1.79)
Target height SDS deficit[e]	−2.51 (−2.69 to −2.32)	−2.32 (−2.62 to −2.02)	−2.14 (−2.56 to −1.71)	−2.91 (−3.11 to −2.71)	−1.81 (−2.61 to −1.01)
Height velocity SDS	−1.49 (−1.71 to −1.27)	−1.89 (−2.23 to −1.54)	−1.29 (−1.75 to −0.83)	−1.16 (−1.44 to −0.89)	−0.25 (−1.32 to 0.83)
GH dose (mg/kg/week)	0.22 (0.21 to 0.23)	0.18 (0.17 to 0.18)	0.20 (0.17 to 0.23)	0.29 (0.28 to 0.29)	0.24 (0.18 to 0.30)
Stimulated peak GH (µg/l)	4.73 (3.99 to 5.47)	2.90 (2.48 to 3.32)	4.15 (3.36 to 4.94)	NA	19.41 (14.65 to 24.18)
NAH					
Age	17.8 (17.6 to 17.9)	18.1 (17.8 to 18.3)	17.6 (17.1 to 18.1)	17.6 (17.3 to 17.9)	17.2 (15.6 to 18.9)
Height SDS	−1.42 (−1.56 to −1.27)	−0.95 (−1.15 to −0.75)	−1.07 (−1.38 to −0.76)	−2.04 (−2.24 to −1.83)	−2.02 (−2.89 to −1.14)
NAH SDS – baseline height SDS	1.17 (1.01 to 1.33)	1.26 (0.98 to 1.54)	1.63 (1.27 to 1.99)	0.96 (0.78 to 1.13)	0.50 (−0.35 to 1.35)
Target height SDS deficit[f]	−1.28 (−1.44 to −1.13)	−0.93 (−1.15 to −0.71)	−0.52 (−0.80 to −0.24)	−1.94 (−2.16 to −1.72)	−1.31 (−2.29 to −0.32)
GH therapy duration (years)	6.46 (6.01 to 6.90)	7.68 (6.93 to 8.44)	5.45 (4.48 to 6.42)	5.71 (5.18 to 6.25)	3.19 (1.97 to 4.42)
Last GH dose (mg/kg/week)	0.22 (0.21 to 0.23)	0.17 (0.16 to 0.18)	0.20 (0.19 to 0.22)	0.29 (0.28 to 0.30)	0.24 (0.18 to 0.30)
Near-adult height SDS > −2 (%)	66%	79%	80%	46%	50%

b) All countries combined (including Canada)

	All patients (n=5076)[g]	OGHD (n=754)[h]	IGHD (n=2322)[i]	Turner syndrome (n=695)	Idiopathic short stature (n=552)[j]
Baseline					
Age	10.9 (10.8 to 11.0)	9.8 (9.5 to 10.1)	11.2 (11.1 to 11.3)	10.0 (9.8 to 10.3)	12.3 (12.0 to 12.5)
Height SDS	−2.42 (−2.45 to −2.40)	−2.27 (−2.38 to −2.17)	−2.38 (−2.41 to −2.34)	−2.65 (−2.71 to −2.58)	−2.37 (−2.43 to −2.30)
Target height SDS deficit[e]	−2.02 (−2.06 to −1.99)	−2.29 (−2.40 to −2.17)	−1.80 (−1.85 to −1.76)	−2.69 (−2.77 to −2.61)	−1.74 (−1.83 to −1.65)
Height velocity SDS	−1.01 (−1.07 to −0.95)	−1.51 (−1.69 to −1.33)	−0.98 (−1.06 to −0.89)	−1.04 (−1.22 to −0.87)	−0.63 (−0.80 to −0.47)
GH dose (mg/kg/week)	0.27 (0.26 to 0.27)	0.22 (0.21 to 0.22)	0.25 (0.24 to 0.25)	0.32 (0.31 to 0.32)	0.33 (0.32 to 0.34)
Stimulated peak GH (µg/l)	9.46 (9.18 to 9.74)	4.18 (3.80 to 4.55)	8.26 (7.95 to 8.57)	14.06 (12.50 to 15.61)	16.49 (15.51 to 17.47)
NAH					
Age	17.3 (17.2 to 17.3)	18.0 (17.8 to 18.2)	17.2 (17.1 to 17.3)	17.1 (16.9 to 17.3)	17.2 (17.0 to 17.4)
Height SDS	−1.18 (−1.21 to −1.15)	−0.80 (−0.90 to −0.69)	−1.01 (−1.05 to −0.97)	−1.70 (−1.77 to −1.63)	−1.26 (−1.34 to −1.18)
NAH SDS – baseline height SDS	1.24 (1.21 to 1.27)	1.46 (1.35 to 1.58)	1.37 (1.33 to 1.41)	0.95 (0.89 to 1.01)	1.10 (1.02 to 1.19)
Target height SDS deficit[f]	−0.76 (−0.79 to −0.77)	−0.73 (−0.83 to −0.62)	−0.43 (−0.47 to −0.39)	−1.74 (−1.81 to −1.66)	−0.60 (−0.70 to −0.51)
GH therapy duration (years)	5.82 (5.72 to 5.91)	7.59 (7.26 to 7.91)	5.51 (5.37 to 5.64)	6.38 (6.12 to 6.63)	4.67 (4.44 to 4.91)
Last GH dose (mg/kg/week)	0.28 (0.28 to 0.28)	0.20 (0.19 to 0.21)	0.27 (0.26 to 0.27)	0.32 (0.31 to 0.33)	0.36 (0.35 to 0.37)
Near-adult height SDS > −2 (%)	81%	84%	86%	66%	82%

Note: GH = growth hormone, IGHD = idiopathic growth hormone deficiency, NA = data available for <60% of patients, NAH = near-adult height, OGHD = organic growth hormone deficiency, SDS = standard deviation score.
Data show mean (95% confidence intervals), except final height SDS > −2, which shows percentage of patients.
[a]50.2% male.

[b]67.9% male.
[c]66.0% male.
[d]90.0% male.
[e]Baseline height SDS minus target height SDS.
[f]Near-adult height SDS minus target height SDS.
[g]50.7% male.
[h]59.4% male.
[i]60.8% male.
[j]65.2% male.

Table 4: Serious and treatment-emergent adverse events reported in Canada[a]

	Patients reporting adverse events, n (% of N)					
	All patients	OGHD	IGHD	Turner syndrome	Idiopathic short stature	Small for gestational age
All GH-treated patients	N=850	N=379	N=147	N=156	N=38	N=19
Deaths[b]	11 (1.3)	7 (1.8)	0	1 (0.6)	0	0
Cause of death considered GH-related[c]	2 (0.2)	2 (0.5)	0	0	0	0
Serious adverse events	97 (11.4)	61 (16.1)	7 (4.8)	9 (5.8)	3 (7.9)	1 (5.3)
Serious adverse events considered GH-related[d]	19 (2.2)	12 (3.2)	1 (0.7)	4 (2.6)	2 (5.3)	0
GH-treated patients with ≥1 follow-up visit	N=833	N=377	N=137	N=153	N=38	N=19
Patients with ≥1 TEAE[e]	587 (70.5)	299 (79.3)	72 (52.6)	108 (70.6)	21 (55.3)	13 (68.4)
Headache	88 (10.6)	55 (14.6)	12 (8.8)	9 (5.9)	2 (5.3)	3 (15.8)
Secondary hypothyroidism	60 (7.2)	45 (11.9)	6 (4.4)	1 (0.7)	0	0
Scoliosis	54 (6.5)	22 (5.8)	10 (7.3)	12 (7.8)	0	3 (15.8)
Ovarian failure	50 (6.0)	9 (2.4)	0	41 (26.8)	0	0
Arthralgia	48 (5.8)	16 (4.2)	5 (3.7)	13 (8.5)	1 (2.6)	1 (5.3)
Upper respiratory tract infection	44 (5.3)	31 (8.2)	5 (3.7)	6 (3.9)	0	1 (5.3)
Hypothyroidism	42 (5.0)	29 (7.7)	4 (2.9)	8 (5.2)	0	0
TEAEs considered GH-related[f]	87 (10.4)	48 (12.7)	6 (4.4)	18 (11.8)	3 (7.9)	2 (10.5)
Headache	19 (2.3)	16 (4.2)	0	2 (1.3)	0	1 (5.3)
Scoliosis	10 (1.2)	9 (2.4)	1 (0.7)	0	0	0
Arthralgia	9 (1.1)	4 (1.1)	0	3 (2.0)	0	0
Insulin-like growth factor increased	9 (1.1)	0	0	5 (3.3)	0	1 (5.3)
Melanocytic nevus	7 (0.8)	4 (1.1)	0	3 (2.0)	0	0
Otitis media	6 (0.7)	4 (1.1)	0	2 (1.3)	0	0

Note: GH = growth hormone, IGHD = idiopathic growth hormone deficiency, OGHD = organic growth hormone deficiency, TEAE = treatment-emergent adverse event.
[a]Serious adverse events and TEAEs reported in all patients in Canada, and by diagnostic groups, for patients who received GH treatment, and TEAEs for GH-treated patients who had at least one post-baseline visit.

[b]See Supplementary Table 2 for details of deaths.
[c]Both deaths were due to recurrence of medulloblastoma.
[d]All GH-related serious adverse events occurred in single patients except for medulloblastoma recurrence for two patients (both with OGHD) and adenoidal hypertrophy for two patients (one with OGHD, one with Turner syndrome). Other serious adverse events reported as GH-related were meningioma, neoplasm progression, aortic valve incompetence, rectal hemorrhage, edema, death, parotitis, upper limb fracture, type 1 diabetes mellitus, optic glioma, anaplastic astrocytoma, adrenal neoplasm, increased intracranial pressure, ischemic stroke, tonsillar hypertrophy, sleep apnea syndrome, scoliosis surgery, meningioma surgery, adenoidectomy, angiodysplasia (patients could experience >1 event).
[e]Any TEAE irrespective of relatedness, with frequency >5% for all patients.
[f]Any TEAE considered related, with frequency >0.5% for all patients.

Supplemental Table 1: Patient characteristics and auxological data at baseline for growth hormone-treated children, by primary diagnostic category (all patients with known diagnosis and baseline height standard deviation score available)

a) Canada

	OGHD	IGHD	Turner syndrome	Idiopathic short stature	Small for gestational age
Number of patients	n=310	n=125	n=148	n=33	n=17
Males (%)	68.1%	69.6%	–	84.8%	41.2%
Age (years)	7.2 (6.7 to 7.7)	10.0 (9.1 to 10.8)	9.3 (8.7 to 9.8)	12.2 (11.1 to 13.2)	6.6 (4.6 to 8.5)
Height SDS	−2.27 (−2.44 to −2.10)	−2.67 (−2.88 to −2.46)	−2.93 (−3.05 to −2.80)	−2.67 (−2.98 to −2.37)	−3.81 (−4.44 to −3.18)
Height velocity (cm/year)	5.18 (4.61 to 5.75)	4.80 (4.27 to 5.33)	4.61 (4.19 to 5.03)	4.91 (4.26 to 5.56)	7.77 (5.74 to 9.81)
Height velocity SDS	−1.79 (−2.03 to −1.54)	−1.29 (−1.58 to −1.01)	−1.20 (−1.56 to −0.83)	−0.35 (−1.16 to 0.46)	0.03 (−1.15 to 1.20)
Target height SDS	0.04 (−0.07 to 0.14)	−0.41 (−0.58 to −0.24)	−0.03 (−0.17 to 0.10)	−0.57 (−0.84 to −0.30)	−0.28 (−0.55 to 0.00)
Target height SDS deficit[a]	−2.45 (−2.65 to −2.26)	−2.27 (−2.53 to −2.00)	−2.92 (−3.07 to −2.77)	−2.08 (−2.43 to −1.74)	−3.44 (−4.10 to −2.79)
Stimulated peak GH (µg/l)	3.3 (2.7 to 4.0)	4.6 (3.9 to 5.3)	NA	24.1 (17.8 to 30.5)	NA
GH dose (mg/kg/week)	0.18 (0.18 to 0.19)	0.19 (0.18 to 0.20)	0.29 (0.28 to 0.29)	0.23 (0.21 to 0.25)	0.23 0.20 to 0.26)

b) All countries combined (including Canada)

	OGHD	IGHD	Turner syndrome	Idiopathic short stature	Small for gestational age
Number of patients	n=2508	n=10189	n=1712	n=2657	n=1209
Males (%)	65.5%	67.6%	–	71.9%	54.7%
Age (years)	8.2 (8.0 to 8.3)	10.1 (10.0 to 10.2)	8.8 (8.6 to 9.0)	11.3 (11.1 to 11.4)	8.2 (8.0 to 8.4)
Height SDS	−2.42 (−2.48 to −2.36)	−2.41 (−2.43 to −2.40)	−2.60 (−2.65 to −2.56)	−2.41 (−2.44 to −2.38)	−2.68 (−2.73 to −2.63)
Height velocity (cm/year)	4.72 (4.55 to 4.90)	4.71 (4.66 to 4.77)	4.99 (4.82 to 5.16)	4.82 (4.71 to 4.93)	5.42 (5.24 to 5.60)
Height velocity SDS	−1.61 (−1.72 to −1.51)	−1.03 (−1.07 to −0.98)	−1.14 (−1.26 to −1.02)	−0.77 (−0.86 to −0.69)	−0.84 (−0.97 to −0.72)
Target height SDS	−0.06 (−0.10 to −0.02)	−0.55 (−0.57 to −0.53)	0.02 (−0.03 to 0.06)	−0.55 (−0.58 to −0.52)	−0.62 (−0.67 to −0.57)
Target height SDS deficit[a]	−2.43 (−2.49 to −2.36)	−1.86 (−1.88 to −1.84)	−2.61 (−2.67 to −2.56)	−1.86 (−1.90 to −1.82)	−2.06 (−2.13 to −1.99)

Stimulated peak GH (µg/l)	4.2 (4.0 to 4.4)	8.2 (8.0 to 8.3)	NA	16.8 (16.4 to 17.2)	NA
GH dose (mg/kg/week)	0.23 (0.22 to 0.23)	0.25 (0.25 to 0.25)	0.32 (0.31 to 0.32)	0.33 (0.33 to 0.34)	0.28 (0.28 to 0.29)

Note: GH = growth hormone, IGHD = idiopathic growth hormone deficiency, NA = data available for <60% of patients, OGHD = organic growth hormone deficiency, SDS = standard deviation score.

Data show mean (95% confidence intervals); patient numbers are for those with height SDS at baseline and 1 year, but not all patients had all other information.

[a]Height SDS minus target height SDS.

Supplemental Table 2: Cause of death and characteristics of growth hormone-treated patients who died during study, grouped by primary diagnosis of growth disorder

Diagnostic group Primary diagnosis	Sex	Age (years)	Time from GH start (years)	GH duration (years)	Cause of death	Probably or possibly related
OGHD						
Acute lymphoblastic leukemia	Male	12	4.8	4.3	Cerebral neuroblastoma	No
Astrocytoma	Male	9	3.3	0.3	Astrocytoma recurrence	No
Astrocytoma	Male	15	6.4	6.2	Astrocytoma recurrence	No
Medulloblastoma	Male	11	3.7	3.3	Medulloblastoma recurrence	Yes
Medulloblastoma	Male	12	1.4	1.5	Medulloblastoma recurrence	Yes
Hypopituitarism	Male	0.6	0.2	0.2	Cardiorespiratory arrest	No
Septo-optic dysplasia and hypopituitarism	Male	1.9	1.5	1.5	Gastrointestinal hemorrhage	No
Turner syndrome						
Turner syndrome	Female	16	9.8	5.5	Metastatic Ewing sarcoma	No
Other						
Chronic renal insufficiency and Down syndrome	Male	3	1.7	1.7	Cardiorespiratory arrest	No
Duchenne muscular dystrophy	Male	15	0.2	0.2	Cardiac arrest	No
Pseudohypoparathyroidism and panhypopituitarism	Male	11	10.7	10.7	Pneumonia	No

Note: GH = growth hormone, OGHD = organic growth hormone deficiency.