Is safety of childhood growth hormone therapy related to dose? Data from a large observational study

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Abstract

Objective: Concerns have been raised of increased mortality risk in adulthood in certain patients who received growth hormone treatment during childhood. This study evaluated the safety of growth hormone treatment in childhood in everyday practice.

Design: NordiNet® International Outcome Study (IOS) is a noninterventional, observational study evaluating safety and effectiveness of Norditropin® (somatropin; Novo Nordisk A/S, Bagsvaerd, Denmark).

Methods: Long-term safety data (1998–2013) were collected on 13 834 growth hormone treated pediatric patients with short stature. Incidence rates (IRs) of adverse events (AEs) defined as adverse drug reactions (ADRs), serious ADRs (SADRs), and serious AEs (SAEs) were calculated by mortality risk group (low/intermediate/high). The effect of growth hormone dose on IRs and the occurrence of cerebrovascular AEs were investigated by the risk group.

Results: We found that 61.0% of patients were classified as low-risk, 33.9% intermediate-risk, and 5.1% high-risk. Three hundred and two AEs were reported in 261 (1.9%) patients during a mean (s.d.) treatment duration of 3.9 (2.8) years. IRs were significantly higher in the high- vs the low-risk group (high risk vs low risk—ADR: 9.11 vs 3.14; SAE: 13.66 vs 1.85; SADR: 4.97 vs 0.73 events/1000 patient-years of exposure; P<0.0001 for all). Except for SAEs in the intermediate-risk group (P=0.0486) in which an inverse relationship was observed, no association between IRs and growth hormone dose was found. No cerebrovascular events were reported.

Conclusions: We conclude that safety data from NordiNet® IOS do not reveal any new safety signals and confirm a favorable overall safety profile in accordance with other pediatric observational studies. No association between growth hormone dose and the incidence of AEs during growth hormone treatment in childhood was found.

Introduction

Recombinant human growth hormone (GH) is approved to treat growth failure or short stature associated with various conditions, including GH deficiency (GHD), Turner syndrome, chronic renal insufficiency (CRI), born small for gestational age (SGA), and idiopathic short stature (ISS) (1). In addition to improving linear growth, GH exerts profound metabolic actions promoting anabolic effects and fat lipolysis (2). Although these actions contribute to the regulation of growth and metabolism, they may be associated with adverse effects when GH is in excess (3). Theoretical concerns of a link between excess GH and increased morbidity in patients with acromegaly (4, 5) resulted in the initiation of several state-regulated, mandatory, registries of GH-treated patients in Europe as well
as post-approval surveillance studies, which were established, managed, and supported by manufacturers of GH in Europe and the USA (6, 7, 8, 9). Accumulated experience of GH treatment captured in these large observational databases supports a favorable safety profile (10, 11). However, in 2012, preliminary data from the French cohort of the Safety and Appropriateness of Growth Hormone Treatments in Europe (SAGhE) study, a retrospective evaluation of 6928 patients diagnosed with GHD, ISS, or born SGA and treated as children with GH, raised concerns regarding the long-term safety of GH therapy and suggested a link between GH use during childhood and premature death (12). In these patients, considered to be at low risk of mortality, the standardized mortality ratio (SMR) was 1.33, with an increased risk of death among patients who had received GH doses >50 μg/kg/day (P<0.04). All type cancer-related mortality was not increased, but the risk of death from the circulatory system disease (SMR 3.07) was higher than expected. The mean follow-up time from the start of childhood GH therapy to death, loss to follow-up, or the study end in the SAGhE cohort was approximately 17 years (12). A later publication by Poidvin et al. (13) documented an increased risk of stroke, particularly hemorrhagic stroke, among patients diagnosed with GHD, ISS, or born SGA and treated with GH during childhood, compared with two population-based registries (standardized incidence ratio from 3.5 to 7.0). By contrast, other reports have not documented any significant impact of GH treatment during childhood (14, 15, 16). No deaths from cancer or cerebrovascular causes were reported among the 2543 patients in the SAGhE study results from Belgium, the Netherlands, and Sweden (14). Furthermore, no increased risk of mortality or incidence of cancer, stroke, or myocardial infarction in adult GHD patients who had previously received GH therapy during childhood was reported in 1204 patients enrolled in Hypopituitary Control and Complications Study (HypoCCS) (15), and data from a cohort of 494 patients from a Danish population-based registry study with childhood-onset GHD did not reveal a relationship between childhood GH therapy and death due to cerebrovascular events (16). Thus, the long-term safety of GH therapy during childhood remains inconclusive and deserves further investigation (17, 18, 19, 20). In particular, the increased risk of cerebrovascular mortality, most notably hemorrhagic stroke, warrants special attention. Evidence of a potential link between GH therapy and cerebrovascular events is supported by preclinical data demonstrating a role for the GH/insulin-like growth factor I (IGF-I) axis in the modulation of vasculogenesis and endothelial function (21) and clinical data, suggesting an increased incidence of cerebral aneurysms in patients with acromegaly (22, 23).

NordiNet® International Outcome Study (IOS; NCT00960128) is a large-scale, non-interventional, observational study designed to gather long-term data on the safety and effectiveness of Norditropin® (somatropin; Novo Nordisk A/S, Denmark) as prescribed by the treating physicians in the everyday clinical practice setting (24).

In this study, we evaluated the incidence rates (IRs) of adverse events (AEs) reported in NordiNet® IOS during GH treatment in pediatric patients with short stature classified by risk for mortality as well as the impact of GH dose on the IRs for AEs during GH treatment. We also aimed to identify the occurrence by risk group of cerebrovascular serious AEs (SAEs) during GH treatment in childhood.

**Methods**

**Patient population**

We report long-term safety data for 13 834 pediatric patients enrolled in NordiNet® IOS (1998–2013), an observational study in 23 countries. Although NordiNet® IOS was initiated in 2006, data from the German GrowthWin study, initiated in 2001, were migrated into NordiNet® IOS (24). As it was possible to enter data retrospectively into GrowthWin study, safety data in the combined database were available from 1998. The study population consisted of children who were receiving treatment with Norditropin® in accordance with normal clinical practice in Belgium, the Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Lithuania, Luxembourg, Montenegro, the Netherlands, Norway, the Russian Federation, Saudi Arabia, Serbia, Slovenia, Spain, Sweden, Switzerland, and the UK. Patient diagnoses were based on the investigator’s decision classified according to the International Classification of Diseases 10th Revision criteria (24). Patients without confirmation of diagnosis at baseline were excluded from the analysis.

All patients were classified into one of three main categories based on the clinical diagnosis at the start of GH therapy and its associated risk for long-term mortality as previously described by Carel et al. (12). Specifically, the risk groups were as follows: (i) high-risk group—patients who were previously treated for cancer, cranioopharyngioma, or CRI; (ii) intermediate-risk group—patients with multiple pituitary hormone deficiency, defined pediatric syndromes known to be associated with an increased mortality risk (e.g. Turner syndrome, Prader–Willi syndrome),
benign pituitary tumors, severe craniofacial or other malformations, or severe, chronic, pediatric disease; and (iii) low-risk group—patients with isolated GHD, ISS, born SGA, or isolated GHD in association with a minor craniofacial malformation such as cleft lip (12). The low-risk group was further subdivided into patients with GHD/ISS and patients with short stature born SGA because risk for mortality is reported as being greater in those born SGA than in patients diagnosed with GHD or ISS (25). Classification was done independently by two physicians who were blinded with respect to patient outcomes.

NordiNet® IOS is conducted in accordance with the Declaration of Helsinki guidelines and all applicable regulatory requirements in the participating countries: guardians provide written informed consent for data collection, and local ethics committee or institutional review board approval is a prerequisite for each center’s inclusion in NordiNet® IOS (24).

### Safety evaluation

The safety evaluation of Norditropin® was based on physicians’ reports of adverse drug reactions (ADRs), serious ADRs (SADRs), and SAEs during GH treatment. NordiNet® IOS employs a spontaneous reporting system for safety information; AEs were collected at regular follow-up visits scheduled according to routine clinical practice at each participating center or reported between clinic visits, depending on when they occurred. An overlap exists between SADRs and SAEs; if the SAE is considered drug related, it will also be an SADR, and between SADRs and ADRs, because all SADRs are also classified as ADRs. Hence, the total number of reported events will be the sum of SAEs and ADRs minus the number of SADRs. Safety information was captured in the study case report form via an electronic, web-based, platform (NordiNet®) (24). All ADRs, SAEs, and SADRs were coded with the Medical Dictionary for Regulatory Activities (MedDRA) terms (Version 14.0) using the System Organ Class (SOC) terminology.

In this report, we aimed to identify and review all cases of SAEs and SADRs due to cerebrovascular events. Therefore, all SAEs and SADRs included within the MedDRA SOC terms as nervous system and vascular disorders were evaluated.

### Statistical analysis

For each patient, the GH treatment period in patient-years of exposure was calculated from the date of the first registration of GH treatment to the end of GH treatment or patient’s last visit. Average GH dose to the first AE, rather than average GH dose during the whole treatment period, was considered as reflecting more accurately the actual GH dose administered to the patient up to the occurrence of an AE, because GH dose may be reduced or GH therapy may be discontinued and not restarted following an AE.

### Table 1  Patient distribution and baseline characteristics of patients included in the analysis by risk group. Data are presented as mean (s.d.) unless stated otherwise.

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Number of patients (n (% of total))</th>
<th>Sex, male/female (%)</th>
<th>Mean age at GH treatment start (years)</th>
<th>Height SDS at baseline</th>
<th>IGF-I SDS at baseline</th>
<th>Target height SDS</th>
<th>Mean duration of GH treatment (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-risk</strong></td>
<td>8432 (61.0)</td>
<td>62.6/37.4</td>
<td>8.8 (3.6)</td>
<td>–2.6 (0.9)</td>
<td>–1.2 (1.6)</td>
<td>–0.9 (1.0)</td>
<td>3.6 (2.7)</td>
</tr>
<tr>
<td>Intermediate-risk</td>
<td>4691 (33.9)</td>
<td>46.8/53.2</td>
<td>8.4 (4.2)</td>
<td>–2.6 (1.3)</td>
<td>–1.5 (1.8)</td>
<td>–0.5 (1.1)</td>
<td>4.4 (3.1)</td>
</tr>
<tr>
<td>High-risk</td>
<td>711 (5.1)</td>
<td>57.5/42.5</td>
<td>10.2 (3.9)</td>
<td>–1.9 (1.3)</td>
<td>–1.9 (2.1)</td>
<td>–0.3 (0.9)</td>
<td>3.4 (2.6)</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td>13 834 (100)</td>
<td>57.0/43.0</td>
<td>8.7 (3.9)</td>
<td>–2.5 (1.1)</td>
<td>–1.4 (1.7)</td>
<td>–0.7 (1.1)</td>
<td>3.9 (2.8)</td>
</tr>
<tr>
<td><strong>Subgroups of the low-risk group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GHD/ISS</td>
<td>5285 (62.7% of low-risk group)</td>
<td>67.6/32.4</td>
<td>9.3 (3.8)</td>
<td>–2.5 (0.9)</td>
<td>–1.6 (1.6)</td>
<td>–0.8 (1.1)</td>
<td>3.6 (2.7)</td>
</tr>
<tr>
<td>SGA</td>
<td>3147 (37.3% of low-risk group)</td>
<td>54.1/45.9</td>
<td>7.9 (3.3)</td>
<td>–2.8 (0.8)</td>
<td>–0.8 (1.6)</td>
<td>–1.0 (0.9)</td>
<td>3.6 (2.6)</td>
</tr>
</tbody>
</table>

GH, growth hormone; GHD, growth hormone deficiency; IGF-I, insulin-like growth factor-I; ISS, idiopathic short stature; s.d., standard deviation; SDS, standard deviation score; SGA, small for gestational age.

*Risk groups: high-risk, patients who were previously treated for cancer, craniopharyngioma or chronic renal insufficiency; intermediate-risk, patients with multiple pituitary hormone deficiency, defined pediatric syndromes known to be associated with an increased mortality risk (e.g. Turner syndrome, Prader–Willi syndrome), benign pituitary tumors, severe craniofacial or other malformations, or severe, chronic, pediatric disease; low-risk, patients with isolated GHD, ISS, born SGA, or isolated GHD in association with a minor craniofacial malformation such as cleft lip (12). **Subgroups of low-risk group: patients in the low-risk group were sub-classified into those with GHD/ISS or born SGA, because short length at birth is associated with increased risk of premature death in adult life in both sexes (25).
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The average GH dose up to the first AE was stratified into four subgroups; 0–20, 20–30, 30–40, and >40 µg/kg/day. IRs for ADRs, SAEs, and SADRs (number of events/1000 patient-years of exposure) during GH treatment were calculated by risk group and by average GH dose group up to the first event. Multiple AEs reported by a single patient with the same onset date were analyzed as a single event unless there was reason to believe that they were separate, unrelated events. Comparison of IRs for AEs (ADRs, SAEs, and SADRs) by risk group was performed using Poisson regression (log-linear model). The effect of average GH dose up to the first AE on the occurrence of AEs was evaluated using Poisson regression (log-linear model) with mean GH dose up to the first AE as a continuous explanatory variable. The effect of reporting country was also included in the model.

The first AE for each patient was described by the patient’s risk group, the average and cumulative GH doses up to the first AE, the GH dose at the onset of AE, the duration of treatment until the AE, and the action taken with GH when the AE occurred. All SAEs reported as nervous system or vascular disorders, irrespective of causality, are reported descriptively in the low-risk group. SADRs (SAEs with causality assessed as probable or possible) reported as nervous system or vascular disorders are described for the intermediate- and high-risk groups.

Results

Patient characteristics

Among the 13 834 (57% male, mean age at treatment start 8.7 years, mean duration of treatment 3.9 years) patients included in the analysis, 61.0% were diagnosed with isolated GHD or ISS, or were born SGA and classified as low-risk patients for long-term mortality, 33.9% were classified as intermediate-risk patients, and 5.1% as high-risk patients (Table 1). Of the low-risk group, 62.7% (n=5285) were diagnosed with GHD or ISS mean (s.d.) duration of treatment of 3.6 (2.7) years; 37.3% (n=3147) were diagnosed with SGA with a mean duration of treatment of 3.6 (2.6) years. Overall exposure to GH for the study population was 53 575 patient-years of exposure. In total, 27 patients were not included in the analysis as their diagnoses at baseline could not be confirmed.

Average GH dose up to the first AE

The average GH dose up to the first AE and the dose at AE onset were significantly higher in the low-risk than
in the high-risk group ($P<0.01$ for both; Table 2) with proportionally more patients in the high-risk (48.2%) than in the low-risk (28.1%) group receiving a GH dose $\leq 30 \mu g/kg/day$. GH doses $\geq 40 \mu g/kg/day$ were received by 21.9% of all patients and were more frequent in the SGA subgroup (30.1%) and intermediate-risk group (28.1%) than in the other risk groups. Duration of treatment up to the first AE, and cumulative absolute GH dose up to the first AE were greater in the high- and intermediate-risk groups than in the low-risk group (Table 2). Following an AE, 45.0% of patients continued GH therapy at the same dose, 4.0% continued at a reduced dose, 29.1% discontinued GH treatment, and 5.3% had another action with their GH dose. Details of GH dose after the AE were missing for 16.6% of patients. Of those who discontinued GH treatment following an AE, 84.1% restarted GH therapy. Compared with patients in the low-risk group, proportionally more patients in the high-risk group discontinued treatment (44.2% vs 20.9%; Table 2) or experienced dose reduction (9.3% vs

Adverse events

Overall, 302 AEs were reported in 261 (1.9%) patients. Of these, 203 (67.2%) AEs were reported between clinic visits with the remaining 99 (32.8%) AEs reported at usual clinic visits. The mean (S.D.) interval between usual clinic visits was 176 (135) days. The proportions of AEs reported between and at visits and the number of days between visits were similar across the three risk groups. Proportionally, more patients in the high-risk (5.3% (38/711)) than in the intermediate- (2.3% (109/4691)) or low- (1.4% (114/8432)) risk groups reported AEs. Similar proportions of patients in the low-risk subgroup with SGA (1.4% (44/3147)) and with GHD/ISS (1.3% (70/5285)) reported

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**Figure 1**

(A) IR (events/1000 patient-years of exposure) for reported ADRs, SAEs, and SADRs by risk group as defined in Table 1. (B) IR (events/1000 patient-years of exposure) for ADRs, SAEs, and SADRs by average GH dose up to the first AE. *$P=0.0486$; **$P<0.0001$ vs low-risk group.

**Figure 2**

(A) IR (events/1000 patient-years of exposure) for reported ADRs, SAEs, and SADRs in the low-risk group by subgroup (GHD/ISS vs SGA). (B) IR (events/1000 patient-years of exposure) for ADRs, SAEs, and SADRs by GH dose up to the first AE. Definitions of risk groups are shown in full in Table 1.
### Table 3  Summary of the available safety information from pediatric somatropin observational studies: NordiNet® IOS, GeNeSIS, KIGS, NCGS, and PATRO children.

<table>
<thead>
<tr>
<th>Study design</th>
<th>NordiNet® IOS children</th>
<th>GeNeSIS</th>
<th>KIGS</th>
<th>NCGS</th>
<th>PATRO children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study period (years) Adverse events</td>
<td>Observational cohort; prospective</td>
<td>Observational cohort; prospective (26)</td>
<td>Observational cohort; prospective (27)</td>
<td>Observational cohort; prospective (28)</td>
<td>Observational cohort; prospective (PASS) (29)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>2006 to December 2016 ADRs, SADRs and SAEs during GH treatment</td>
<td>April 1999 to September 2015 (26) All AEs are reported irrespective of causality</td>
<td>December 1987 to October 2012 (27) All AEs are reported irrespective of causality (31)</td>
<td>September 2012 to present (29) SAEs potentially related to GH treatment (28)</td>
<td>September 2012 to present (29) All AEs are recorded (29)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>13 834</td>
<td>11 686 (30)</td>
<td>56 123 (31)</td>
<td>54 996 (11)</td>
<td>4397 (32)</td>
</tr>
<tr>
<td>Patient-years exposure</td>
<td>53 575</td>
<td>37 562 (30)</td>
<td>165 558 (31)</td>
<td>195 419 (11)</td>
<td>Not available</td>
</tr>
<tr>
<td>Number of AEs</td>
<td>302</td>
<td>Not available</td>
<td>16 971 (31)</td>
<td>4084 (11)</td>
<td>Not available</td>
</tr>
<tr>
<td>Incidence rate (per 100 000 patient-years of exposure)</td>
<td>5.6</td>
<td>Not available</td>
<td>103.1 (31)</td>
<td>20.9 (11)</td>
<td>Not available</td>
</tr>
</tbody>
</table>

AE, adverse event; SAE, serious adverse event; ADR, adverse drug reaction; GH, growth hormone; IOS, International Outcome Study; SADR, serious adverse drug reaction; GH, growth hormone; PASS, post-authorization safety study.

*GrowthWin study (initiated 2001) was migrated into the NordiNet® IOS (24). All AEs or laboratory findings were reported that may be potentially related to GH as well as all instances of targeted events (new/recurrent malignancies and central nervous system tumors as well as diabetes mellitus, intracranial hypertension, slipped capmal femoral epiphysis, scoliosis and pancreatitis). A suspected association was sufficient to report an AE, but it was not necessary to be certain of causality. However, if GH had been unequivocally ruled out as a possible cause, the event did not need to be reported unless it was a targeted event, as defined by the protocol.

AEs. IRs for all event types were significantly higher in the high-risk than in the low-risk group (high risk vs low risk—ADR: 9.11 vs 3.14; SAE: 13.66 vs 1.85; SADR: 4.97 vs 0.73 events/1000 patient-years of exposure; *P*<0.0001 for all comparisons) (Fig. 1A). Except for SAEs, for which the IR was significantly higher in the intermediate-risk vs the low-risk group (3.89 vs 1.85 events/patient-years of exposure; *P*<0.0001), IRs were not significantly different between the intermediate- and low-risk group (Fig. 1A), or between the GHD/ISS subgroup vs the SGA subgroup (Fig. 2A).

Comparison of the IRs for AEs reported in NordiNet® IOS with those reported in other GH observational studies can be seen in Table 3 (11, 26, 26, 27, 28, 29, 30, 31, 32).

With the exception of SAEs in the intermediate-risk group, the IR for all AEs was independent of GH dose (Figs 1B and 2B). When evaluating the mean GH dose up to the first AE as a continuous explanatory variable, a significant inverse relationship with GH dose was shown only for SAEs in the intermediate-risk group (*P*=0.0486). IRs (events/1000 person-years) for SAEs for the four categories of GH dose were 0–20 µg/kg/day (5.09), 20–30 µg/kg/day (4.17), 30–40 µg/kg/day (4.59), and >40 µg/kg/day (2.13). Of the seven patients in the intermediate-risk group receiving low-dose GH (0–20 µg/kg/day) who experienced SAEs, all had comorbid conditions. No significant relationship between IR and GH dose was observed for any event type in the GHD/ISS or SGA subgroups of the low-risk group. No significant country effect on any of the event IRs was found.

### Safety profile

All SAEs reported during GH treatment were screened for events classified as cerebrovascular events, especially stroke. No SAEs related to stroke, and in particular to subarachnoid or intracerebral hemorrhage, were reported in any risk group. AEs reported as SAEs (low-risk group) or SADRs (intermediate- and high-risk groups) in the nervous or vascular system are detailed in Table 4 and described below.

### Low-risk group

Among patients in the low-risk group, 12 SAEs were reported in the nervous (n=11) or vascular system (n=1; Table 4). The GH dose up to these events ranged from 23.6 to 54.3 µg/kg/day and treatment duration from
Table 4  Characteristics of individual patients by risk group who reported SAEs (low-risk) and SADRs (intermediate- and high-risk) in the vascular or nervous system.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Gender</th>
<th>Preferred term</th>
<th>Body system class</th>
<th>Duration of GH treatment (years)</th>
<th>Age at AE onset (years)</th>
<th>Average GH dose up to AE (μg/kg/day)</th>
<th>Causality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISS</td>
<td>Female</td>
<td>Convulsion</td>
<td>Nervous system</td>
<td>2.8</td>
<td>15.8</td>
<td>33.5</td>
<td>Unlikely</td>
</tr>
<tr>
<td>GHD</td>
<td>Male</td>
<td>Convulsion</td>
<td>Nervous system</td>
<td>3.2</td>
<td>12.0</td>
<td>38.8</td>
<td>Unlikely</td>
</tr>
<tr>
<td>GHD</td>
<td>Male</td>
<td>Headache</td>
<td>Nervous system</td>
<td>3.3</td>
<td>8.2</td>
<td>Not recorded</td>
<td>Probable</td>
</tr>
<tr>
<td>GHD</td>
<td>Female</td>
<td>Headache</td>
<td>Nervous system</td>
<td>0.3</td>
<td>13.4</td>
<td>36.4</td>
<td>Possible</td>
</tr>
<tr>
<td>GHD</td>
<td>Male</td>
<td>Headache</td>
<td>Nervous system</td>
<td>24 days</td>
<td>10.7</td>
<td>23.6</td>
<td>Possible</td>
</tr>
<tr>
<td>GHD</td>
<td>Male</td>
<td>Hypotension</td>
<td>Vascular system</td>
<td>3.5</td>
<td>9.8</td>
<td>41.5</td>
<td>Possible</td>
</tr>
<tr>
<td>SGA</td>
<td>Female</td>
<td>Benign intracranial hypertension</td>
<td>Nervous system</td>
<td>5.1</td>
<td>11.4</td>
<td>33.5</td>
<td>Possible</td>
</tr>
<tr>
<td>IUGR</td>
<td>Male</td>
<td>Convulsion</td>
<td>Nervous system</td>
<td>5.8</td>
<td>12.5</td>
<td>54.3</td>
<td>Unlikely</td>
</tr>
<tr>
<td>SGA</td>
<td>Female</td>
<td>Convulsion</td>
<td>Nervous system</td>
<td>1.5</td>
<td>8.1</td>
<td>42.2</td>
<td>Unlikely</td>
</tr>
<tr>
<td>SGA with GHD</td>
<td>Female</td>
<td>Epilepsy</td>
<td>Nervous system</td>
<td>1.3</td>
<td>14.9</td>
<td>31.0</td>
<td>Unlikely</td>
</tr>
<tr>
<td>SGA</td>
<td>Female</td>
<td>Epilepsy</td>
<td>Nervous system</td>
<td>2.5</td>
<td>16.1</td>
<td>32.1</td>
<td>Unlikely</td>
</tr>
<tr>
<td>SGA</td>
<td>Female</td>
<td>Syncope</td>
<td>Nervous system</td>
<td>1.0</td>
<td>5.7</td>
<td>34.4</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Intermediate-risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>Female</td>
<td>Convulsion</td>
<td>Nervous system</td>
<td>0.5</td>
<td>3.0</td>
<td>Not known</td>
<td>Possible</td>
</tr>
<tr>
<td>SGA with vitamin D deficient rickets</td>
<td>Female</td>
<td>Headache</td>
<td>Nervous system</td>
<td>3.7</td>
<td>8.0</td>
<td>35.2</td>
<td>Probable</td>
</tr>
<tr>
<td>GHD due to pituitary tumor or its treatment</td>
<td>Female</td>
<td>Headache</td>
<td>Nervous system</td>
<td>4 days</td>
<td>12.0</td>
<td>18.2</td>
<td>Possible</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>Female</td>
<td>Hypertension</td>
<td>Vascular system</td>
<td>6.0</td>
<td>10.7</td>
<td>41.5</td>
<td>Possible</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>Male</td>
<td>Increased intracranial pressure</td>
<td>Nervous system</td>
<td>2.8</td>
<td>7.6</td>
<td>31.3</td>
<td>Possible</td>
</tr>
<tr>
<td>Multiple pituitary hormone deficiencies</td>
<td>Female</td>
<td>Increased intracranial pressure</td>
<td>Nervous system</td>
<td>9 days</td>
<td>13.7</td>
<td>33.3</td>
<td>Probable</td>
</tr>
<tr>
<td>High-risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>Female</td>
<td>Headache</td>
<td>Nervous system</td>
<td>1.1</td>
<td>8.4</td>
<td>28.4</td>
<td>Possible</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>Female</td>
<td>Headache</td>
<td>Nervous system</td>
<td>2.6 months</td>
<td>13.6</td>
<td>22.5</td>
<td>Probable</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>Male</td>
<td>Increased intracranial pressure</td>
<td>Nervous system</td>
<td>2.7</td>
<td>12.8</td>
<td>26.6</td>
<td>Possible</td>
</tr>
</tbody>
</table>

AE, adverse event; GH, growth hormone; GHD, growth hormone deficiency; ISS, idiopathic short stature; IUGR, Intrauterine growth restriction; SADR, serious adverse drug reaction; SAE, serious adverse event; SGA, small for gestational age.

*Risk groups are defined in full in Table 1.

24 days to 5.8 years. Of these 12 SAEs that were reported in 12 patients, five (benign intracranial hypertension (n=1), headache (n=3), hypotension (n=1)) were considered possibly or probably related to GH treatment. Except for the case of benign intracranial hypertension, which was reported in a patient with short stature born SGA, all these SAEs were in patients diagnosed with GHD. The single vascular event, hypotension, was reported coincidentally with night sweats and abdominal distension in a patient diagnosed with GHD; as discontinuation of GH was associated with symptom relief, a causal role for GH was assigned. However, food allergy, viral infection, or tuberculosis has been considered as a possible underlying diagnosis.

**Intermediate- and high-risk groups**

Overall, nine SADRs in the nervous (n=8) and vascular (n=1) systems were reported in nine patients in the intermediate- (n=6) and high-risk (n=3) groups (Table 4). Eight SADRs in the nervous system were reported in eight patients (intermediate-risk, n=5; high-risk, n=3; Table 4). Increased intracranial pressure was reported in three patients (intermediate risk, n=2; high risk, n=1) with diagnoses of GHD, hydrocephalus, and medulloblastoma after a treatment duration of 9 days to 2.8 years. In these patients, GH dose ranged from 26.6 to 33.3 μg/kg/day. Headache was reported in four patients (intermediate risk, n=2; high risk, n=2) following a short duration of treatment in two patients (4 days and 2.6 months), and after 1.1 and 3.7 years in the remaining patients. One patient (intermediate-risk group) with Turner syndrome experienced a convulsion at 3 years of age following 0.5 years of GH therapy. The single vascular SADR was in a patient with Turner syndrome (intermediate-risk group) who experienced hypertension following 6 years of GH treatment at an average daily dose of 41.5 μg/kg/day.
Discussion

The safety profile of GH treatment reported in our study is consistent with findings from other observational studies (11, 29, 33, 34). Furthermore, our data collected from a large, multinational, observational study demonstrate no association between GH dose up to the event and the occurrence of ADRs in patients with short stature across various indications. No cerebrovascular events were reported during GH treatment in our study.

As could be expected, IRs for all types of AEs were significantly higher in the high-risk than in the low-risk group. However, with the exception of SAEs in the intermediate-risk group, in which an inverse relationship between IR and GH dose was observed, we found no relationship between GH dose up to the AE and the occurrence of AEs in any of the risk groups. This was also true in the subgroups of the low-risk group for patients with GHD/ISS or with SGA in whom no association between GH dose and IRs of AEs of any type was observed. In the intermediate-risk group, patients in the low GH dose (0–20 µg/kg/day) group who reported SAES had other comorbidities in their medical history that would have increased their risk for SAES. Indeed, the data in our study support observations from clinical practice in which it could be expected that patients with comorbidities, such as those in the high-risk group and those in the intermediate-risk group with associated comorbidities, are likely to start GH therapy on a low dose and may explain, at least in part, the inverse dose relationship with SAES observed in the intermediate-risk group. Evidence also supports that AEs may be more common following treatment initiation, which is frequently at a low GH dose than when patients are on a maintenance dose.

Our finding of no relationship between GH dose and the occurrence of AEs during GH therapy in childhood is reassuring. Carel et al. (12) documented an increased risk of mortality in adulthood among patients in the low-risk group who were formerly treated with a GH dose greater than 50 µg/kg/day during childhood. Such higher doses are predominantly used in children with short stature born SGA who, as a group, may have an inborn risk for cardiovascular disorders (25, 35) and may also suffer from genetic disorders (36). Moreover, short stature may be associated with an increased risk for cerebrovascular hemorrhage (37). It should be noted, however, that the number of events in the French SAGHe cohort was too small to allow testing for a relationship between the dose of GH treatment and the incidence of stroke in the later report from the same patient cohort (13). Further studies are warranted to investigate the potential of a link between GH dose and the occurrence of AEs either during or after treatment.

There is high variability in the reporting rates for AEs across the three largest GH registries Kabi International Growth Study (KIGS), National Cooperative Growth Study (NCGS) (NordiNet® IOS). The lower IRs for AEs reported in our study compared with other observational studies may be a consequence of the differences in study time periods (38) as well as differences in the types of AEs reported in each study. Differences in the types of events reported may at least partly explain the higher IRs for AEs reported in KIGS (103.1 events per 100 000 patient-years of exposure) (31) compared with NCGS (20.9 events per 100 000 patient-years of exposure) (11). In particular, it was mandatory to report all AEs in the KIGS registry; by contrast, only adverse clinical or laboratory findings suspected to be related to GH treatment, irrespective of causality, were required to be reported in NCGS (39). Differences in the study time periods and therefore reporting periods may underlie the observed differences in IRs between NCGS (20.9 events per 100 000 patient-years exposure) (11) and NordiNet® IOS (5.6 events per 100 000 patient-years of exposure) as the number of reports of AEs is found to be highest in the first years after product launch to the market and decline thereafter (40). It is also worth noting that the safety data reported in the present analysis of NordiNet® IOS are restricted to ADRs and SAES (including SADRs). Also, since the 1980s, when some of the registry studies, including NCGS, were initiated, greater restrictions have been imposed on the types of patients treated with GH, resulting in a more homogeneous study population in NordiNet® IOS than in earlier registry study databases. Furthermore, a higher number of AEs could be anticipated to be reported in a post-authorization safety study, such as PATients TReated with Omnitrope® (PATRO) children, which requires active surveillance for AEs, than in an observational study such as NordiNet® IOS. The types of cardiovascular and neurological AEs and SADRs reported across risk groups in our study were similar to those reported in other observational studies. Headache, a relatively frequent complication among children receiving GH treatment, was reported across all risk groups with duration of GH therapy to start of AE showing wide variation as has previously been reported in KIGS (41, 42). Benign intracranial hypertension, previously reported in association with GH therapy (29, 41, 42), was reported in a single patient with SGA in our study, although it is recognized to be more common among children with GHD, Turner syndrome, Prader–Willi syndrome and CRI.
(11, 29, 41). Hypertension, which is frequent in patients with Turner syndrome, and may be unrelated to GH therapy (43), was reported in a single patient in our study. In our study, no cerebrovascular or related events were identified in children during treatment with GH. In a report from the SAGHE study, Poidvin et al. (13) identified an increased risk for stroke among adults who were treated with GH during childhood; however, a number of constraints, including the small number of events identified and absence of a control group of patients with GHD not treated with GH and followed into adulthood, limit the interpretation of the data reported by that group. Although reassuring that no cerebrovascular events were identified in our study during childhood GH treatment, it is evident that further studies are required to more clearly define the cause and effect relationship between GH therapy in childhood and adult-onset cerebrovascular disease, especially with respect to dose, treatment duration, and age at treatment start, in addition to a positive family history of cerebrovascular disease and other vascular predisposing factors.

A major challenge in interpreting data from observational studies is to draw inferences that are acceptably free from influences by overt biases, as well as evaluate the influence of potential hidden biases. The robustness of the conclusions based on safety data collected in observational studies of patients treated as per everyday clinical practice is affected by the lack of an appropriate untreated control group and the integration of data from different institutions and countries where reporting standards may vary. However, analysis of between-country reporting rates for AEs in NordiNet® IOS revealed no obvious differences. Even though observational studies are considered as an active pharmacovigilance measure, spontaneous reporting is linked with several limitations that may be related both to under-reporting and to the variable quality of the reported data pertinent to information on exposure to the drug that may have an impact on results. Differences in population genetics, environmental or other unidentified confounding factors, as well as variable local clinical practices may also have an impact on study results. Nevertheless, it is worth noting that validation of data at data entry (24), systematic checks for outliers, and elimination of obvious data entry errors were undertaken methodically. The finding that approximately two-thirds of AEs were reported outside of the regular scheduled clinic visits also suggests that the degree of under-reporting of AEs was limited. Furthermore, reconciliation of the NordiNet® IOS database with the company’s central database for AEs was performed prior to data analysis to ensure consistency of AE reporting. In addition, a quality check on the data was represented through the meticulous classification of patients into the respective risk groups for mortality by two physicians working independently. Finally, the clinical history of patients with SAEs in the intermediate-risk group was thoroughly reviewed to determine if comorbidities might have predisposed them to those events.

In conclusion, the reported safety evaluation based on an interim analysis of NordiNet® IOS involving data from children currently receiving GH therapy collected in usual clinical practice does not reveal any association between GH dose and the occurrence of AEs during GH therapy. Furthermore, no cerebrovascular events were reported during GH therapy in any risk group in our study. No new safety signals were revealed, further supporting the favorable safety profile of GH treatment in childhood in accordance with other pediatric observational studies. Further studies are warranted to investigate any cause-and-effect relationships between childhood GH treatment and adult-onset morbidity and mortality.

Declaration of interest
L S is a member of the NordiNet® International Study Committee (Novo Nordisk) and a recipient of investigator-initiated independent research award from Merck Serono, Darmstadt, Germany, Stockholm, Sweden (GGI award) and lecture honoraria from Novo Nordisk, Malmo, Sweden, Pfizer Walton Oaks, UK, and Merck Serono, Stockholm, Sweden. E P and B T P are employees of Novo Nordisk. O B is a member of the NordiNet® International Study Committee and a NordiNet® IOS investigator.

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Author contribution statement
All authors provided (i) substantial contributions to the conception and design, or the acquisition, analysis, or interpretation of the data; (ii) the drafting of the article or critical revision for important intellectual content; (iii) final approval of the version to be published; and (iv) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved, and therefore fulfil the authorship criteria of the International Committee of Medical Journal Editors (ICMJE). All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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