Safety and effectiveness of long-term growth hormone therapy in Japanese patients with adult growth hormone deficiency: a postmarketing, multicenter, observational study

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Abstract. We aimed to evaluate the long-term safety and effectiveness of growth hormone (GH) therapy in Japanese patients with adult growth hormone deficiency (AGHD). In this observational, multicenter study, Norditropin® (Novo Nordisk A/S, Bagsvaerd, Denmark) was administered as injections of 0.021 mg/kg/week as a starting dose divided into 6–7 doses/week. The dose was increased according to clinical response. Patients’ data were obtained from medical records. Measurements (lipids, glucose metabolism, and body composition) taken at baseline; 3, 6, and 12 months; and yearly until the end of the study were collected. Adverse drug reactions (ADRs), serious ADRs, and serious adverse events (SAEs) were evaluated. Of 387 registered patients, 334 were eligible for safety. After GH treatment initiation, a marked decrease in total cholesterol was observed earlier in the child-onset group than in the adult-onset group. LDL-cholesterol also decreased, but no significant differences in changes in LDL-cholesterol between adult-onset and child-onset groups were found. A significant increase in HDL-cholesterol starting 1 year after GH treatment initiation was found in the adult-onset group. There was no effect of GH treatment on glucose metabolism. Because of the small number of dual-energy X-ray absorptiometry data, the overall assessment of changes of body composition was difficult. Fifty-six (16.8%), 12 (3.6%), and 35 (10.5%) patients experienced ADRs, serious ADRs, and SAEs, respectively. This study demonstrated a favorable long-term safety and effectiveness profile of GH therapy in AGHD patients in the real-life Japanese clinical practice setting.

Key words: Growth hormone deficiency, Japan, Postmarketing, Safety, Somatropin

The onset of growth hormone deficiency (GHD) can be during childhood or adulthood [1]. In adults, GHD is most commonly the result of pituitary or hypothalamic tumors and their treatment, with pituitary adenoma being a common cause, whilst GHD can be idiopathic, congenital, or acquired in children [1, 2]. The clinical characteristics of adult GHD (AGHD) include abnormal body composition such as increased trunk fat and reduced lean body mass, impaired glucose metabolism, and abnormal serum lipid profile leading to an increased risk of cardiovascular and cerebrovascular morbidity and mortality [3, 4].

Growth hormone (GH) therapy is used to reverse the negative effects of GHD on body composition, glucose metabolism, and lipid profile [4]. Norditropin® (Novo Nordisk A/S, Bagsvaerd, Denmark) is a recombinant DNA-derived human GH, somatropin. As of November 2008, it has been approved for the treatment of AGHD in 94 countries, including Japan [5].

The objective of this postmarketing observational study was to assess the safety and effectiveness of long-term GH therapy under normal clinical practice conditions in Japan. The results concerning effectiveness on quality of life will be discussed in a separate manuscript to follow.
Subjects and Methods

Study design and setting

The present study was an observational, multicenter study in patients with severe AGHD. The study was conducted at 92 centers in Japan, from 1 Oct 2009 to 30 Sep 2014. Enrolment was from 1 Oct 2009 to 30 Sep 2012, with observation periods ranging from 2 to 5 years.

The study sample included somatropin-experienced patients and somatropin-naïve patients. All somatropin-naïve patients were started on Norditropin® only. Patient recruitment was on a sequential basis. Patients with severe AGHD were included. Severe AGHD was defined as a peak GH response of less than 1.8 ng/mL in GH stimulation tests (less than 9 ng/mL if growth hormone-releasing peptide-2 was used). Those with known or suspected allergy to the study product or related products, diabetes mellitus, malignancy, pregnancy or a likelihood of becoming pregnant, and those with any prior participation in a study were excluded. These exclusion criteria were based on the drug contraindications noted in the Japanese package insert [5].

In general, GH was administered as injections of 0.021 mg/kg/week as a starting dose divided into six to seven doses, based on the treatment guidelines in Japan [5]. The dose could be increased once every 4 weeks according to each patient’s clinical response based on their symptoms and insulin-like growth factor-1 (IGF-1) levels. The dose could be increased incrementally to 0.084 mg/kg/week, according to clinical response, but did not exceed a daily dose of 1 mg. The dose was adjusted as needed to prevent adverse drug reactions (ADRs) and to maintain blood IGF-1 levels within the normal range for age and sex.

Data collection and measurements

Measurements taken at baseline; 3, 6, and 12 months; and then yearly until the end of the study were collected. Visit windows were from −90 days to +30 days for baseline, ±30 days for 3 and 6 months, and ±90 days for 12 months and yearly data. Data were collected from the patients’ medical records. The data collected included the following: demographic data (date of birth, sex, concomitant illness, past medical history, predisposition to allergies, smoking status); body measurements (height, weight) and vital signs (blood pressure); family history (e.g., diabetes mellitus, pituitary tumor, cardiovascular disorders, osteoporosis); results and diagnoses of any underlying disease; laboratory assessments (e.g., endocrinological tests including IGF-1 at the time of diagnosis, GH secretion stimulation test, and secretion of other pituitary hormones; blood chemistry; lean body mass; body fat percentage; bone mineral density; markers of fatty liver such as gamma-glutamyltransferase [γGTP] and alanine aminotransferase [ALT]); treatments (Norditropin® and concomitant medications including hormone replacement therapy, cholesterol-lowering statins, other drugs) and treatment compliance; edema and details of the tumor; and other adverse events (AEs).

Safety assessments were made at each visit, except at visit 1. An ADR was defined as an AE for which a causal relationship between the product and the occurrence was suspected (i.e., judged possible or probable by the reporting or reviewing healthcare professional). A serious ADR was defined as follows: death, a life-threatening experience, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. A serious AE (SAE) was defined as an event not necessarily having a causal relationship with the treatment that at any dose results in any of the following: death, a life-threatening experience, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Diabetes mellitus and impaired glucose tolerance were diagnosed by an attending physician according to the criteria of the Japan Diabetes Society [6].

Analyses of the baseline characteristics and safety data were based on the full analysis set (FAS). The FAS comprised all subjects who were prescribed GH at least once during the study. Analyses of the effectiveness outcome variables were based on the effectiveness analysis set (EAS). The EAS, which included only patients who were GH-naïve at baseline, comprised all patients from the FAS with at least one post-baseline measurement of IGF-1, triglycerides (TG), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), blood pressure, body fat percentage, lean body mass, bone mineral density, serum glucose, or glycosylated hemoglobin. Patients were excluded from the EAS if they were noncompleters or had no post-baseline effectiveness data. All data, including outliers, were used for analysis. The proportions of patients receiving antidyslipidemic agents were calculated among patients who had LDL-C data at each time point.
Statistical methods
ADRs and AEs were recorded by the physician and coded by Novo Nordisk using the Medical Dictionary for Regulatory Activities System Organ Class (SOC) and Preferred Term terminology. Categorical variables were summarized in frequency tables, and continuous variables were summarized as descriptive statistics and analyzed by paired $t$-test. The influence of explanatory variables on the change in outcome variables was evaluated by analysis of covariance models for continuous outcome variables. All statistical analyses were performed using SAS, Version 9 (SAS Institute, Cary, NC, USA). A 5% significance level was used for all statistical analyses, and tests were two-sided. No corrections for multiple testing were performed, and missing data were imputed using the last observation carried forward (LOCF) method.

Ethical considerations
The study was conducted in accordance with the Declaration of Helsinki. All participants or their legally acceptable representative provided written informed consent, and patients were able to withdraw at will at any time. The study was approved by the ethics committees or discretionary ethics committees of all participating institutions and was registered in JapicCTI and clinicaltrials.gov (JapicCTI-101122 and NCT01109017).

Results

Patient demographics
Out of 387 registered patients, 334 were eligible for the FAS after excluding those who did not meet the inclusion criteria or who were lost-to-follow-up. Patient disposition and reasons for exclusion are shown in Fig. 1.

Overall, 164 patients (80.0%) had adult-onset GHD, 89 (54.3%) of whom were male. In the child-onset group, 25 patients (61.0%) were male (Table 1). The mean ± SD ages of patients were 31.3 ± 10.2 and 51.7 ± 14.3 years in the child-onset and adult-onset groups, respectively.

The baseline IGF-1 standard deviation score (SDS) was lower in child-onset than in adult-onset patients (male, $p<0.001$; female, $p<0.001$) and in females compared with males (adult-onset, $p<0.05$; child-onset, $p<0.01$).

IGF-1 level and GH dose
The GH dose and IGF-1 SDS significantly increased in both males and females at 1 year after the initiation of GH treatment, and yearly thereafter, regardless of the time of disease onset (Fig. 2).

The mean GH dose at 4 years after the initiation of study treatment was significantly higher in the
Table 1  Baseline characteristics of patients

|                               | Overall     | Child-onset | Adult-onset |
|-------------------------------|-------------|-------------|-------------|
|                               | Total       | Subtotal    | Male        | Female      | Subtotal | Male | Female |
| Number of patients            | 205         | 41          | 25          | 16          | 164      | 89   | 75     |
| Age, years                    | 47.6 ± 15.8 (205) | 31.3 ± 10.2 (41) | 31.5 ± 9.6 (25) | 31.1 ± 11.4 (16) | 51.7 ± 14.3 (164) | 50.6 ± 14.6 (89) | 52.9 ± 14.0 (75) |
| BMI, kg/m²                    | 25.03 ± 4.90 (193) | 24.72 ± 6.63 (39) | 24.05 ± 7.55 (23) | 25.68 ± 5.12 (16) | 25.11 ± 4.38 (154) | 25.70 ± 4.30 (84) | 24.39 ± 4.39 (70) |
| IGF-1, ng/mL at diagnosis     | 72.10 ± 44.52 (191) | 48.45 ± 35.00 (35) | 45.20 ± 37.60 (14) | 77.41 ± 44.80 (156) | 78.53 ± 41.61 (86) | 76.03 ± 48.70 (70) |
| IGF-1, SDS at diagnosis       | −3.16 ± 2.40 (188) | −4.96 ± 2.05 (35) | −4.35 ± 1.48 (21) | −5.87 ± 2.46 (14) | −2.74 ± 2.28 (153) | −2.57 ± 1.79 (83) | −2.95 ± 2.76 (70) |
| Treatment period, years       | 3.05 ± 1.30 (205) | 3.06 ± 1.30 (41) | 3.10 ± 1.31 (25) | 3.00 ± 1.32 (16) | 3.05 ± 1.31 (164) | 2.91 ± 1.36 (89) | 3.22 ± 1.22 (75) |
| Maximum GH level*, ng/mL      | 1.83 ± 2.56 (169) | 0.86 ± 1.47 (33) | 0.97 ± 1.58 (20) | 0.69 ± 1.31 (13) | 2.06 ± 2.71 (136) | 1.69 ± 2.09 (71) | 2.46 ± 3.23 (65) |
| Maximum GH level**, ng/mL     | 0.56 ± 0.58 (85) | 0.26 ± 0.33 (14) | 0.25 ± 0.36 (10) | 0.27 ± 0.27 (4) | 0.62 ± 0.61 (71) | 0.43 ± 0.42 (38) | 0.84 ± 0.71 (33) |

Underlying disease, n (%)

|                               | Total       | Male        | Female      | Subtotal | Male | Female |
|-------------------------------|-------------|-------------|-------------|----------|------|--------|
| Idiopathic                    | 28 (13.7)   | 12 (48.0)   | 3 (18.8)    | 13 (79.4)| 5 (60) | 1 (11.1)|
| Organic                       | 177 (86.3)  | 13 (52.0)   | 0 (0.0)     | 151 (92.6)| 49 (55.5)| 4 (44.4)|
| Neoplasm                      | 137 (66.8)  | 9 (36.0)    | 12 (75.0)   | 116 (70.7)| 67 (75.3)| 9 (10.5)|
| Pituitary adenoma             | 87 (42.4)   | 1 (4.0)     | 0 (0.0)     | 86 (52.4)| 49 (55.1)| 3 (3.6)|
| Hypothalamic tumor            | 50 (24.4)   | 8 (32.0)    | 12 (75.0)   | 30 (18.3)| 18 (20.2)| 12 (16.0)|
| Non-neoplastic                | 40 (19.5)   | 4 (16.0)    | 1 (6.3)     | 35 (21.3)| 18 (20.2)| 17 (22.7)|
| Other pituitary diseases      | 37 (18.0)   | 3 (12.0)    | 1 (6.3)     | 33 (20.1)| 16 (18.0)| 17 (22.7)|
| Other hypothalamic lesion     | 3 (1.5)     | 1 (4.0)     | 0 (0.0)     | 2 (1.2) | 2 (2.2) | 0 (0.0) |
| Treatment-related             | 0 (0.0)     | 0 (0.0)     | 0 (0.0)     | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Others                        | 0 (0.0)     | 0 (0.0)     | 0 (0.0)     | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Unknown                       | 0 (0.0)     | 0 (0.0)     | 0 (0.0)     | 0 (0.0) | 0 (0.0) | 0 (0.0) |

* Growth hormone-releasing peptide-2 (GHRP-2) only. ** Arginine, insulin, glucagon, and L-DOPA. Data in the table are presented as mean ± SD or n (%). BMI, body mass index; GH, growth hormone; IGF-1, insulin-like growth factor-1; SD, standard deviation; SDS, standard deviation score.

Fig. 2  GH dose and IGF-1 SDS

A) GH, B) IGF-1 SDS. GH, growth hormone; IGF-1, insulin-like growth factor-1; NS, not significant; SDS, standard deviation score. ** p<0.01, † p<0.001, vs. baseline. (In green font): ‡ p<0.005, ‡ p<0.001, adult-onset vs. child-onset at each time point.
child-onset group than in the adult-onset group among males. However, the mean IGF-1 SDS remained significantly lower in the child-onset group in both males and females, even at 4 years after the initiation of study treatment. Notably, the mean IGF-1 SDS in the child-onset group was approximately −2 at 4 years after the initiation of GH treatment (male, −1.91 ± 1.47; female, −2.00 ± 1.99) (Fig. 2).

Regarding sex differences, the mean GH dose at 4 years after the initiation of GH treatment was higher in females, although statistical significance was only seen in the adult-onset group (adult-onset, \( p < 0.001 \); child-onset, \( p = 0.705 \)). The mean IGF-1 SDS, which was lower in females at the initiation of GH treatment, reached the level of males after 4 years of treatment (Fig. 2). The proportion of females receiving oral estrogen treatment was 11.1% in the adult-onset group and 50.0% in the child-onset group.

**Lipid metabolism**

At the initiation of GH treatment, the mean total cholesterol (TC) level was significantly higher in the child-onset group than in the adult-onset group (\( p < 0.05 \), Fig. 3). Although the mean LDL-C level was higher in the child-onset group, the difference was not statistically significant. The proportion of patients receiving antidiyslipidemic agents at the initiation of GH treatment was 16.9% in the child-onset group and 37.7% in the adult-onset group.

After the initiation of GH treatment, a marked decrease in TC was observed earlier in the child-onset group than in the adult-onset group (Figs. 3 and 4).

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**Fig. 3** Effects of treatment on lipid metabolism

A) TC, B) LDL-C, C) HDL-C (upper panels). Changes in respective lipid parameters are shown in the lower panels. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol. * \( p < 0.05 \), ** \( p < 0.01 \), † \( p < 0.005 \), ‡ \( p < 0.001 \), vs. baseline. (In green font): * \( p < 0.05 \), adult-onset vs. child-onset.
Decreases were also observed for LDL-C, although there were no statistically significant differences in changes in LDL-C between adult-onset and child-onset groups. The proportion of patients receiving anti-dyslipidemic agents after the initiation of GH treatment increased to 23.1% in the child-onset group and 63.0% in the adult-onset group at year 4.

After the initiation of GH treatment, significant decreases in the mean TC and LDL-C levels were observed earlier in males than in females in each onset group (Fig. 4). However, also in females, LDL-C and TC decreased significantly by the end of the 4-year study treatment, except TC in the adult-onset group.

High-density lipoprotein cholesterol (HDL-C) was significantly higher in females than in males from baseline throughout the entire 4-year study (Fig. 4). In females in the adult-onset group, a significant increase in HDL-C was observed 3 and 4 years after the initiation of GH treatment. Data combining males and females showed a significant increase in HDL-C, starting 1 year after the initiation of GH treatment, in the adult-onset group (Fig. 3).

**Body composition**

Regarding body fat percentage and lean body mass, it was difficult to evaluate the effect of GH treatment on body composition because of the small number of dual-energy X-ray absorptiometry data obtained, but a significant increase in lean body mass was observed in females from 2 to 4 years after the initiation of GH treatment (data not shown).

**Glucose metabolism**

There was no significant effect of GH treatment on glucose metabolism during the 4-year period (glycated hemoglobin [HbA1c]: baseline, 5.73 ± 0.53%; year 4, 5.81 ± 0.64%; \( p=0.982 \); fasting plasma glucose: baseline, 93.9 ± 14.2 mg/dL; year 4, 99.2 ± 9.0 mg/dL; \( p=0.069 \)).

**Markers of fatty liver**

The mean levels of ALT and γGTP decreased from 57.7 U/L and 91.8 U/L at baseline to 39.8 U/L and 52.8 U/L after 1 year and to 22.8 U/L and 43.7 U/L after 4 years of GH treatment, respectively.

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**Fig. 4** Effects of treatment on lipid metabolism, stratified by sex

A) TC, B) LDL-C, C) HDL-C. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol. * \( p<0.05 \), ** \( p<0.01 \), † \( p<0.005 \), ‡ \( p<0.001 \), vs. baseline. (In green font): * \( p<0.05 \), ** \( p<0.01 \), † \( p<0.005 \), ‡ \( p<0.001 \), male vs. female within onset.
Safety
In total, 334 patients were included in the safety analysis set for the observation period of 3.1 ± 1.3 years.

AEs were reported in 97 patients (29.0%), and the majority of them were mild to moderate in severity. AEs reported in ≥1% of patients are shown in Table 2.

Incidence rates (events per 1,000 patient-years) of clinically significant AEs were 6.8 (seven patients) for pituitary tumor (progressed or recurrent), 3.9 (four patients) for Rathke’s cleft cyst (progressed or recurrent), 2.9 (three patients) for craniopharyngioma (progressed or recurrent), 1.0 each (one patient each, all new onset) for meningioma, thyroid cancer, enchondroma, and gastrointestinal tract submucosal tumor, 7.8 (eight patients) for new onset diabetes mellitus, and 8.7 (eight patients) for impaired glucose tolerance.

The details of 16 patients reported to have diabetes mellitus or impaired glucose tolerance in the present study are shown in Table 3. Of those with available data at the initiation of study treatment, 67% (10/15) had a body mass index (BMI) of ≥25, 60% (9/15) had triglyceride (TG) concentrations ≥150 mg/dL, 40% (4/10) had HbA1c concentrations of ≥6.0%, and 47% (7/15) had a history of or concomitant impaired glucose tolerance (non-diabetic). One patient without abnormal laboratory findings initiated the study treatment at the advanced age of 71 years. There was one patient (7%) in whom the mean IGF-1 SDS during the treatment period exceeded +2.

The details of 18 patients reported to have AEs associated with tumors are shown in Table 4. Tumor progression/recurrent tumors and new onset tumors were reported in 14 and 4 patients, respectively. All tumor-associated AEs were of mild/moderate severity. The number of days to AE onset was ≤365 days in 44% (8/18) of these patients; no patient had a mean or maximum IGF-1 SDS exceeding +2.

A total of 56 patients (16.8%) experienced ADRs. Common ADRs (≥2%), by SOC, were metabolism and nutrition disorders (19 of 334, 5.7%); general disorders and administration site conditions (13 of 334, 3.9%); neoplasms benign, malignant, and unspecified (incl. cysts and polyps) (9 of 334, 2.7%); and SOC investigations (7 of 334, 2.1%). The total number of patients with SAEs was 35; 12 out of 35 patients with SAEs (34.3%) had serious ADRs. The total number of SAEs was 53; 19 out of 53 SAEs (35.8%) were serious ADRs. The most frequent serious ADR was ‘neoplasms benign, malignant, and unspecified (incl. cysts and polyps)’ which occurred in 9 (2.7%) patients.

Three patients died during the study; a relationship between GH and these deaths was considered unlikely by the reporting healthcare professionals. A 56-year-old (at baseline) man died 1,024 days after the initiation of treatment. The patient was found dead after not returning home overnight, and the cause of death was unknown. A 76-year-old (at baseline) woman experienced congestive cardiac failure 36 days after the initiation of treatment, which led to death at 147 days post-treatment initiation. The patient had a history of myocardial infarction at baseline. A 73-year-old (at baseline) man died of Parkinson’s disease, which occurred at 758 days and led to death 853 days after the initiation of GH treatment. No medication was administered for Parkinson’s disease, and his death was considered a result of the natural course of the disease.

Table 2 Frequent adverse events (≥1%)

| Category                                                                 | n     | (%) |
|--------------------------------------------------------------------------|-------|-----|
| Neoplasms - benign, malignant, and unspecified (incl. cysts and polyps) |       |     |
| Pituitary tumor                                                          | 7     | 2.1 |
| Metabolism and nutrition disorders                                       |       |     |
| Diabetes mellitus                                                        | 8     | 2.4 |
| Impaired glucose tolerance                                               | 8     | 2.4 |
| Dyslipidemia                                                             | 17    | 5.1 |
| Vascular disorders                                                       |       |     |
| Hypertension                                                             | 10    | 3.0 |
| Gastrointestinal disorders                                               |       |     |
| Gastroesophageal reflux disease                                           | 5     | 1.5 |
| Congenital, familial, and genetic disorders                              |       |     |
| Rathke’s cleft cyst                                                      | 4     | 1.2 |
| General disorders and administration site conditions                     |       |     |
| Edema                                                                    | 11    | 3.6 |
| Investigations                                                           |       |     |
| Liver function test abnormal                                             | 9     | 2.7 |
Table 3  Adverse events associated with diabetes mellitus and impaired glucose tolerance

| Sex | Age | Onset | History of concomitant IGT | Cause of AGHD | Baseline | Diabetes mellitus |
|-----|-----|-------|---------------------------|--------------|----------|------------------|
|     |     |       |                           |              | BMI (kg/m²) | TC (mg/dL) | LDL-C (mg/dL) | HDL-C (mg/dL) | TG (mg/dL) | PG (mg/dL) [timing] | HbA1c (%) | Mean IGF-1 SDS | Max IGF-1 SDS | Days to AE onset |
| 1   | F   | 42    | AO                         | NA           | 27.0      | 185.0     | 49.0         | 340.0        | NA         | NA         | −2.14      | −1.23      | 1,194      |                     |
| 2   | M   | 39    | AO                         | NA           | 35.5      | 201.0     | 131.0        | 33.0         | 255.0      | NA         | 0.68       | 2.30       | 875        |                     |
| 3   | M   | 62    | AO                         | NA           | 29.0      | 213.0     | 137.0        | 41.0         | 299.0      | 99.0 [FPG] | 5.8        | −0.12      | 1.04       | 1,246      |
| 4   | F   | 71    | AO                         | NA           | 19.6      | 224.0     | 122.0        | NA           | 101.0      | 107.0 [2-hr PG] | NA        | −0.89      | 0.88       | 1,135      |
| 5   | F   | 29    | CO                         | Yes          | 36.0      | 146.0     | 83.0         | 46.0         | 97.0       | NA         | 6.2        | −3.06      | −0.76      | 182        |
| 6   | F   | 32    | CO                         | Yes          | 33.9      | 252.0     | 181.0        | 55.4         | 137.0      | NA         | −3.95      | −3.24      | 182        |
| 7   | F   | 55    | AO                         | Yes          | 22.9      | 229.0     | 142.0        | 57.0         | 215.0      | 94.0 [FPG] | 7.1        | 0.22       | 1.48       | 741        |
| 8   | F   | 37    | NA                         | NA           | NA        | NA        | NA           | NA           | NA         | NA         | NA         | NA         | NA         | 147        |

Table 4  List of adverse events associated with tumor

| Sex | Age | Onset | Cause of AGHD | Disease | Location | Mean IGF-1 SDS | Max IGF-1 SDS | History of irradiation | AE | Days to AE onset | Relationship to GH treatment |
|-----|-----|-------|--------------|---------|----------|---------------|---------------|------------------------|----|-----------------|-------------------------------|

2-hr PG, 2-hour plasma glucose; ACTH, adrenocorticotropic hormone; AE, adverse event; AO, adult-onset; BMI, body mass index; CO, child-onset; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IGF-1 SDS, insulin-like growth factor-1 standard deviation score; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; NA, not available; PG, plasma glucose; TC, total cholesterol; TG, triglycerides.
**Discussion**

We conducted a post-marketing observational study to evaluate the safety and effectiveness of long-term GH therapy in AGHD patients in a real-life clinical practice setting in Japan. Here we describe the effect of GH therapy on lipids, glucose metabolism, and body composition as well as the incidence of AEs.

During the observation period, the GH dose in females increased more than in males. The finding that the IGF-1 SDS in females reached the level of males at 4 years after the initiation of the study treatment suggests that IGF-1 may be useful as an effective index for GH treatment monitoring. However, the IGF-1 SDS in the child-onset group did not reach the level seen in the adult-onset group, regardless of the higher doses of GH treatment. IGF-1 SDS remained at approximately −2 even 4 years after the initiation of treatment. As a reason for this, it is unlikely that administered GH doses were insufficient in the child-onset group, since patients in the child-onset group were already receiving high doses of GH by year 4 (0.038 ± 0.018 mg/kg/week for males and 0.041 ± 0.025 mg/kg/week for females). While the GH dose varied widely between child-onset and adult-onset male cases, the increase in IGF-1 was greater in adult-onset male cases. This may imply a difference in the sensitivity to GH treatment depending on the time of onset. Resistance to GH treatment in child-onset cases has been confirmed in clinical trials in both Caucasian [7] and Japanese [8] patients. Moreover, most adult-onset patients develop GHD over a short period of time as a consequence of organic disease (e.g., tumor), or surgery required to treat such disease. In these patients, subjective symptoms and changes in laboratory values, as well as treatment-induced changes, are more notable. Conversely, child-onset patients suffer from GHD over a longer period of time. During that time, homeostatic changes help patients adapt to the physical and mental changes induced by GHD. In these patients, treatment-induced changes tend to be less notable. Furthermore, the proportion of females receiving oral estrogen was as high as 50.0% in the child-onset group, while the proportion of females receiving oral estrogen was 11.1% in the adult-onset group, which may have contributed to the low IGF-1 SDS in the child-onset group [9].

In our study, TC and LDL-C decreased after the initiation of GH treatment. It has been reported that the incidence of coronary artery disease increases as LDL-C increases [10]. Additionally, high cardiovascular mortality has been suggested in AGHD patients [11]. The results from the present study suggest that GH treatment may improve lipid metabolism in AGHD patients, possibly leading to a reduction in the incidence and mortality of cardiovascular disease.

Regarding TC, the magnitude of the decrease was significantly greater in the child-onset group than in the adult-onset group; however, this is at odds with previous studies reporting that significant decreases were observed only in adult-onset patients [12, 13]. A similar trend was observed for LDL-C. A reason for this discrepancy may be that the baseline TC and LDL-C levels in the child-onset group were particularly high in the present study (237.2 ± 55.1 mg/dL and 139.5 ± 36.4 mg/dL, respectively), requiring different regimens of antidyplipidemic agents from those used in the adult-onset group. Additionally, some studies report that patients who show higher baseline TC and LDL-C levels have greater decreases in these parameters after the initiation of study treatment [14-16]. Moreover, because GH was used at high doses in the child-onset group, there is a possibility that the direct action of GH may have been involved (GH increases the expression of LDL receptors [17] and enhances the metabolism of LDL [18]).

In the present study, because baseline TC and LDL-C levels tended to be high also in the adult-onset group (214.0 ± 41.8 mg/dL and 132.8 ± 40.5 mg/dL, respectively), there may be a selection bias in that TC and LDL-C data were obtained mainly from patients with dyslipidemia.

The number of patients receiving antidyplipidemic agents increased during the first year of treatment; this increase was maintained up to 4 years of treatment. The observed decreases in cholesterol levels may be the result of the combined effect of antidyplipidemic agents and GH replacement therapy.

Significant decreases in TC and LDL-C were observed early on in males. These changes were considered to reflect the changes over time in GH dose and IGF-1 SDS; a previous study also reported a similar trend [12]. Conversely, Elbornsson et al. (2013) reported that the magnitude of the decrease in LDL-C was significantly greater in females [19]. However, in that report, the high IGF-1 SDS in females after the initiation of GH treatment may have affected the result [20].

We found that HDL-C levels were higher in females than in males, a similar result to that reported by...
Nakamura et al. [21]. The increase in HDL-C was particularly marked in adult-onset females. Although there are studies reporting that a significant improvement was observed only in males [13, 22], the trend was similar, suggesting that the number of samples may have affected the result.

Regarding body fat percentage and lean body mass, significant changes were found in lean body mass among females from 2 to 4 years. This finding is inconsistent with that of a previous report [3], and this may be attributable to age-related changes in the proportions of lean and fat tissue mass, GH dose, and the number of patients with available data. Furthermore, GH therapy had a beneficial effect on the markers of fatty liver in the present study, as the levels of ALT and γGTP decreased throughout the study period.

GH treatment in AGHD patients was well tolerated in this study, consistent with the results reported in a recent meta-analysis [23]. AEs occurred in 29.0% of the patients, which is comparable with the results of a previous observational study [12] and lower than the results of clinical studies in Japanese AGHD patients [3, 8, 14, 24-26]. The reasons for the lower AE incidence in our study may be that the GH dose remained low, and the frequency and form of reporting were different.

In our study, eight patients (2.4%, 7.8 per 1,000 patient-years) developed diabetes mellitus. This incidence is similar to that of the general Japanese population in studies reported by Waki et al. and Noda et al. [27, 28] and also to the results from overseas studies on GH treatment in AGHD patients [29-31]. Furthermore, Hartman et al. reported that the incidence of diabetes mellitus in AGHD patients receiving GH treatment was <2%, which was similar to that in AGHD patients not receiving GH treatment [32].

Among patients who developed diabetes mellitus in the present study, most had risk factors present at baseline, such as higher than normal HbA1c (≥5.6%), TG (≥150 mg/dL), or BMI (≥25 kg/m²), and a history of or concomitant impaired glucose tolerance at the initiation of GH treatment. According to Appelman-Dijkstra et al., although GH treatment improved body composition abnormalities in AGHD patients, some patients showed increased insulin resistance and aggravated glucose tolerance [33]. This suggests that when GH treatment is administered to patients at high risk of developing diabetes mellitus, it is necessary to carefully observe their clinical course. The mean IGF-1 SDS during GH treatment exceeded +2 in one patient, whereas it was −2 or lower in five patients. Taken together, although it is possible that diabetes mellitus and impaired glucose tolerance were induced by an excessive dose of GH, it seems unlikely that this was the case.

During the observation period (mean, 3.1 years), tumor enlargement or recurrence was observed in 5.8% (3/52) of patients with underlying craniopharyngioma and 7.1% (7/98) of patients with underlying non-functioning pituitary adenoma. This result is comparable with the results of studies in AGHD patients with underlying craniopharyngioma [34, 35] and with underlying non-functioning pituitary adenoma [36, 37], suggesting that Norditropin® treatment does not increase the risk for the development of these diseases. In fact, a recently published statement asserts that available data do not indicate an increased risk of new primary cancers or recurrence of primary cancer in AGHD patients [38].

Of four patients with new onset tumors, three developed tumors within 1 year after the initiation of GH treatment, and the remaining patient was found to have a history of radiotherapy. Furthermore, no patients had mean or maximum IGF-1 SDS values exceeding +2. These results suggest that Norditropin® treatment has less impact on the development of new tumors as supported by previous reports [32, 39], although continuous observation will be needed due to the relatively short follow-up period of this study.

The three deaths in the present study were judged unlikely to be related to Norditropin®. Interestingly, a recent meta-analysis reported that GH treatment improved the high standardized mortality ratio in patients with hypopituitarism to the level observed in the general population [40].

Our study has some limitations, including the observational nature of the study and lack of a control group. Additionally, the use of the LOCF method to manage missing data could have introduced bias because the outcomes of patients who dropped out were judged as “no change” from the dropout point. In patients who have TC, LDL-C, HDL-C, or TG data, there might be a selection bias that they mainly consisted of patients with dyslipidemia. Finally, it is possible that there may have been some variability in the diagnoses of diabetes mellitus and impaired glucose tolerance based on the physicians’ decision.

In conclusion, GH treatment in AGHD patients was well tolerated and demonstrated a favorable long-term...
safety and effectiveness profile in a real-life clinical practice setting in Japan. The results of the quality of life analysis will be reported in the near future.

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