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Original Article

Incidence of diabetes mellitus and neoplasia in Japanese short-statured children treated with growth hormone in the Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS)

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Abstract. The primary goal of the Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS) was to assess the safety and effectiveness of Humatrope®, a GH preparation, in the treatment of pediatric patients with short stature. We report our findings in the GH-treated Japanese pediatric population focusing on the incidence of type 2 diabetes (T2D) and occurrence of neoplasms. A total of 2,345 Japanese patients were assessed for safety. During a mean observation period of 3.2 yr, T2D occurred in 3 patients (0.13%) and slowly progressive insulin-dependent diabetes mellitus (SPIDDM) related to underlying mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) in 1 patient (0.04%). Neoplasms were reported in 13 patients (0.56%), including 1 patient with brain tumor (germinoma) and 5 with craniopharyngiomas (4 recurrences); the remainder were benign, typically dermatological, neoplasms. The incidence of diabetes mellitus determined in the study did not differ from previous reports in GH-treated pediatric patients, and there was no apparent increase in the risk of new neoplastic lesions or malignant tumors.

Key words: diabetes mellitus, neoplasia, pediatric GH treatment, safety, short stature

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Introduction

Recombinant human GH was initially approved in Japan in November 1988 for the treatment of children with significant GH deficiency (GHD) (1, 2). Humatrope® (somatropin [recombinant DNA (rDNA) origin]; Eli Lilly and Company [Indianapolis, IN, USA]) is a GH preparation marketed around the world; dosing varies across countries. Humatrope was launched in Japan in November 1989.

Treatment of short-statured children with recombinant human GH is associated with significant improvements in growth, leading to attainment of normal or near-normal final height (3, 4). Treatment with GH also has a beneficial impact on body composition (5), and GH is considered to be well tolerated, with few reported adverse reactions (3, 4, 6, 7).

In addition to its growth promotion effects, GH is responsible for critical parts of the metabolism of glucose, lipids, and proteins in humans. It reduces oxidation of glucose and uptake of glucose in the muscles and fosters gluconeogenesis (8, 9); it also accelerates lipolysis, lipid oxidation, and protein synthesis; lessens breakdown of proteins and amino acids; and reduces formation of hepatic urea.

Based on the physiologic actions of endogenous GH (and exogenous somatropin) as an insulin antagonist, it has been suggested that treatment with somatropin may cause alterations in glucose metabolism, and children with some growth disorders may already be at risk for impaired glucose metabolism. New-onset cases of diabetes have been reported in some GH-treated children, and the risks are of clinical interest (10–12).

The possibility of increased risk of cancer in patients receiving GH treatment has been discussed since the first report of leukemia in a GH-deficient child undergoing GH replacement therapy shortly after its approval in the United States (2, 10, 13). The role of the GH-IGF-I axis in tumorigenesis has been studied extensively; although it is known that IGF-I is a mitogen, animal models suggest permissive rather than causative roles for both IGF-I and GH in tumorigenesis (2, 14).

Because there are few reports on the incidence of diabetes or neoplastic disease in GH-treated children who have received the relatively lower dose of GH used in Japan, we analyzed the incidence of both of these conditions among Japanese short-statured children treated with GH and followed in the observational Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS).

Subjects and Methods

Study design and overall study population

GeNeSIS was an open-label, multinational observational study (ClinicalTrials.gov, NCT01088412). It began in 1999 and ran through 2015, enrolling 22,845 patients in 30 countries around the world, including Japan. The goal of GeNeSIS was to assess the safety and effectiveness of Humatrope in the treatment of pediatric patients with short stature. Primary safety objectives of the study included examining the important potential risk of diabetes in subgroups of somatropin-treated children and the occurrence of new cases of neoplasias in children treated with somatropin. The study collected information on the clinical management and treatment outcomes of pediatric patients with growth disorders who were treated with the recombinant human GH somatropin.

The study met international guidelines for postmarketing surveillance studies (15) and was conducted in accordance with the Declaration of Helsinki. The protocol was approved at each study site by an Institutional Review Board, and written informed consent was provided for pediatric patients by parents or guardians according to national regulations.

We assessed the safety of GH treatment in Japanese pediatric patients enrolled in GeNeSIS, in particular to determine the incidence of type 2

diabetes (T2D) and the occurrence of treatment-emergent neoplasms during GH replacement therapy. Inclusion criteria and other background information for this population have been previously reported (16). An interim report, which included approximately one-half of the enrolled Japanese patients, was published in 2013 (17). In that paper, the mean GH doses ranged from 0.19 mg/kg/week for patients with GHD to 0.33 mg/kg/week for patients with Turner syndrome.

Analysis methods

Adverse events occurring in temporal association with somatropin treatment were collected on case report forms by study site personnel. Serious adverse events (SAEs) were defined as in the International Conference on Harmonisation guidelines (E2A 1994).

Patients were included in safety analyses as long as date of birth and treatment status (treated or untreated) were available. For patients to be included in analyses of diabetes or primary cancer, the following data were required to be available: gender, dates of first and last visits, and information on history of neoplasia or diabetes (yes or no), respectively.

Results

Patients and disposition

A total of 2,345 GH-treated Japanese patients enrolled between 2000 and 2013 who met the safety evaluable criteria were included in the analyses. The majority of these patients (n = 2,106 [89.8%]) had been diagnosed with GHD; the only other growth-related condition affecting 5% or more of enrolled patients was Turner syndrome (n = 125 [5.3%]). A total of 57 patients had been diagnosed with GHD resulting from an intracranial tumor; 25 of these patients had a preexisting craniopharyngioma.

Key demographic characteristics for the 2,234 GH-treated Japanese patients who met criteria for safety analyses (described above) and had a baseline height measurement available are presented in Table 1. More than half of the patients (59.4%) were male. Mean (SD) age at the start of GH treatment was 8.94 (3.50) yr, and mean (SD) bone age SD score (SDS) (Greulich-Pyle [GP] method) was −2.46 (1.35). Mean (SD) height SDS was −2.66 (0.68). Mean (SD) weight was 22.39 (9.39) kg; mean (SD) weight SDS and body mass index (BMI) SDS were −1.49 (2.52) and −0.06 (0.96), respectively. The mean (SD) GH dose for GHD during the study was 0.19 (0.03) mg/kg/wk. Mean and median follow-up periods in the study for these patients were 3.2 yr and 2.7 yr, respectively.

Table 2 presents reasons for discontinuation of the patients during the study by baseline GHD condition and overall. Due to the nature of Japanese regulatory assessments of observational studies, GeNeSIS Japan was conducted in 2 separate segments, requiring the discontinuation of several patients by the sponsor at the end of the first segment, and sponsor decision was the most frequent reason for patient discontinuation overall (n = 1,458 [64.6%]). The only other reason for discontinuation of 10% or more of patients overall was patients who attained final height according to the investigator (n = 236 [10.5%]). Patient disposition for all patients is presented in Fig. 1.

General safety

Treatment-emergent adverse events (TEAEs), including relatedness to GH therapy as assessed by the investigators, are summarized in Table 3 for patients who had at least 1 follow-up visit. Approximately 16% of patients overall experienced at least 1 TEAE. The only TEAEs occurring in 1% or more of patients were hypothyroidism (n = 55 [2.4%]) and precocious puberty (n = 34 [1.5%]). Diagnoses of precocious puberty were as recorded by the investigators according to Tanner stages (18, 19).

SAEs occurring in more than 1 patient, including relatedness to GH therapy as assessed by the investigators, are summarized in Table 4.

Table 1 Baseline characteristics of subjects (safety population, baseline height available)

Variable	All N = 2,234	GHD N = 2,001	TS N = 120	ISS N = 5	SHOX-D N = 1	SGA N = 29	Other N = 60	UNK N = 18
Male, n (%)	1,326 (59.4)	1,263 (63.1)	1 * (0.8)	1 (20.0)	0 (0.0)	17 (58.6)	32 (53.3)	12 (66.7)
CA (y)	8.94 (3.50)	9.01 (3.49)	8.23 (3.61)	12.36 (2.54)	4.65 (NA)	7.63 (2.83)	8.13 (3.69)	9.81 (2.93)
BAGP (SDS)	−2.46 (1.35)	−2.51 (1.34)	−1.84 (1.36)	−1.21 (1.24)	– (NA)	−1.79 (1.26)	−2.66 (1.53)	−2.06 (0.56)
Ht (SDS)	−2.66 (0.68)	−2.64 (0.67)	−2.84 (0.66)	−2.41 (0.66)	−2.56 (NA)	−2.76 (0.82)	−3.11 (0.83)	−2.57 (0.36)
Ht (SDS) –TH (SDS)	−2.03 (0.97)	−1.98 (0.95)	−2.70 (0.90)	−1.86 (0.90)	−0.90 (NA)	−1.98 (1.02)	−2.34 (1.19)	−2.06 (0.62)
Weight (kg)	22.39 (9.39)	22.47 (9.28)	22.53 (11.30)	29.84 (7.49)	14.00 (NA)	18.39 (6.88)	20.54 (9.95)	23.28 (7.63)
Weight (SDS)	−1.49 (2.52)	−1.50 (2.65)	−1.18 (0.77)	−1.60 (0.26)	−1.05 (NA)	−1.62 (0.74)	−1.57 (0.60)	−1.57 (0.39)
BMI (SDS)	−0.06 (0.96)	−0.09 (0.96)	0.45 (0.98)	−0.45 (0.47)	0.50 (NA)	−0.17 (0.75)	0.16 (0.82)	−0.50 (0.93)
IGF-I (SDS)	−1.35 (1.68)	−1.41 (1.73)	−0.88 (1.30)	−2.25 (NA)	−0.66 (NA)	−0.77 (0.96)	−1.14 (1.12)	−0.65 (0.97)
GH dose (mg/kg/wk)								
Mean (SD)	0.20 (0.05)	0.19 (0.03)	0.33 (0.09)	0.18 (0.02)	0.20 (NA)	0.19 (0.04)	0.19 (0.03)	0.19 (0.02)
Median	0.18	0.18	0.35	0.17	0.20	0.18	0.18	0.18
Min, Max	0.02, 0.86	0.02, 0.50	0.04, 0.86	0.15, 0.20	0.20, 0.20	0.03, 0.29	0.09, 0.30	0.16, 0.26

Data are mean (SD) unless otherwise indicated. BAGP, bone age (Greulich-Pyle method); BMI, body mass index; CA, chronological age at diagnosis; GHD, GH deficiency; Ht, height; ISS, idiopathic short stature; Max, maximum; Min, minimum; NA, not applicable; SD, standard deviation; SDS, standard deviation score; SGA, short children born small for gestational age; SHOX-D, short stature homeobox-containing gene deficiency; TH, target height; TS, Turner syndrome; UNK, unknown. * Male gender was indicated for 1 patient with reported diagnosis of Turner syndrome. It is unclear whether the entry was in error or represented a case of male Turner syndrome (ie, Noonan syndrome).

The only SAEs occurring in more than 1 patient overall were craniopharyngioma (n = 4 [0.17%]); pneumonia (n = 3 [0.13%]); and inguinal hernia, gastroenteritis, and influenza (n = 2 [0.09%], each).

Diabetes

New-onset T2D occurred in 3 patients (0.13%), and slowly progressive insulin-dependent diabetes mellitus (SPIDDM) related to the underlying syndrome of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) occurred in 1 patient (0.04%; Table 5). Risk factors were identified for all 3 of the patients with new-onset T2D: a patient with Turner syndrome with preexisting impaired glucose tolerance also reported, a patient with a small for gestational age (SGA) diagnosis (Russell-Silver syndrome), and a patient with organic GHD following total body irradiation for acute lymphocytic leukemia. The patient with Russell-Silver syndrome

Table 2 Reasons for study discontinuation for GH-treated patients by diagnostic group at baseline (safety evaluable population)

Reason	All	GHD	TS	ISS	SHOX-D	SGA	Other	UNK
	N = 2,345	N = 2,106	N = 125	N = 5	N = 1	N = 29	N = 61	N = 18
Unable to contact patient (lost to follow-up)	99 (4.4)	96 (4.7)	1 (0.8)	0	0	0	2 (3.3)	0
Patient moved	59 (2.6)	50 (2.5)	6 (5.0)	0	0	2 (6.9)	1 (1.7)	0
Sponsor decision (study or patient discontinued by sponsor)	1,458 (64.6)	1,316 (64.5)	83 (69.7)	3 (60.0)	1 (100.0)	19 (65.5)	34 (56.7)	2 (40.0)
Patient/parent decision	158 (7.0)	149 (7.3)	4 (3.4)	0	0	3 (10.3)	2 (3.3)	0
Physician decision	109 (4.8)	97 (4.8)	7 (5.9)	1 (20.0)	0	2 (6.9)	1 (1.7)	1 (20.0)
Adverse event	8 (0.4)	7 (0.3)	0	0	0	0	1 (1.7)	0
Final height attained	236 (10.5)	216 (10.6)	7 (5.9)	1 (20.0)	0	3 (10.3)	7 (11.7)	2 (40.0)
Patient transferred to HypoCCS study	1 (0.0)	1 (0.0)	0	0	0	0	0	0
Third party required patient to change brand of GH	10 (0.4)	8 (0.4)	1 (0.8)	0	0	0	1 (1.7)	0
Other	120 (5.3)	99 (4.9)	10 (8.4)	0	0	0	11 (18.3)	0
Study summary completed	2,258	2,039	119	5	1	29	60	5

Data are number (%) of patients. GHD, GH deficiency; HypoCCS, Hypopituitary Control and Complications Study; ISS, idiopathic short stature; SGA, short children born small for gestational age; SHOX-D, short stature homeobox-containing gene deficiency; TS, Turner syndrome; UNK, unknown.

was diagnosed with T2D 2.9 yr after starting treatment with GH. The patient discontinued GH treatment and was hospitalized for 2 wk. The blood glucose level was rapidly improved and normalized by diet therapy without diabetes medication. A second patient was diagnosed with T2D after GH treatment for 2.6 yr. He received total body irradiation and chemotherapy due to acute lymphocytic leukemia. His fasting blood glucose level was 259 mg/dL and HbA1c value was 6.7% at the diagnosis of diabetes. After he discontinued GH treatment, his blood glucose level was normalized by diet therapy.

Neoplasms

Treatment-emergent neoplasms were reported for 13 patients (0.56%), including 5 patients with craniopharyngiomas and 1 patient with brain neoplasm. The brain neoplasm, identified as *de novo* germinoma, was the only treatment-emergent malignancy observed. Besides the craniopharyngiomas and the brain neoplasm, the other 6 patients with treatment-emergent neoplasms had benign neoplasms: melanocytic naevus in 2 patients and benign hair follicle tumour, lipoma, neurofibroma, and benign tongue neoplasm in 1 patient each. Among the 5 patients with craniopharyngioma, 4 were recurrences. Three

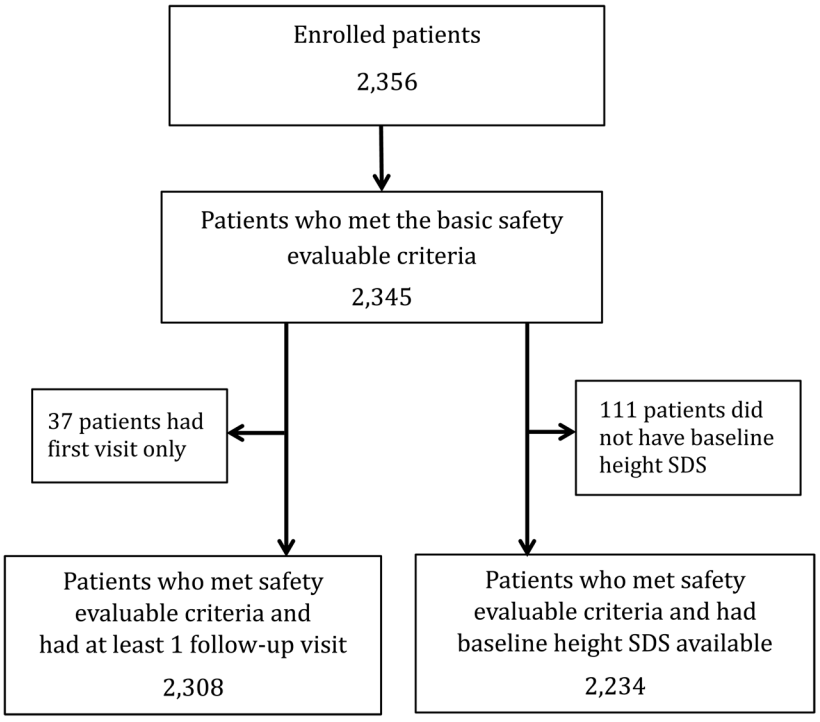

Fig. 1. Patient disposition.

of the cases were considered causally unrelated to GH treatment; the causal relationship was undetermined for 2 of the cases. The patient with *de novo* germinoma had a preexisting diagnosis of hypophysitis but was subsequently diagnosed with germinoma approximately 1 month after starting GH therapy. Table 6 provides key information for the 7 patients considered to have noteworthy neoplasms: in addition to the 6 cases discussed above, this includes a case of recurrent medulloblastoma that was reported as a TEAE but was found to have existed prior to initiation of therapy; causal relation with GH treatment was ruled out.

Discussion

Among Japanese patients treated in GeNeSIS, new-onset T2D was diagnosed in 3 patients (0.13%). Preexisting craniopharyngioma was found in 25 of the 57 patients with organic GHD due to intracranial tumors and recurred in 4 of these patients (16%). Data from the Pfizer International Growth Study (KIGS) have indicated an incidence rate of 0.36% for diabetes mellitus during a median GH treatment period of 2.9 years (11) and a recurrence-free survival rate of 63% for craniopharyngioma patients during a mean GH treatment period of 10.3 yr (20), neither of which was significantly different from our results.

Data from global GeNeSIS demonstrated that GH treatment did not affect the incidence of type 1 diabetes; however, the incidence of T2D in KIGS was 34.4 cases per 100,000 patient-years of GH treatment (11), and in a previous analysis of global GeNeSIS it was reported to be six-fold higher than the rate reported in the general population, stratified for age and ethnicity (12). In the latter analysis, among the 11 patients with new-onset T2D during the study, risk factors for diabetes were identified in 10 patients (12). In Japanese patients, risk factors were identified for all 3 of the patients

Table 3 Summary of TEAEs and specific medical conditions for GH-treated patients (safety population with at least 1 follow-up visit available)

	All (N = 2,308)	GH relatedness		
		Yes	No	UNK
Patients with at least 1 TEAE	368 (15.94)	46 (1.99)	313 (13.56)	9 (0.39)
Common TEAEs				
Hypothyroidism	55 (2.38)	6 (0.26)	41 (1.78)	8 (0.35)
Precocious puberty	34 (1.47)	0	33 (1.43)	1 (0.04)
Upper respiratory tract inflammation	19 (0.82)	0	19 (0.82)	0
Asthma	17 (0.74)	0	17 (0.74)	0
Arthralgia	16 (0.69)	12 (0.52)	4 (0.17)	0
Bronchitis	13 (0.56)	0	12 (0.52)	1 (0.04)
Influenza	13 (0.56)	0	13 (0.56)	0
Hypogonadism	11 (0.48)	0	11 (0.48)	0
Pharyngitis	11 (0.48)	0	11 (0.48)	0
Rhinitis allergic	11 (0.48)	0	10 (0.43)	1 (0.04)
Secondary hypothyroidism	10 (0.43)	0	10 (0.43)	0
Scoliosis	10 (0.43)	4 (0.17)	6 (0.26)	0
Specific medical conditions related to neoplasia and diabetes				
Craniopharyngioma	5 (0.22)	1	4	0
Type 2 diabetes mellitus	2 (0.09)	0	1	1
Diabetes mellitus [a]	2 (0.09)	2	0	0
Melanocytic naevus	2 (0.09)	0	1	1
Medulloblastoma [b]	1 (0.04)	0	1	0
Tongue neoplasm benign	1 (0.04)	0	1	0
Neurofibroma	1 (0.04)	1	0	0
Lipoma	1 (0.04)	0	1	0
Hair follicle tumour benign	1 (0.04)	0	1	0
Brain neoplasm [c]	1 (0.04)	0	1	0

Data are number of patients (%). Data are for patients with a Visit 1 and at least 1 follow-up visit available. GH relatedness assigned by investigators. Events coded using MedDRA version 18.1. MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; UNK, unknown. [a] Includes type 2 diabetes and slowly progressive insulin dependent diabetes mellitus (SPIDDM). [b] Recurrence (not TEAE). [c] Germinoma.

Table 4 SAEs occurring in 2 or more patients (safety evaluable population)

	All (N = 2,345)	GH relatedness		
		Yes	No	Unknown
Patients with at least 1 SAE	32 (1.36)	6	25	1
Craniopharyngioma	4 (0.17)	1	3	0
Pneumonia	3 (0.13)	0	3	0
Gastroenteritis	2 (0.09)	0	2	0
Influenza	2 (0.09)	0	2	0
Inguinal hernia	2 (0.09)	0	2	0

Data are number of patients (%). Events coded using MedDRA version 18.1. GH relatedness assigned by investigators. MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

Table 5 Listing of new-onset diabetes cases and relevant patient histories for GH-treated patients (safety evaluable population)

Type of DM	Diagnosis	DM onset age (yr)	Time to DM from start of GH therapy (yr)	Puberty at start of GH therapy	Additional risk factors	BMI (SDS) at Visit 1	GH dose (mg/kg/wk)	GH status
Type 2	Turner syndrome	17.4	5.0	No	IGT	1.15	0.34	Discontinued
Type 2	SGA (Russell-Silver syndrome)	10.1	2.9	No	NR	−0.74	0.29	Discontinued
Type 2	Idiopathic GHD	15.3	2.6	No	Total body irradiation	−0.42	0.18	Discontinued
SPIDDM	Organic GHD (mitochondrial disease)	16.8	3.0	No	FH (+) Mother: DM	0.98	0.19	Discontinued

BMI, body mass index; DM, diabetes mellitus; FH, family history; GHD, GH deficiency; IGT, impaired glucose tolerance; NR, none recorded; SDS, standard deviation score; SGA, small for gestational age; SPIDDM, slowly progressive insulin-dependent diabetes mellitus.

Table 6. Summary of key cases of neoplasia

Recurrent events

Type of neoplasm diagnosed	Sex	Age at enrollment (yr)	Age at first diagnosis of neoplasm (yr)	Age at start of GH treatment (yr)	Age at detection of recurrence (yr)	Duration of GH treatment before recurrence (yr)	GH status [a]	Investigator-assessed causal relationship to GH
Craniopharyngioma	F	8	9	8	10	1.6	Restarted	Unknown
Craniopharyngioma	F	11	7	11	13	2.8	Discontinued	Unknown
Craniopharyngioma	M	8	8	8	10	2	Continued	No
Craniopharyngioma	M	7	5	7	9	2 yr	Restarted	No
Medulloblastoma	F	9	3	9	9	Preexisting	Continued	No

Neoplasms detected for the first time after the start of GH treatment

Type of neoplasm diagnosed	Sex	Age at enrollment (yr)	Age at start of GH treatment (yr)	Age at detection of neoplasm (yr)	Duration of GH treatment before detection of neoplasm	GH status [a]	Investigator-assessed causal relationship to GH
Craniopharyngioma	M	10	10	10	43 days	Discontinued	No
Germinoma (brain neoplasm)	F	8	8	7 (suspected)	1 month	Discontinued	No

F, female; GHD, GH deficiency; M, male; N/A, not available. [a] Status immediately following recurrence or detection.

with new-onset T2D: a patient with Turner syndrome with preexisting impaired glucose tolerance also reported, a patient with a small for gestational age (SGA) diagnosis (Russell-Silver syndrome), and a patient with organic GHD following total body irradiation for acute lymphocytic leukemia. A study of patients with Turner syndrome suggested that GH impairs beta-cell function and predisposes patients to diabetes (21). A hyperinsulinemic clamp study in children born SGA showed reduced insulin sensitivity, which may contribute to an increased risk of diabetes later in life (22). In a retrospective study that compared childhood cancer survivors with their siblings, the survivors treated with total-body or abdominal irradiation had an increased risk of diabetes in later life that appeared to be unrelated to their BMI or physical activity levels (23). Additionally, there was a case of SPIDDM in the patient with underlying MELAS; mitochondrial dysfunction might play an important role in diabetes pathophysiology due to the consequences of decreased energy production (ATP), and mitochondrial diseases have been associated with diabetes (24).

The possibility that patients receiving GH are at increased risk of cancer (*de novo* cases as well as recurrence of previously treated tumors) has been discussed for many years (13, 25). However, based on the KIGS data, there was no evidence that GH treatment in growth-disordered pediatric patients resulted in an increased risk compared with the general population (26), and children without a history of malignancy treated with GH in global GeNeSIS did not have a higher risk of cancer during treatment when compared with general-population cancer registries (2). Following the early report of cases of leukemia in GH-treated pediatric patients (13), multiple studies have found the rates of leukemia in GH-treated patients without leukemia risk factors to be similar to those of the general population (27–29). There was only a single case of potential new-onset primary cancer reported in Japanese patients: the case of pituitary germinoma, which was identified 5 wk after initiation of somatropin therapy. Previous magnetic resonance imaging (MRI) in this patient had identified hypophysitis, and cases of hypophysitis preceding or masking a diagnosis of germinoma have previously been described (30). This fact, coupled with the short time between the start of GH treatment and diagnosis of the tumor, suggests that the germinoma may have been present before initiation of GH therapy, but misdiagnosed as hypophysitis. Generally, germinoma has been identified in the pineal or the hypothalamic-pituitary region in which teratoma, astrocytoma, and hypophysitis, including Langerhans cell histocytosis and sarcoidosis, has been diagnosed. A manuscript on neuroimaging suggests that the common pineal region tumors have no pathognomonic imaging patterns (31). Additionally, some biopsies are either nondiagnostic or misdiagnosed due to the complexity of the masses and their high vascularity, leading to insufficient tissue (32), which indicates that one imaging study would be insufficient for definitive diagnosis. Mootha *et al*. suggested that a contrast-enhanced brain MRI and serial follow-up scan in a short term was useful for detecting subtle abnormalities in the hypothalamic-pituitary region (33).

In a recently published analysis of the global GeNeSIS database, the standardized incidence ratio (95% confidence interval [CI]) for primary cancer in GH-treated children compared with a country-, age-, and sex-matched cohort of the general population was 1.02 (0.54–1.75), and the crude incidence (95% CI) was 20.1 (10.7–34.3) cases per 100,000 person-years (2). These findings were based on 13 observed primary cancer cases, including the case of germinoma from Japan. Reports from the Childhood Cancer Survivor Study (CCSS) indicated that GH treatment was associated with an increased relative risk of second neoplasms (SN) (34, 35): the rate ratio of GH-treated survivors developing an SN compared with non-GH-treated survivors was 2.15 (95% CI 1.3–3.5; $p < 0.002$) (34). However,

a more recent analysis specifically for SN of the central nervous system (CNS) showed that the overall risk of occurrence of a CNS SN was not statistically significantly increased with GH exposure (36). In Japanese GeNeSIS patients, no cases of SN were reported. Of the 57 GH-treated patients in the study with any type of intracranial tumor, 25 patients had craniopharyngioma; 4 of these 25 (16%) had a recurrence of the tumor while participating in GeNeSIS. It has been reported that craniopharyngiomas account for approximately 5–10% of intracranial tumors in pediatric patients (37). A recent meta-analysis of 15 studies indicated that the recurrence or progression of intracranial tumors was not associated with GH therapy for any age group (relative risk [RR] 0.48; 95% CI 0.39–0.56) (38). Similarly, for children, the pooled RR (95% CI) was 0.44 (0.34–0.50), indicating that GH therapy did not increase the risk of recurrence or progression of intracranial tumors, craniopharyngioma, medulloblastoma, astrocytoma, or glioma (38). Rates of recurrence of craniopharyngiomas (including those that were excised, and across pediatric and adult studies) have been reported to range from 5–57% (39); the frequency of recurrence in the KIGS data was 11.7% (20).

Our study has a number of limitations to consider. First, because it was an observational study, it has limited value for assessing causality. There was no comparator treatment group, and without sponsor monitoring of patient medical records, the reporting of incident cases was dependent on the investigative sites. Although the sites were reminded of the importance of adverse event reporting throughout the study, potential underreporting of event cases must be considered because multiple data modules from the GeNeSIS and corporate pharmacovigilance databases were used to ascertain cases. Second, although the overall duration of GeNeSIS was approximately 15 yr, the average follow-up time per patient in Japan GeNeSIS was relatively short (a mean of 3.2 yr for GH-treated patients) because data from patients previously treated with GH before entering the study were excluded from the analyses. This comparatively short duration might not have been sufficient to assess incident rates by calculating events per patient-year. However, the large number of patients enrolled allowed detection of adverse events occurring even infrequently, and the observational study design allowed evaluation of typical GH treatment in real-world Japanese clinical practice.

In conclusion, new-onset cases of T2D were reported in Japanese patients followed in GeNeSIS, but all had risk factors for development of abnormal glucose metabolism, and our findings did not differ from previous reports of diabetes in GH-treated pediatric patients with short stature. There was no apparent increase in the risk of new neoplastic lesions or malignant tumors in Japanese patients followed in GeNeSIS.

Conflict of Interest: NJ and CJC are employees of Eli Lilly and Company. KI, JF, and NI are employees of Eli Lilly Japan K.K. Other authors have no conflict of interest to disclose.

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