Mortality in Children Receiving Growth Hormone Treatment of Growth Disorders: Data From the Genetics and Neuroendocrinology of Short Stature International Study

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Context: Although pediatric growth hormone (GH) treatment is generally considered safe for approved indications, concerns have been raised regarding potential for increased risk of mortality in adults treated with GH during childhood.

Objective: To assess mortality in children receiving GH.

Design: Prospective, multinational, observational study.

Setting: Eight hundred twenty-seven study sites in 30 countries.

Patients: Children with growth disorders.

Interventions: GH treatment during childhood.

Main Outcome Measure: Standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) using age- and sex-specific rates from the general population.

Results: Among 9504 GH-treated patients followed for ≥4 years (67,163 person-years of follow-up), 42 deaths were reported (SMR, 0.77; 95% CI, 0.56 to 1.05). SMR was significantly elevated in patients with history of malignant neoplasia (6.97; 95% CI, 3.81 to 11.69) and borderline elevated for those with other serious non–GH-deficient conditions (2.47; 95% CI, 0.99-5.09). SMRs were not elevated for children with history of benign neoplasia (1.44; 95% CI, 0.17 to 5.20), idiopathic GHD (0.11; 95% CI, 0.02 to 0.33), idiopathic short stature (0.20; 95% CI, 0.01 to 1.10), short stature associated with small for gestational age (SGA) birth (0.66; 95% CI, 0.08 to 2.37), Turner syndrome (0.51; 95% CI, 0.06 to 1.83), or *short stature homeobox-containing* (SHOX) gene deficiency (0.83; 95% CI, 0.02 to 4.65).

Conclusions: No significant increases in mortality were observed for GH-treated children with idiopathic GHD, idiopathic short stature, born SGA, Turner syndrome, SHOX deficiency, or history of benign neoplasia. Mortality was elevated for children with prior malignancy and those with underlying serious non–GH-deficient medical conditions. (***J Clin Endocrinol Metab* 102: 3195–3205, 2017**)

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 23 January 2017. Accepted 18 May 2017.
First Published Online 26 May 2017

Abbreviations: CCSS, Childhood Cancer Survivor Study; CI, confidence interval; CNS, central nervous system; CRI, chronic renal insufficiency; GeNeSIS, Genetics and Neuroendocrinology of Short stature International Study; GH, growth hormone; GHD, growth hormone deficiency; IGHD, idiopathic growth hormone deficiency; ISS, idiopathic short stature; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episode; PWS, Prader-Willi syndrome; SAGhE, Safety and Appropriateness of Growth hormone treatments in Europe; SGA, small for gestational age; *SHOX*, *short stature homeobox-containing*; SHOX-D, *short stature homeobox-containing* gene deficiency; SMR, standardized mortality ratio; TS, Turner syndrome.

Growth hormone (GH) treatment during childhood is approved for a number of conditions that result in short stature or growth failure. Although the most frequent diagnosis is growth hormone deficiency (GHD), other growth-related indications for GH treatment in various countries are Turner syndrome (TS), *short stature homeobox-containing* (*SHOX*) gene deficiency (SHOX-D), Noonan syndrome, Prader-Willi syndrome (PWS), growth failure associated with chronic renal insufficiency (CRI), short stature in children born small for gestational age (SGA) who do not demonstrate catch-up growth, and idiopathic short stature (ISS) (1–7). GH treatment during childhood is generally considered safe when used at approved doses for approved indications (8–10). However, concerns have been raised about potential associations between GH treatment and development or recurrence of neoplasms, intracranial hemorrhage, and premature mortality (11–15).

In the French cohort of a multinational study examining long-term safety of European patients treated with GH during childhood [Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE)], the risk of mortality was increased in a cohort of 6928 adults who had received childhood GH for conditions considered by the authors not to increase mortality risk [isolated idiopathic growth hormone deficiency (IGHD), GH neurosecretory dysfunction, ISS, and SGA] (14). Overall and condition-specific standardized mortality related to bone tumors, cerebrovascular disease, and "symptoms, signs and ill-defined conditions" were increased, based on expected deaths using age- and sex-specific rates for the French general population (14). However, analysis of a smaller (N = 2543) Belgian, Dutch, and Swedish SAGhE cohort did not replicate these findings (16). Furthermore, the Childhood Cancer Survivor Study (CCSS) found no association between GH treatment and mortality risk in patients previously treated for malignancy (11).

Because of long-held concerns, particularly regarding the potential impact of GH treatment on development or recurrence of neoplasia, investigation of mortality among patients who receive pediatric GH, whatever the indication, remains important. The observational Genetics and Neuroendocrinology of Short stature International Study (GeNeSIS) was conducted between 1999 and 2015 to examine safety and effectiveness of GH treatment in children with short stature of various etiologies followed under conditions of typical pediatric endocrine practice. Although GeNeSIS followed pediatric patients during the course of their GH treatment, rather than after completion, we nevertheless felt it was relevant to examine mortality risk in GH-treated children using similar methodology to that used in the French SAGhE study. We therefore assessed mortality for children followed in GeNeSIS using standardized mortality ratios (SMRs) by comparing observed deaths in the study population with expected deaths based on age- and sex-specific general population rates.

Patients and Methods

Patients

Patient data were obtained from the prospective, multinational (827 study sites in 30 countries), open-label, GeNeSIS observational research program (ClinicalTrials.gov no. NCT01088412, conducted March 1999-September 2015) for pediatric patients receiving GH treatment of growth disorders; in addition, small cohorts of non–GH-treated patients were followed for certain conditions (history of neoplasia or SHOX-D diagnoses). Patients were investigated and treated at the discretion of their physicians, and no specific tests or procedures were required before or during study participation.

The study was approved by local ethics committees and conducted according to the ethical principles of the Declaration of Helsinki and all applicable regulatory requirements in participating countries. Written consent for data collection, processing, and publication was obtained from parent(s)/legal guardian(s).

At study closure in September 2015, the database included 22,294 GH-treated patients whose data met basic predefined quality standards, of whom 21,106 had known sex and at least one follow-up visit, allowing assessment for safety. Supplemental Table 1 provides the numbers of patients enrolled from each of the 30 participating countries.

Study evaluations

Baseline data requested from records of routine clinical visits included date of birth, medical history, investigator-defined short stature/growth failure diagnosis, medications (including prior GH treatment), bone age, height, weight, and results of hypothalamic-pituitary axis investigations. Database modules containing information potentially related to previous neoplasia were reviewed, including short stature diagnoses, historical conditions, diagnoses collected in a specific neoplasia substudy, preexisting conditions, and adverse events. Assignment of malignant vs benign status for patients with history of neoplasia was based on guidelines from the Surveillance, Epidemiology and End Results program (17) and World Health Organization classification (18).

Follow-up data were collected for height, weight, and other auxologic variables, laboratory results, occurrence of adverse events, and responses to specific questions regarding development of neoplasia and other relevant medical conditions. All adverse events were categorized according to the Medical Dictionary for Regulatory Activities (version 18.1). Where appropriate, histories and causes of death were cross-referenced to serious adverse event reports in the Lilly pharmacovigilance database. All reports of death were followed-up to determine cause of death and the investigator's assessment of relationship to GH treatment.

Statistics

Standard deviation scores for height and weight were calculated using US general population data (19), and for body

mass index (kg/m^2) using European reference data (20); Japanese standards were used for Japanese patients (21). To reduce potential bias because of limited duration of follow-up, the primary analyses of demographics, mortality rates, and SMRs used GH-treated children who had at least 4 years of follow-up in the study or died within this time frame (Fig. 1, 4-year treated population). For comparability, the same analyses were performed for all GH-treated patients who had at least one postbaseline visit, irrespective of duration of follow-up (Fig. 1; Supplemental Fig. 1, full treated population). Mortality in the small non–GH-treated group of patients was also assessed.

Expected numbers of deaths were calculated using sex- and age-specific general population mortality rates and patient-years in GeNeSIS. US Centers for Disease Control and Prevention data were used for US general population mortality rates (http://wonder.cdc.gov), and World Health Organization data were used for all other countries (http://apps.who.int/ghodata). US age-specific mortality rates were available by age groups <1 year, 1 to 4 years, and 5-year intervals thereafter. For other countries, only limited age ranges and wide age bands were available; therefore, countries were grouped into geographic regions (Supplemental Table 1), allowing use of narrower age bands (0 to 4 years, 5 to 14 years, and 15-year intervals thereafter). SMRs were calculated as the ratio of number of deaths observed in GeNeSIS and expected number of deaths. Exact 95% confidence intervals (CIs) were calculated for mortality rate and SMRs, assuming that the observed number of deaths followed a Poisson distribution.

Data are presented as mean ± standard deviation or mean (95% CI), unless otherwise specified. SMR results were considered significant if the 95% CI did not include 1.0. Cumulative incidence of death was estimated as 1 minus the Kaplan-Meier survival estimate at a given point in time.

Results

Baseline demographics and information regarding GH dose and duration are summarized in Table 1 for the 9504 patients in the 4-year treated population (primary analysis cohort), representing 45% of the full treated population (Fig. 1). The equivalent data for the 21,106 GH-treated patients in the full treated population are provided in Table 2.

Among the 9504 patients included in the 4-year treated population, approximately two-thirds had a diagnosis of GHD (Fig. 1), with the remaining one-third comprising a collection of non–GH-deficient conditions. Within the GH-deficient group, the primary diagnostic categories were IGHD (n = 4324; 45% of the 4-year treated population) and GHD resulting from an organic cause (n = 1612; 17% of the 4-year treated population). Of the group with organic GHD, approximately 70% had nonneoplastic conditions (n = 1130; 12% of the 4-year treated population), such as disturbances of hypothalamic and/or pituitary development, septo-optic dysplasia, and other central nervous system (CNS) anomalies; the other 30% (n = 482; 5% of the 4-year treated population) had history of neoplastic conditions, including intracranial tumor and sequelae of treatment of neoplasia. Diagnoses among the 3549 non–GH-deficient patients (37% of the 4-year treated population) included TS (n = 948; 10% of the 4-year treated population), ISS (n = 1018; 11% of the 4-year treated population), and children born SGA (n = 622; 7% of the 4-year treated population). The proportion of male to female patients was 59%/41%; mean age at start of GH for the 4-year treated population was 8.5 ± 3.7 years overall, 9.0 ± 3.5 years for patients with IGHD, 6.8 ± 4.3 years for patients with organic GHD (10.0 ± 2.7 years for the subgroup with history of malignant neoplasia), and 10.3 ± 3.2 years for patients with ISS (Table 1). Average duration of follow-up was 7.1 ± 2.6 years for the 4-year treated population and 4.3 ± 3.1 years for the full treated population.

At study closure, 42 deaths had been reported among GH-treated patients with at least one postbaseline visit during 67,163 person-years of follow-up for the 4-year treated population

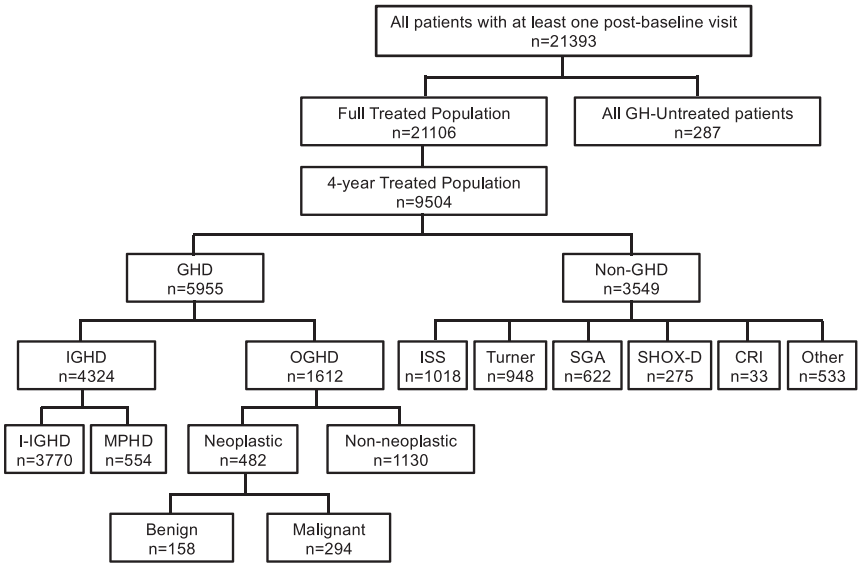

Figure 1. Patient populations used for analysis of mortality rates, with classification of the 4-year treated population according to investigator-provided diagnosis. Full treated population includes all GH-treated patients with at least one postbaseline visit. The 4-year treated population includes all GH-treated patients who had at least 4 years of follow-up within GeNeSIS or died within this time frame. Data were as reported by investigators, and patient numbers do not necessarily add up for subgroups because some information may have been lacking or incomplete. I-IGHD, isolated IGHD; MPHD, multiple pituitary hormone deficiency; OGHD, organic GH deficiency.

Table 1. Demographic and GH Treatment Data for the 4-Year Treated Population,[a] Grouped According to Reported Diagnosis

Diagnosis	No. of Patients	Sex, % F/M	Height SDS	BMI SDS	Initial GH Dose (mg/kg/wk)	Average GH Dose (mg/kg/wk)	Age at GH Start (y)	Age at Study Entry (y)	Years on GH	Age at Last Visit (y)
All	9504	41/59	−2.5 ± 1.0	−0.4 ± 1.6	0.27 ± 0.15	0.26 ± 0.10	8.5 ± 3.7	9.2 ± 3.6	7.3 ± 3.3	16.3 ± 4.0
GHD	5955	34/66	−2.4 ± 1.1	−0.4 ± 1.6	0.25 ± 0.16	0.24 ± 0.09	8.4 ± 3.9	9.2 ± 3.7	7.5 ± 3.4	16.3 ± 4.0
IGHD	4324	32/68	−2.4 ± 0.9	−0.6 ± 1.5	0.25 ± 0.12	0.24 ± 0.09	9.0 ± 3.5	9.5 ± 3.4	7.0 ± 3.0	16.5 ± 3.7
Isolated IGHD	3770	31/69	−2.4 ± 0.8	−0.6 ± 1.5	0.26 ± 0.13	0.24 ± 0.09	9.1 ± 3.4	9.6 ± 3.3	6.9 ± 2.9	16.5 ± 3.7
Multiple pituitary hormone deficiencies	554	39/61	−2.8 ± 1.2	−0.5 ± 1.9	0.23 ± 0.09	0.23 ± 0.10	8.1 ± 4.0	9.1 ± 3.8	8.2 ± 3.6	16.8 ± 3.8
Organic GHD	1612	38/62	−2.4 ± 1.5	−0.0 ± 1.8	0.23 ± 0.24	0.23 ± 0.10	6.8 ± 4.3	8.4 ± 4.3	8.6 ± 4.2	15.9 ± 4.6
Neoplastic cause	482	42/58	−1.7 ± 1.2	0.7 ± 1.6	0.20 ± 0.11	0.21 ± 0.10	9.9 ± 3.0	10.8 ± 3.0	7.1 ± 3.6	17.8 ± 3.7
Malignant	294	41/59	−1.8 ± 1.2	0.5 ± 1.4	0.21 ± 0.11	0.22 ± 0.10	10.0 ± 2.7	10.9 ± 2.7	6.7 ± 3.4	17.7 ± 3.5
Benign	158	44/56	−1.5 ± 1.4	1.4 ± 1.6	0.18 ± 0.12	0.20 ± 0.09	9.4 ± 3.5	10.5 ± 3.6	8.0 ± 4.0	17.7 ± 4.2
Nonneoplastic cause	1130	37/63	−2.8 ± 1.5	−0.4 ± 1.8	0.24 ± 0.28	0.23 ± 0.10	5.5 ± 4.1	7.3 ± 4.3	9.3 ± 4.2	15.1 ± 4.7
ISS	1018	24/76	−2.4 ± 0.7	−0.7 ± 1.4	0.34 ± 0.12	0.33 ± 0.10	10.3 ± 3.2	10.7 ± 3.1	7.3 ± 2.9	17.9 ± 3.9
TS	948	99/1	−2.5 ± 0.9	0.1 ± 1.4	0.30 ± 0.10	0.32 ± 0.09	7.9 ± 3.3	8.7 ± 3.3	7.5 ± 3.1	16.1 ± 3.8
SHOX-D	275	54/46	−2.4 ± 0.7	0.0 ± 1.3	0.31 ± 0.09	0.31 ± 0.10	8.8 ± 3.0	9.1 ± 3.0	5.9 ± 2.5	15.6 ± 3.4
SGA	622	46/54	−2.7 ± 0.8	−1.5 ± 1.8	0.28 ± 0.09	0.28 ± 0.09	7.8 ± 3.2	8.2 ± 3.2	6.4 ± 2.5	14.6 ± 3.5
CRI	33	39/61	−2.4 ± 1.0	−0.8 ± 2.0	0.32 ± 0.12	0.34 ± 0.11	6.9 ± 3.7	7.8 ± 3.6	6.8 ± 3.7	14.6 ± 3.4
Other[b]	533	39/61	−2.7 ± 1.2	−0.6 ± 1.9	0.27 ± 0.11	0.27 ± 0.09	8.3 ± 3.8	9.0 ± 3.7	7.1 ± 3.0	16.0 ± 4.1

Values are mean ± standard deviation or as otherwise specified.

Abbreviations: BMI, body mass index, F, female; M, male; SDS, standard deviation score.

[a] GH-treated patients who had at least 4 years of follow-up or died within this time frame.

[b] Diagnoses not in the listed categories include genetic and cytogenetic conditions, clinical syndromes, skeletal dysplasias, and other non-GHD disturbances of the GH/insulinlike growth factor-I axis (*e.g.*, bioinactive GH, GH insensitivity).

(Table 3) and 91,582 person-years of follow-up for the full treated population (Supplemental Table 2). The overall SMR was 0.77 (95% CI, 0.56 to 1.05) for the 4-year treated population and 0.58 (95% CI, 0.42 to 0.78) for the full treated population. SMRs were not significantly elevated for any of the main diagnostic groups (GHD, ISS, TS, SGA, SHOX-D, and CRI) (Table 3). However, SMRs were elevated for patients with organic GHD, particularly influenced by patients with history of malignant neoplasia (4-year treated population: n = 294; SMR, 6.97; 95% CI, 3.81 to 11.69; full treated population: n = 530; SMR, 5.72; 95% CI, 3.13 to 9.60). Of 14 children with history of malignant neoplasia whose deaths were reported during follow-up, seven had history of medulloblastoma, three had history of astrocytoma, two had history of leukemia, and one had history of neuroblastoma; in addition, one had history of Hodgkin lymphoma together with Down syndrome and CRI (Supplemental Table 3). Of the seven children with medulloblastoma history, four died after tumor recurrences, one died after developing acute myeloid leukemia as a second neoplasm, one died of complications of graft-vs-host disease after a bone marrow transplant for secondary myelodysplastic syndrome, and one died in a road accident.

No other patient category had a significantly increased SMR; however, the group with a diverse collection of disorders such as genetic conditions and clinical syndromes had an SMR of 2.47 (95% CI, 0.99 to 5.09) in the 4-year treated population (Table 3) and 1.75 (95% CI, 0.70 to 3.61) in the full treated population (Supplemental Table 2). The seven reported deaths among 533 children in this category in the 4-year treated population (n = 1168 in the full treated population) were a boy with adrenoleukodystrophy who died of progression of his underlying condition; a boy with Down syndrome and CRI who stopped breathing unexpectedly; a girl with history of Fanconi anemia who died of her disease; a boy with history of pseudohypoparathyroidism, panhypopituitarism, and other anomalies who died of pneumonia; a boy with hypoplastic left heart syndrome who died of congestive heart failure; and two patients receiving glucocorticoid treatment (one with Duchenne muscular dystrophy and cardiac involvement, and the other with systemic lupus erythematosus) (Supplemental Table 3).

In contrast with the increased SMR for patients with malignant neoplasia, the SMR for 158 patients with GHD after benign neoplasia was not significantly elevated (1.44; 95% CI, 0.17 to 5.20). The two reported deaths in this group were both patients with history of craniopharyngioma: one was found dead in bed 3 weeks after a head injury, and the other died of respiratory failure after development of hypothalamic dysfunction

Table 2. Demographic and GH Treatment Data for the Full Treated Population,[a] Grouped According to Reported Diagnosis

Diagnosis	No. of Patients	Sex, % F/M	Height SDS	BMI SDS	Initial GH Dose (mg/kg/wk)	Average GH Dose (mg/kg/wk)	Age at GH Start (y)	Age at Study Entry (y)	Years on GH	Age at Last Visit (y)
All	21,106	40/60	−2.4 ± 1.0	−0.4 ± 1.6	0.28 ± 0.17	0.27 ± 0.10	9.6 ± 3.9	10.5 ± 3.8	5.0 ± 3.5	14.8 ± 4.1
GHD	13,301	34/66	−2.4 ± 1.1	−0.3 ± 1.6	0.25 ± 0.15	0.25 ± 0.10	9.5 ± 4.0	10.5 ± 3.9	5.1 ± 3.7	14.9 ± 4.1
IGHD	10,423	32/68	−2.4 ± 0.9	−0.4 ± 1.5	0.26 ± 0.12	0.25 ± 0.10	10.0 ± 3.7	10.7 ± 3.6	4.7 ± 3.2	14.9 ± 3.9
Isolated IGHD	9356	32/68	−2.4 ± 0.9	−0.4 ± 1.5	0.26 ± 0.12	0.25 ± 0.10	10.1 ± 3.6	10.7 ± 3.5	4.5 ± 3.1	14.8 ± 3.8
Multiple pituitary hormone deficiencies	1067	35/65	−2.7 ± 1.3	−0.4 ± 1.8	0.24 ± 0.10	0.25 ± 0.11	9.3 ± 4.3	10.5 ± 4.1	6.0 ± 4.0	15.6 ± 4.1
Organic GHD	2830	38/62	−2.4 ± 1.5	−0.0 ± 1.9	0.23 ± 0.21	0.23 ± 0.10	7.7 ± 4.7	9.6 ± 4.7	6.8 ± 4.5	14.8 ± 4.9
Neoplastic cause	893	40/60	−1.8 ± 1.3	0.7 ± 1.6	0.21 ± 0.18	0.22 ± 0.10	10.5 ± 3.2	11.8 ± 3.3	5.5 ± 3.6	16.6 ± 3.8
Malignant	530	41/59	−1.9 ± 1.2	0.4 ± 1.4	0.22 ± 0.21	0.22 ± 0.10	10.7 ± 2.9	11.8 ± 3.1	5.3 ± 4.6	16.6 ± 3.6
Benign	285	42/58	−1.7 ± 1.4	1.2 ± 1.8	0.19 ± 0.12	0.20 ± 0.10	9.9 ± 3.7	11.5 ± 3.7	6.3 ± 4.1	16.5 ± 4.2
Nonneoplastic cause	1937	37/63	−2.7 ± 1.5	−0.4 ± 1.9	0.24 ± 0.23	0.23 ± 0.09	6.4 ± 4.8	8.6 ± 4.9	7.4 ± 4.7	14.0 ± 5.1
ISS	2663	28/72	−2.4 ± 0.8	−0.6 ± 1.4	0.34 ± 0.11	0.33 ± 0.09	11.2 ± 3.2	11.8 ± 3.1	4.5 ± 3.2	15.7 ± 3.8
TS	1787	99/1	−2.6 ± 0.9	0.3 ± 1.4	0.32 ± 0.33	0.32 ± 0.09	8.7 ± 3.8	9.8 ± 3.8	5.6 ± 3.4	14.7 ± 4.2
SHOX-D	563	58/42	−2.3 ± 0.8	0.1 ± 1.4	0.30 ± 0.09	0.30 ± 0.09	9.3 ± 3.2	9.7 ± 3.2	4.3 ± 2.5	14.1 ± 3.7
SGA	1222	45/55	−2.7 ± 0.9	−1.4 ± 1.8	0.29 ± 0.18	0.28 ± 0.09	8.2 ± 3.6	8.9 ± 3.6	4.9 ± 2.9	13.3 ± 3.9
CRI	77	35/65	−2.6 ± 1.0	−0.6 ± 2.0	0.30 ± 0.12	0.32 ± 0.10	8.2 ± 3.9	9.3 ± 4.3	4.5 ± 3.5	13.4 ± 4.2
Other[b]	1168	39/61	−2.7 ± 1.3	−0.4 ± 1.9	0.28 ± 0.13	0.28 ± 0.11	9.2 ± 4.1	10.2 ± 4.1	5.0 ± 3.3	14.5 ± 4.3

Values are mean ± standard deviation or as otherwise specified.

Abbreviations: BMI, body mass index, F, female; M, male; SDS, standard deviation score.

[a]GH-treated patients with at least one postbaseline visit.

[b]Diagnoses not in the listed categories include genetic and cytogenetic conditions, clinical syndromes, skeletal dysplasias, and other non-GHD disturbances of the GH/insulinlike growth factor-I axis (*e.g.*, bioinactive GH, GH insensitivity).

2 weeks after surgical resection of multicystic craniopharyngioma (Supplemental Table 3).

Of the eight patients who had a history of organic GHD resulting from nonneoplastic causes and were reported to have died, four were very young children—three with septo-optic dysplasia and hypopituitarism (two receiving corticosteroids for central hypoadrenalism) who died during acute illnesses, and one with probable hypopituitarism (GHD and small penis) accompanied by a number of dysmorphic features, who died of cardiorespiratory arrest after a mild upper respiratory illness; this child's adrenal function and corticosteroid treatment status were unknown. Three other children in this group (two with hypopituitarism, one of whom was receiving hydrocortisone for central hypoadrenalism; one with GHD as a result of perinatal hypoxia who was receiving no concomitant medications) died after acute illness or injury, and one girl with holoprosencephaly, whose adrenal function and corticosteroid treatment status were unknown, died of unknown causes. Overall, adrenal function and corticosteroid treatment status were unclear or unknown for three of the eight children in this diagnostic subgroup (Supplemental Table 3).

Three deaths were reported among 4324 patients in the 4-year treated population with the diagnosis of IGHD (SMR, 0.11; 95% CI, 0.02 to 0.33). One child died in a road accident and one died of respiratory failure after a respiratory infection. The third patient had a history of sideroblastic anemia and GHD, followed by diagnosis of type 2 diabetes mellitus after approximately 8 months of GH treatment, with death during an episode of diabetic ketoacidosis approximately 11 months later.

A single death was reported among 1018 patients with investigator-provided diagnosis of ISS in the 4-year treated population, resulting in an SMR of 0.20 (95% CI, 0.01 to 1.10). The teenage girl who died had a history of lupus erythematosus, anemia, and nephritis, treated with multiple concomitant medications, including prednisolone. Six months after GH was discontinued, died of septic meningitis caused by *Enterococcus faecalis* (Supplemental Table 3).

Death attributable to cerebrovascular disease (brainstem infarction) was reported for a child born SGA; however, this girl had a coexisting diagnosis of the congenital syndrome of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). The second death in a child born SGA was because of a disconnected ventriculoperitoneal shunt in a boy with the coexisting congenital syndrome, vertebral anomalies, anal atresia, congenital cardiac disease, tracheoesophageal fistula, renal anomalies, radial dysplasia, and other limb defects accompanied by hydrocephalus. These two deaths among 275 SGA children in our 4-year

Table 3. Summary of Mortality Data for GH-Treated Patients Who Had at Least 4 Years of Follow-Up or Died Within This Time Frame, Grouped According to Reported Diagnosis

Diagnosis	No. of Patients	Person-Years	Reported Deaths[a]	Mortality Rate per 100,000 Person-Years (95% CI)	Expected Deaths	SMR	95% CI
All	9504	67,163	42	63 (45–85)	54.33	0.77	0.56–1.05
GHD	5955	42,412	28[b]	66 (44–95)	37.38	0.75	0.50–1.08
IGHD	4324	30,095	3	10 (2–29)	26.58	0.11	0.02–0.33
Isolated IGHD	3770	25,859	3	12 (2–34)	22.39	0.13	0.03–0.39
Multiple pituitary hormone deficiencies	554	4236	0	0 (0–87)	4.19	0.00	0.00–0.88
Organic GHD	1612	12,184	24	197 (126–293)	10.72	2.24	1.43–3.33
Neoplastic cause	482	3336	16	480 (274–779)	3.63	4.41	2.52–7.16
Malignant	294	1983	14	706 (386–1185)	2.01	6.97	3.81–11.69
Benign	158	1154	2	173 (21–626)	1.39	1.44	0.17–5.20
Nonneoplastic cause	1130	8848	8	90 (39–178)	7.09	1.13	0.49–2.22
ISS	1018	7311	1	14 (0–76)	5.06	0.20	0.01–1.10
TS	948	6934	2	29 (3–104)	3.95	0.51	0.06–1.83
SHOX-D	275	1760	1	57 (1–317)	1.20	0.83	0.02–4.65
SGA	622	4020	2	50 (6–179)	3.04	0.66	0.08–2.37
CRI	33	219	1	457 (12–2544)	0.20	4.95	0.13–27.60
Other[c]	533	3704	7	189 (76–389)	2.83	2.47	0.99–5.09

[a] Three additional deaths (diagnoses: PWS, hypopituitarism with progressive and convulsive encephalopathy, and septo-optic dysplasia) were reported but not included in calculations because of the lack of on-study follow-up visit.

[b] Includes one patient for whom type of GHD was not specified.

[c] Diagnoses not in the listed categories include genetic and cytogenetic conditions, clinical syndromes, skeletal dysplasias, and other non-GHD disturbances of the GH/insulinlike growth factor-I axis (*e.g.*, bioinactive GH, GH insensitivity).

treated population resulted in an SMR of 0.66 (95% CI, 0.08 to 2.37).

In general, average GH dosages over the duration of study participation in the 4-year treated population were similar for patients who died and those who did not (Supplemental Table 4). Patients from the subgroup with diagnoses such as genetic conditions and clinical syndromes who died had a somewhat higher median (quartile 1, quartile 3) GH dosage of 0.31 (0.18, 0.47) mg/kg/wk than those who did not die [0.25 (0.20, 0.31) mg/kg/wk]. Similarly, a minor difference was observed for the subgroup with organic, nonneoplastic causes of GHD [deaths: 0.24 (0.21, 0.29) mg/kg/wk; nondeaths: 0.21 (0.18, 0.26) mg/kg/wk].

Few differences in SMRs were found when data were analyzed for male and female patients separately (data not shown), and minor differences observed were likely because of the relatively lower numbers of girls.

Three additional reported deaths among GH-treated patients were not included in the statistical analyses because no on-study follow-up visit data were available, therefore, the patients were not evaluable for safety according to predefined analysis procedures (Supplemental Table 3b). A 5-year-old boy with PWS died in an airplane accident; a 1-year-old boy with septo-optic dysplasia and pituitary hypoplasia died in his sleep; and a 1-year-old girl with hypopituitarism, progressive convulsive encephalopathy, and bronchopulmonary *Klebsiella pneumoniae* infection died after cardiorespiratory arrest.

The cumulative incidence of death (Fig. 2) increased gradually with duration of follow-up, such that the approximate cumulative incidence was 0.5% overall after 12 years. For patients with organic GHD, cumulative incidence was ~1.5% at 7 years, largely driven by patients with history of malignancy for whom cumulative incidence of death was > 4% at 7 years. In contrast, the cumulative incidence of death for patients with IGHD remained <0.05%.

The 45 reported deaths for GH-treated patients (including the three deaths excluded from SMR calculations because of lack of on-study follow-up) are summarized by general cause of death in Table 4. The most common cause of death was an acute illness or event, reported for 13 patients, followed by death associated with neoplasia in 12 patients. Cause of death was an underlying condition or its treatment in seven patients, accident/trauma in four patients, postoperative complications in three patients, and was unclear in six patients.

In addition to the deaths for GH-treated patients, six deaths were reported among 287 non–GH-treated patients with at least one follow-up visit (Supplemental Table 3c). All reported deaths in this group resulted from progression of disease in children with history of neoplasia (astrocytoma and hypopituitarism, astrocytoma and GHD, brainstem glioma, medulloblastoma, primitive neuroectodermal tumor, and atypical rhabdoid tumor). The six reported deaths in the non–GH-treated group vs expected count of 1.15 resulted in a

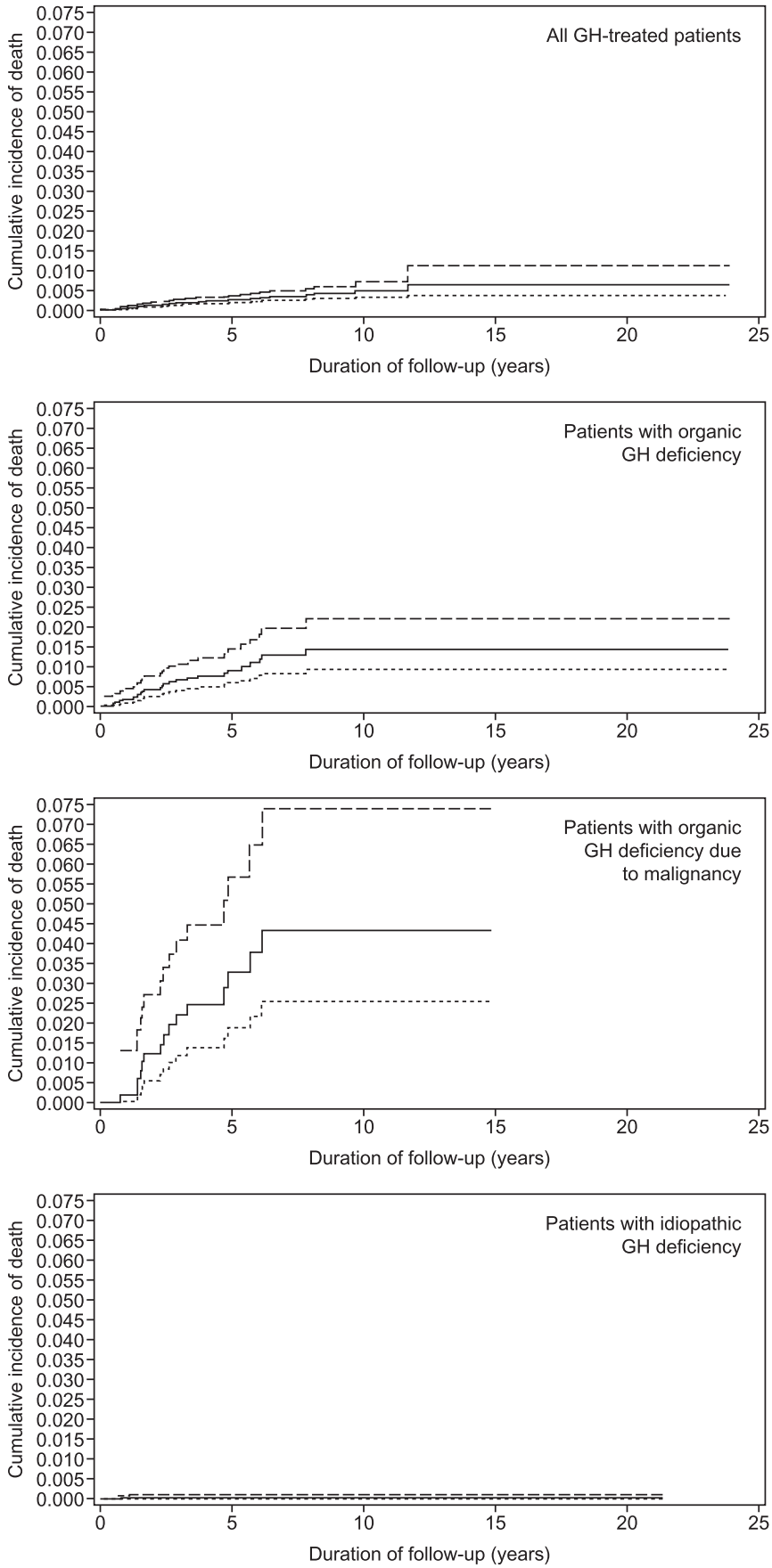

Figure 2. Cumulative incidence plots of mortality by duration of follow-up for selected diagnoses. Graphs show cumulative incidence (solid lines) with standard errors (dashed lines).

significantly elevated SMR of 5.22 (95% CI, 1.91 to 11.35).

Discussion

This analysis of a large multinational database sought to determine whether risk of death was increased in GH-treated children followed under conditions of standard clinical practice, compared with children in the general population. Our analyses of 9504 GH-treated children followed for at least 4 years, representing >67,000 person-years of follow-up, revealed no elevated mortality risk for most diagnostic groups, including children with IGHD, children with ISS, children with TS, those born SGA, or those with history of benign neoplasia. However, a sevenfold increase in risk of death relative to the general population was observed for patients with GHD associated with history of malignant neoplasia (approximately sixfold increase in the full treated population). Similarly, analyses of data from almost 24,000 patients at risk for mortality in the SAGhE cohort demonstrated an increased risk of mortality from a number of second primary malignancies in patients whose original diagnosis was cancer (22). In addition, data from a Danish national registry study of 494 GH-treated patients with childhood-onset GHD demonstrated a mortality hazard ratio of 48.1 (95% CI, 25.7 to 90.2) for patients with history of malignancy (23).

The elevated mortality risk for GH-treated children with history of malignancy is not unexpected given the severity of the underlying diseases, the propensity for recurrence of these malignancies, and the increased risk of second neoplasm associated with oncologic therapies, particularly cranial irradiation (15, 24, 25). Lack of a matched group of non–GH-treated controls precludes assessment of cause and effect between GH treatment and risk of death; nevertheless, our findings may be relevant for counseling GH-deficient survivors of malignancy and

Table 4. Reported Deaths of GH-Treated Patients, Grouped According to General Cause of Death

Death Category	No.	Reported Cause of Death
1. Acute illness or event	13	Pneumonia (n = 2); sepsis (n = 2); acute respiratory distress syndrome (after graft-vs-host disease in patient with medulloblastoma and myelodysplastic syndrome); appendicitis; convulsions; dehydration; diabetic ketoacidosis in patient with sideroblastic anemia and diabetes mellitus; disconnected ventriculoperitoneal shunt; gastrointestinal hemorrhage; meningitis; postanoxic encephalopathy after pneumonia
2. Neoplasia	12	
Recurrence or progression of primary	9	Medulloblastoma (n = 4); astrocytoma (n = 3); acute myeloid leukemia; neuroblastoma
Second (new) neoplasm	2	Acute lymphoblastic leukemia (first) followed by cerebral neuroblastoma (second); medulloblastoma (first) followed by acute myeloid leukemia (second)
De novo neoplasm	1	Ewing sarcoma
3. Underlying condition and/or treatment	7	Adrenoleukodystrophy; congenital heart disease; Duchenne muscular dystrophy/cardiac disease; Fanconi anemia; MELAS syndrome; microangiopathy in patient with lupus; pulmonary fibrosis after radiation for Hodgkin lymphoma in a child with Down syndrome
4. Accident/trauma	4	Car accident (n = 2, one with history of medulloblastoma); airplane accident; sequelae to status epilepticus and head trauma
5. Postoperative complications	3	Hypothalamic dysfunction after craniopharyngioma surgery; sepsis after scoliosis surgery; stroke after renal transplant
6. Unspecified or unclear	6	Cardiorespiratory arrest (n = 2); cardiac arrest of unknown cause; died in sleep; unknown (n = 2)
Total	45[a]	

Information on individual patients is provided in Supplemental Table 3.

Abbreviation: MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes.

[a]Includes three deaths in patients (PWS, hypopituitarism with progressive and convulsive encephalopathy, and septo-optic dysplasia) who were not evaluable for safety according to predefined standard study analysis procedures (no study follow-up visit had occurred) and, therefore, were excluded from the statistical analyses for calculation of SMRs.

their families. Of the 14 children with a history of malignancy who died, medulloblastoma was the primary diagnosis in seven. Medulloblastoma, the most common malignant brain tumor in childhood (26), is a primitive neuroectodermal tumor with a historical 5-year survival rate of approximately 60% to 80%, depending on baseline risk factors, including age at diagnosis, degree of initial tumor dissemination, and adequacy of surgical removal (26, 27). Because craniospinal irradiation often results in hypothalamic-pituitary dysfunction accompanied by poor spinal growth, these children develop substantial growth failure and represent the most common group of GH-treated childhood cancer survivors (15). However, based on data from various studies, there is no evidence that GH treatment itself increases the risk of tumor recurrence or death. A multicenter retrospective study of >500 medulloblastoma survivors, diagnosed and treated between 1980 and 1993, found no effect of GH treatment on risk of tumor recurrence (28), and the CCSS reported reduced risk of tumor recurrence among 73 GH-treated medulloblastoma survivors compared with 245 non–GH-treated survivors (relative risk, 0.13; $P = 0.04$) (11). Analyses of 194 GH-treated survivors of childhood medulloblastoma followed in the National Cooperative Growth Study determined a recurrence rate of 7.2% (29). Similarly, an analysis from the Kabi International Growth Study of tumor recurrence rates in brain tumor survivors reported 92% relapse-free survival at 4.6 years in a cohort of 655 GH-treated medulloblastoma survivors (30). These 7% to 8% medulloblastoma recurrence rates in GH-treated children in large observational studies are lower than reported in a French study of 136 patients treated for their primary disease in the 1990s, of whom ~70% did not receive GH treatment, and in which the 5-year recurrence-free survival was 72% (31).

In our cohort, death after a second neoplasm was reported for one patient with a primary diagnosis of acute lymphoblastic leukemia and one medulloblastoma survivor. In a previous analysis of the GeNeSIS database, specifically focused on second neoplasms (32), 140 GH-treated survivors of medulloblastoma and cranial irradiation were identified, of whom 10 (7%) were reported to have developed a second neoplasm. Risk of a second neoplasm [most commonly meningioma and glioma (33)] in patients previously treated for childhood malignancy was initially reported to be increased in GH-treated patients in two analyses from the CCSS (11, 12). However, the most recent CCSS analysis found no increase in relative risk of CNS second neoplasm for GH-treated vs

non–GH-treated survivors when controlled for exposure to cranial irradiation, highlighting that risk of CNS second neoplasm declined in this cohort with longer duration of follow-up (25).

Apart from children with history of malignancy, the only other group in our study with elevated mortality risk relative to the general population (albeit not statistically significant: SMR, 2.47; 95% CI, 0.99 to 5.09) was the group with a variety of conditions such as clinical syndromes and genetic anomalies. All seven children in this group who died during follow-up had diagnoses associated with increased baseline mortality risk, irrespective of exposure to GH treatment: adrenoleukodystrophy (34), congenital heart disease (35), Down syndrome (36) accompanied by CRI, Fanconi anemia (37), systemic lupus erythematosus (38), Duchenne muscular dystrophy with cardiac involvement (39), and pseudohypoparathyroidism accompanied by congenital hypopituitarism (40) and hydrocortisone treatment of central hypoadrenalism (41) (Table 4; Supplemental Table 3). Thus, it seems unlikely that the increased SMR in this group was directly related to GH exposure. Nevertheless, the decision to initiate GH treatment in such patients, as well as those with organic causes of GHD, should be made cautiously.

Other groups for whom an increased risk of early death has been a concern include children with PWS (7) and girls with TS (42). Although sudden unexplained deaths have been reported in GH-treated children with PWS who are severely obese or have upper airway obstruction, sleep apnea, or intercurrent respiratory illness (7), we received no such reports; the only death of a child with PWS occurred in an airplane accident. Two deaths were reported among 948 patients with TS in our study: an 11-year-old girl developed postoperative pneumonia and sepsis after surgery for scoliosis, and a 16-year-old girl developed *de novo* Ewing sarcoma with translocation involving the *EWSR1* gene at chromosome 22q12. *EWSR1* gene translocations are believed to result in tumor development because of failure of the encoded mutant protein to perform appropriate DNA damage repair, leading to abnormal proliferation, maturation, and survival of cells (43). No deaths were reported because of aortic dissection or ruptured aortic aneurysm, the most dangerous cardiovascular complications of TS (44, 45) and previously reported as fatal in five teenage patients in a National Cooperative Growth Study cohort of >5000 girls with TS (45).

The current analyses were prompted in part by the 2012 publication of the French SAGhE data, in which mortality was increased in a cohort of almost 7000 adults previously treated with GH during childhood for conditions considered by the authors unlikely to confer an increased risk of mortality: isolated IGHD, ISS, and short stature associated with SGA birth (14). Increased bone tumor–related mortality (SMR, 5.00; 95% CI, 1.01 to 14.63) and mortality resulting from diseases of the circulatory system (SMR, 3.07; 95% CI, 1.40 to 5.83), specifically intracranial hemorrhage (SMR, 6.66; 95% CI, 1.79 to 17.05), were observed for this combined patient population compared with the French general population. Although our study cannot be considered comparable because we examined deaths in children during active GH treatment rather than in adulthood many years after GH completion, we found no evidence of increased risk in these patient groups compared with general population mortality rates. Unlike the French study, we received no reports for patients with IGHD or ISS of death resulting from malignancy (specifically bone tumors) or cerebrovascular disease and SMRs for these patient groups were not elevated. Death attributable to cerebrovascular disease was reported for a child born SGA who also had MELAS syndrome, which increases risk for cerebrovascular disease. Because SGA birth is a frequent finding in many syndromic and chromosomal/genetic conditions, and has been reported to be a risk factor for early mortality (46), the inclusion of the SGA cohort among those considered at low risk of mortality in the French study may have been inappropriate. Furthermore, a Swedish study found no increase in mortality in GH-treated patients with IGHD, ISS, or born SGA using a mortality model of the Swedish general population adjusting for birth characteristics, sex, age intervals, and calendar year (47).

The three deaths in children with IGHD resulted from disparate causes (road accident, respiratory infection/failure, and diabetic ketoacidosis), suggesting no relationship with GH treatment. Although iron overload may have impaired pancreatic function in the patient with sideroblastic anemia who died in ketoacidosis. In addition, GH treatment may induce insulin resistance, thereby increasing risk of type 2 diabetes for certain GH-treated patients, as previously reported in separate analyses of the GeNeSIS and Kabi International Growth Study databases (48, 49).

Our data indicate that increased mortality risk in GH-treated children appears to be limited to patients with prior history of malignancy and those with underlying non–GH-deficient medical conditions associated with increased mortality; however, our results should be interpreted in light of some limitations. First, similar to other observational studies, low numbers of untreated children with the same underlying conditions precluded comparison of mortality rates for GH-treated vs non–GH-treated patients, necessitating the use of general population data for SMR calculations. Second, these

observational study data may not be generalizable to all GH-treated children. Third, although reporting of serious adverse events was mandatory, some deaths could have been unreported for patients lost to follow-up. Fourth, the relatively limited follow-up duration may have impaired detection of fatal events with long latency periods, such as malignancy or cardiovascular/cerebrovascular disease. Fifth, for smaller patient groups (*e.g.*, CRI, SHOX-D, SGA) the relatively small numbers of observed and expected deaths and patient-years of observation resulted in wide CIs for SMR estimates.

In summary, this analysis of >67,000 patient-years of data, for >9500 GH-treated children followed for at least 4 years in an observational study, found no increase in risk of mortality compared with children in the general population for most diagnostic groups. However, we found a not unexpected increase in mortality risk for children with history of malignant neoplasia.

Acknowledgments

Medical writing assistance was provided by Peter C. Bates, Cambridge Medical Writing Services, UK, and Caroline Spencer, Rx Communications, Mold, UK, funded by Eli Lilly and Company. The authors thank the patients, families, and investigators who participated in the study.

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This work was supported by Eli Lilly and Company.

Clinical trial registry: ClinicalTrials.gov no. NCT 01088412 (registered 25 February 2010).

Disclosure Summary: C.J.C. and A.G.Z. are employees, and C.A.Q. and W.F.B. are former employees, of Eli Lilly and Company. R.G.R. and L.L.R. are former members of the GeNeSIS International Advisory Board that was sponsored by Eli Lilly and Company until 2012.

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