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Malignancy risk in adults with growth hormone deficiency undergoing long-term treatment with biosimilar somatropin (Omnitrope®): data from the PATRO Adults study

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Abstract

Background: To assess the safety (particularly the occurrence of malignancies) of growth hormone (GH) replacement (Omnitrope®) in adults with GH deficiency, using data from the ongoing PATRO Adults post-marketing surveillance study.

Methods: PATRO Adults is being conducted in hospitals and specialized endocrinology clinics across Europe. All enrolled patients who receive ⩾1 dose of Omnitrope® are included in the safety population. Malignancies are listed as adverse events under the MedDRA System Organ Class 'neoplasms, benign, malignant and unspecified (including cysts and polyps)'.

Results: As of July 2018, 1293 patients had been enrolled in the study and 983 (76.0%) remained active in the study. Approximately half [*n* = 637 (49.3%)] of the patients were GH treatment-naïve on study entry. The majority of enrolled patients had multiple pituitary hormone deficiency (*n* = 1128, 87.2%). A total of 41 on-study malignancies were reported in 33 patients (2.6%; incidence rate 7.94 per 1000 patient-years). The most common cancers were basal cell carcinoma (*n* = 13), prostate (*n* = 6), breast, kidney and malignant melanoma (each *n* = 3). Treatment with Omnitrope® was discontinued following diagnosis of malignancy in 16 patients. The tumors occurred after a mean of 79.4 months of recombinant hormone GH (rhGH) treatment overall.

Conclusion: Based on this snapshot of data from PATRO Adults, Omnitrope® treatment is tolerated in adult patients with GH deficiency in a real-life clinical practice setting. Our results do not generally support a carcinogenic effect of rhGH in adults with GH deficiency, although an increased risk of second new malignancies in patients with previous cancer cannot be excluded based on the current dataset.

Keywords: adult growth hormone deficiency, incidence, malignancies, recombinant human growth hormone, risk

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Introduction

The estimated prevalence of adult growth hormone deficiency (GHD) is 2–3 per 10,000 population, with the most common causes (accounting for 57% of cases) being pituitary adenomas and craniopharyngiomas.[1] Other causes include irradiation, head injury and vascular, infiltrative, infectious or autoimmune diseases.[1] Adults with severe GHD are eligible for treatment with GH replacement therapy, which aims to correct the

metabolic, functional and psychological abnormalities that are associated with adult GHD.[1–3] Treatment with GH replacement therapy is effective for improving body composition, exercise capacity, skeletal integrity, blood lipid profile and overall quality of life in adult patients with GHD.[3]

Multiple lines of evidence suggest a role for the GH/insulin-like growth factor (IGF-I) axis in cancer incidence and progression.[4] Since GH replacement therapy increases levels of IGF-I, there has long been concern about its potential to influence the risk of cancer.[4,5] Six relatively large studies in GH-treated adults with mixed etiologies of GHD found no increased rate of fatal or non-fatal malignancies, compared with the general population, during follow-up periods ranging from 2.3 to 9.6 years.[6] Moreover, evidence from adult patients treated with GH replacement therapy suggests that recombinant human GH (rhGH) treatment does not increase the rate of recurrence or progression of hypothalamic–pituitary tumors, compared with similar patients who did not receive rhGH treatment.[6,7] However, in adult patients with GHD who were childhood cancer survivors and received rhGH treatment in childhood, there may be an increased risk of secondary malignancies *versus* the general population.[7–10] The Safety and Appropriateness of Growth Hormone Treatments in Europe study suggested possible effects of rhGH therapy on bone cancer, bladder cancer and Hodgkin lymphoma.[10] In the same cohort, although cancer incidence risk was unrelated to duration or cumulative dose of rhGH treatment, cancer mortality risk in patients with previous cancer increased significantly with increasing daily rhGH dose ($p < 0.001$).[10]

Therefore, although existing data do not, in general, support a carcinogenic effect of GH replacement therapy in adult patients, additional safety findings from long-term surveillance studies are important to confirm and extend current knowledge in this area. PAtients TReated with Omnitrope® (PATRO) Adults is an ongoing post-marketing surveillance study conducted since 2007 in hospitals and specialized endocrinology clinics across Europe.[11] The primary objective of PATRO Adults is to assess the long-term safety of rhGH (Omnitrope®) in adults with GHD treated in routine clinical practice. Secondary objectives include monitoring effectiveness parameters, including IGF-I levels, lipid profile, body composition and quality of life.[11] As Omnitrope® was approved in Europe as a biosimilar rhGH, the study is also important for confirming that its long-term safety profile in adults with GHD is comparable to that of the reference medicine. This paper focuses on safety, and specifically the occurrence of malignancies in the PATRO Adults population, based on an interim data analysis performed in July 2018.

Methods

The design of the PATRO Adults study has been described in detail elsewhere.[11] Briefly, eligible patients are male and female adults in receipt of rhGH treatment in accordance with the recommendations in the Summary of Product Characteristics.[12] The study is performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Patients who received treatment with a different rhGH medicine before starting Omnitrope® therapy are also eligible for inclusion.[11]

The PATRO Adults study protocol was approved by the ethics review committee of participating centers in accordance with national laws and regulations. All procedures performed were in accordance with the ethical standards of these committees and with the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participating subjects.

All clinic visits and assessments are conducted as part of routine clinical practice according to the prescribing physician's preference, and data are collected at each routine visit during Omnitrope® treatment. Safety assessments include monitoring and recording of all adverse events (AEs), including AEs considered serious according to the definition provided in the ICH Guideline for Good Clinical Practice.[13] The relationship between AEs and Omnitrope® treatment is independently evaluated by investigator and sponsor assessment, and classified according to the worse case. Particular emphasis is placed on the recording of malignancies and recurrence of hypothalamic–pituitary tumors during treatment with Omnitrope®.

All enrolled patients who receive ≥ 1 dose of Omnitrope® are included in the safety population. For the current analysis, profiles containing all available database information for each specific

Table 1. Patient characteristics at enrollment (safety population, *N* = 1293).

Indication	Pre-treatment	Total, *n* (%)	Male, *n* (%)	Female, *n* (%)	Mean age (±SD), years	Mean body mass index, (±SD) kg/m²
Isolated GHD	Naïve	94 (7.3)	39 (3.0)	55 (4.3)	46.9 (15.4)	29.7 (6.6)
	Pre-treated	61 (4.7)	27 (2.1)	34 (2.6)	42.7 (16.2)	31.3 (8.8)
MPHD	Naïve	537 (41.5)	289 (22.4)	248 (19.2)	49.5 (14.7)	29.7 (6.3)
	Pre-treated	591 (45.7)	305 (23.6)	286 (22.1)	50.4 (15.6)	29.0 (6.2)
Other	Naïve	6 (0.5)	4 (0.3)	2 (0.2)	44.9 (13.1)	29.0 (0.6)
	Pre-treated	4 (0.3)	2 (0.2)	2 (0.2)	31.7 (9.1)	26.0 (5.7)
Total		**1293 (100.0)**	**666 (51.5)**	**627 (48.5)**	**49.3 (15.3)**	**29.4 (6.4)**

GHD, growth hormone deficiency; MPHD, multiple pituitary hormone deficiency; SD, standard deviation.

patient were generated for all patients that developed malignancies while receiving Omnitrope®. Malignancies were listed as AEs under the Medical Dictionary for Regulatory Activities System Organ Class 'neoplasms benign, malignant and unspecified (including cysts and polyps)'.

Results

Patient characteristics

As of July 2018, 1293 patients had been enrolled into the study from 76 centers in 8 European countries (Czech Republic, France, Germany, Italy, Netherlands, Spain, Sweden, UK). Of these, 983 (76.0%) patients were still active in the study while 310 (24.0%) had discontinued. All outcome data presented include patients who have discontinued the study. The majority of enrolled patients had multiple pituitary hormone deficiency (MPHD; *n* = 1128, 87.2%), while the remaining patients had isolated GHD (*n* = 155, 12.0%) or other indications (*n* = 10, 0.8%). Among patients with MPHD, 768 (68.1%) had adrenocorticotropic hormone deficiency, 791 (70.1%) had luteinizing hormone/follicle-stimulating hormone deficiency and 914 (81.0%) had thyroid-stimulating hormone deficiency. Overall, 203 (15.7%) patients had childhood-onset GHD and 1080 (83.5%) had adulthood-onset GHD (onset not available for the remaining 10 patients). Prior to enrollment into the study, 637 (49.3%) patients were rhGH-naïve and 656 (50.7%) had previously been treated with rhGH.

Additional patient characteristics at the point of enrollment are shown in Table 1. In total, just over half of the enrolled patients were male (51.7%) and the mean [±standard deviation (SD)] age of enrolled patients was 49.3 (±15.3) years. Overall, 90 (7.0%), 411 (31.8%), 449 (34.7%) and 343 (26.5%) patients were aged <25, 25 to <45, 45 to <60 and ⩾60 years, respectively.

Of the 310 patients who discontinued the study, 71 (5.5%) did so due to an AE; other reasons for discontinuation included the patient not wanting to continue with injections (*n* = 66, 5.1%), patient lost to follow-up (*n* = 32, 2.5%), switch to a different rhGH treatment (*n* = 24, 1.9%), referral to another endocrinologist (*n* = 16, 1.2%), patient non-compliant (*n* = 10, 0.8%) and other (*n* = 91, 7.0%).

Treatment

The mean (range) duration of any rhGH pre-treatment was 9.9 (1–32) years for patients with isolated GHD and 11.0 (0–42) years for those with MPHD. The mean (range) duration of Omnitrope® treatment in PATRO Adults was 39.7 (0–112) months and 38.6 (0–134) months for patients with isolated GHD and MPHD, respectively.

At baseline, the mean (±SD) Omnitrope® dose for patients with isolated GHD was 0.31 (±0.27) mg/day [rhGH-naïve patients, 0.20 (±0.14) mg/

Table 2. Summary of AEs (safety population, $N = 1293$).

	Patients, *n* (%)[a]	Adverse events, *n*
Any AE	872 (67.4)	3828
Relationship to study drug		
Not suspected	837 (64.7)	3670
Suspected	92 (7.1)	153
Missing/not assessable	4 (0.3)	5
Intensity		
Mild	702 (54.3)	2513
Moderate	426 (32.9)	945
Severe	125 (9.7)	214
Missing	60 (4.6)	156
Changes to Omnitrope® treatment		
Not changed	808 (62.5)	3494
Increased	26 (2.0)	35
Reduced	64 (4.9)	101
Interrupted	54 (4.2)	82
Permanently discontinued	70 (5.4)	103
Missing	8 (0.6)	13
SAE		
Any SAE	353 (27.3)	702
Fatal SAE	20 (1.5)	31
SAE relationship to study drug		
Not suspected	342 (26.5)	679
Suspected	18 (1.4)	23

[a]Because patients report multiple AEs, categories in this column are not mutually exclusive.
AE, adverse event; SAE, serious adverse event.

day (start dose of rhGH); pretreated patients, 0.47 (±0.33) mg/day]. Split by GHD onset in childhood or in adulthood, the mean (±SD) baseline Omnitrope® dose was 0.47 (±0.34) mg/day and 0.26 (±0.22) mg/day, respectively.

For patients with MPHD, the mean (±SD) Omnitrope® dose at baseline was 0.29 (±0.22) mg/day [rhGH-naïve patients, 0.20 (±0.10) mg/day (start dose of rhGH); pretreated patients, 0.37 (±0.26) mg/day]. For those with childhood-onset GHD the mean baseline (±SD) dose was 0.41 (±0.28) mg/day, and for those with adult-onset GHD the mean dose was 0.26 (±0.19) mg/day.

Overall safety

A total of 3828 AEs were reported in 872 (67.4%) patients. There was no obvious difference in baseline characteristics in patients who had an AE *versus* those who did not (data not shown). A total of 702 AEs in 353 (27.3%) patients were regarded as serious. The majority of AEs (90.3%; $n = 3458$) were mild to moderate in intensity, and most (91.3%; $n = 3494$) did not result in any change to Omnitrope® treatment. A summary of the reported AEs is provided in Table 2.

Occurrence of malignancies

Of the 1293 patients enrolled in PATRO Adults as of July 2018, 33 (20 male, 13 female) developed on-study malignancies (2.6%; incidence rate of 7.94 per 1000 patient-years), including seven patients who experienced more than one ($n = 41$ total malignancies). In total, 3 out of 33 patients had no previous medical history of malignancies or tumors (Table 3). The most common cancers were basal cell carcinoma ($n = 13$), prostate ($n = 6$), breast ($n = 3$), kidney ($n = 3$) and malignant melanoma ($n = 3$) (Table 3). The malignancies occurred largely in patients aged over 50 years (35 out of 41 cases). All of the patients with prostate cancer had testosterone listed among concomitant medications, and none of the patients with breast cancer had estrogen listed as a concomitant medication. Treatment with Omnitrope® was discontinued following diagnosis of malignancy in 15 patients. The tumors occurred after a mean of 79.4 months of rhGH treatment overall. Among all patients who developed a malignancy, only a small number ($n = 5$) were considered to have high levels of IGF-I.

Most malignancies developed in patients with adult-onset MPHD ($n = 16$ and $n = 8$ who were rhGH-naïve and pretreated, respectively); the remaining malignancies occurred in five patients with childhood-onset MPHD (rhGH-naïve, $n = 3$; pretreated, $n = 2$) and three patients with adult-onset isolated GHD (rhGH-naïve, $n = 1$; pretreated, $n = 2$). The GHD etiologies in patients who developed malignancies were pituitary tumors [$n = 23$ including one macroprolactinoma

Table 3. Treatment-related AEs and SAEs relating to malignancies.

MedDRA preferred term (AE/SAE)	Kind of malignancy	Indication and onset, pre-treatment status	Age at baseline	Time to AE/SAE onset (days)[a]	Total duration of any GH treatment at AE/SAE onset (days)	Intensity	Causality[b]	Outcome	Action taken with Omnitrope®	Relevant medical history/concomitant medication
Basal cell carcinoma (SAE)	Primary	MPHD in adulthood, naïve	56	669	669	Moderate	Not suspected	Resolved completely	Not changed	GHD etiology, sphenoidalis meningioma
Basal cell carcinoma (SAE)	Primary	MPHD in adulthood, pretreated	52	536	5353	Mild	Not suspected	NR	Not changed	GHD etiology, pituitary tumor
Basal cell carcinoma (SAE)	Primary	MPHD in childhood, naïve	31	136	136	Moderate	Suspected	Ongoing	Not changed	GHD etiology, total body irradiation for acute lymphoblastic leukemia
Breast cancer (SAE)	Primary			2612	2612	Severe	Not suspected	Ongoing	Permanently discontinued	
Basal cell carcinoma (SAE)	Primary	MPHD in adulthood, naïve	23	556	556	Moderate	Not suspected	Resolved with sequelae	Not changed	GHD etiology, pediatric medulloblastoma
Basal cell carcinoma (SAE)	Primary	MPHD in adulthood, pretreated	55	526	1038	Moderate	Not suspected	Ongoing	Not changed	GHD etiology, pituitary tumor
Basal cell carcinoma (SAE)	Primary	MPHD in adulthood, naïve	63	498	498	Moderate	Not suspected	Resolved completely	Not changed	GHD etiology, pituitary tumor
Basal cell carcinoma (SAE)	Primary			2513	2513	Moderate	Not suspected	Resolved completely	Not changed	
Basal cell carcinoma (SAE)	Primary	MPHD in adulthood, pretreated	71	1104	7904	Mild	Not suspected	Resolved completely	Not changed	GHD etiology, pituitary tumor
Basal cell carcinoma (SAE)	Primary	MPHD in childhood, pretreated	52	721	2891	Mild	Not suspected	Resolved completely	Not changed	GHD etiology, idiopathic
Squamous cell carcinoma of the skin (SAE)	Primary	MPHD in adulthood, pretreated	67	229	990	Mild	Not suspected	Resolved completely	Not changed	GHD etiology, pituitary tumor

(Continued)

Table 3. (Continued)

MedDRA preferred term (AE/SAE)	Kind of malignancy	Indication and onset, pre-treatment status	Age at baseline	Time to AE/SAE onset (days)[a]	Total duration of any GH treatment at AE/SAE onset (days)	Intensity	Causality[b]	Outcome	Action taken with Omnitrope®	Relevant medical history/concomitant medication
Basal cell carcinoma (SAE)	Primary			2557	3318	Mild	Not suspected	Resolved completely	Not changed	
Prostate cancer (SAE)	Primary	MPHD in adulthood, naïve	70	231	231	Severe	Not suspected	Ongoing	Permanently discontinued	GHD etiology, pituitary tumor/ testosterone
Prostate cancer (SAE)	Primary	MPHD in adulthood, naïve	77	41	41	Mild	Not suspected	Ongoing	Not changed	GHD etiology, pituitary tumor/ testosterone
Prostate cancer (SAE)	Primary	MPHD in adulthood, naïve	67	1834	1834	Severe	Not suspected	Ongoing	Permanently discontinued	GHD etiology, pituitary tumor/ testosterone
Prostate cancer (SAE)	Primary	MPHD in adulthood, naïve	52	561	561	Severe	Not suspected	Ongoing	Permanently discontinued	GHD etiology, pituitary tumor/ testosterone
Prostate cancer (SAE)	Primary	MPHD in adulthood, naïve	73	51	51	Severe	Not suspected	Ongoing	Interrupted	GHD etiology, pituitary tumor/ testosterone
Metastases to lymph nodes (SAE)	Secondary			141	141	Moderate	Not suspected	Resolved completely	Interrupted	
Breast cancer (SAE)	Primary	Isolated GHD in adulthood, pretreated	66	940	2993	Severe	Not suspected	NR	Permanently discontinued	GHD etiology, malformation
Breast cancer (SAE)	Primary	MPHD in childhood, naïve	56	795	795	Severe	Not suspected	Ongoing	Permanently discontinued	GHD etiology, pituitary tumor
Renal cell carcinoma (AE)	Primary	MPHD in adulthood, naïve	51	1264	1264	Moderate	Not suspected	Resolved completely	Not changed	GHD etiology, hypothalamic tumor

(Continued)

Table 3. (Continued)

MedDRA preferred term (AE/SAE)	Kind of malignancy	Indication and onset, pre-treatment status	Age at baseline	Time to AE/SAE onset (days)[a]	Total duration of any GH treatment at AE/SAE onset (days)	Intensity	Causality[b]	Outcome	Action taken with Omnitrope®	Relevant medical history/concomitant medication
Renal neoplasm (SAE)	Primary	MPHD in adulthood, naïve	68	NR	NR	Severe	Not suspected	Resolved completely	Interrupted	GHD etiology, total body irradiation
Renal cancer (SAE)	Primary	MPHD in adulthood, naïve	61	2182	2182	Moderate	Not suspected	Resolved with sequelae	Not changed	GHD etiology, GH-producing pituitary tumor
Malignant melanoma (SAE)	Primary	MPHD in adulthood, pretreated	51	950	6863	Severe	Not suspected	Resolved completely	Not changed	GHD etiology, pituitary tumor
Malignant melanoma (SAE)	Primary	MPHD in adulthood, pretreated	69	364	5410	Severe	Not suspected	Resolved completely	Not changed	GHD etiology, craniopharyngioma
Basal cell carcinoma (AE)	Primary			891	5937	Mild	Not suspected	Resolved completely	Not changed	
Malignant melanoma (SAE)	Primary	MPHD in childhood, naïve	71	313	313	Moderate	Suspected	Resolved with sequelae	Permanently discontinued	GHD etiology, pituitary tumor
Hepatic cancer (SAE)	Primary	MPHD in adulthood, pretreated	73	603	4002	Moderate	Not suspected	Resolved with sequelae	Permanently discontinued	GHD etiology, pituitary tumor
Pancreatic carcinoma (SAE)	Primary	Isolated GHD in adulthood, naïve	76	NR	NR	Severe	Not suspected	Fatal	Permanently discontinued	GHD etiology, pituitary tumor
Pancreatic carcinoma (SAE)	Primary	MPHD in adulthood, pretreated	76	97	5067	Severe	Not suspected	Ongoing	Permanently discontinued	GHD etiology, pituitary tumor
Metastases to lung (SAE)	Secondary			97	5067	Severe	Not suspected	Ongoing	Permanently discontinued	

(Continued)

Table 3. (Continued)

MedDRA preferred term (AE/SAE)	Kind of malignancy	Indication and onset, pre-treatment status	Age at baseline	Time to AE/SAE onset (days)[a]	Total duration of any GH treatment at AE/SAE onset (days)	Intensity	Causality[b]	Outcome	Action taken with Omnitrope®	Relevant medical history/concomitant medication
Metastases to liver (SAE)	Secondary			97	5067	Severe	Not suspected	Ongoing	Permanently discontinued	
Lung neoplasm malignant (SAE)	Primary	MPHD in adulthood, naïve	75	426	426	Severe	Not suspected	Ongoing	Permanently discontinued	GHD etiology, pituitary tumor
Metastases to CNS (SAE)	Secondary		75	426	426	Severe	Not suspected	Ongoing	Permanently discontinued	
Lung neoplasm malignant (SAE)	Primary	Isolated GHD in adulthood, pretreated	79	119	4243	Severe	Not suspected	Fatal	Permanently discontinued	GHD etiology, empty sella
Osteosarcoma (SAE)	Primary	MPHD in childhood, pretreated	17	NR	NR	Mild	Not suspected	Ongoing	Not changed	GHD etiology, total body irradiation
GI carcinoma (SAE)	Primary	MPHD in adulthood, naïve	66	1439	1439	Severe	Not suspected	Ongoing	Permanently discontinued	GHD etiology, pituitary tumor
Brain stem glioma (SAE)	Primary	MPHD in adulthood, naïve	65	178	178	Severe	Not suspected	Fatal	Permanently discontinued	GHD etiology, radiotherapy for macroprolactinoma
Transitional cell carcinoma (SAE)	Primary	MPHD in adulthood, naïve	68	126	126	Severe	Not suspected	Ongoing	Not changed	GHD etiology, pituitary tumor
Hodgkin's disease (SAE)	Primary	MPHD in adulthood, naïve	47	1365	1365	Moderate	Not suspected	Ongoing	Permanently discontinued	GHD etiology, macroprolactinoma

[a]Time to SAE onset after start of Omnitrope® treatment.
[b]Assessment of relationship to study drug according to Investigator and Sponsor (worst case).
AE, adverse event; CNS, central nervous system; GH, growth hormone; GHD, growth hormone deficiency; GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; MPHD, multiple pituitary hormone deficiency; NR, not recorded; SAE, serious adverse event.

and one radiotherapy for macroprolactinoma (Table 3)], traumatic brain injury ($n=2$), sphenoidalis meningioma, malformation, craniopharyngioma, irradiation for acute lymphoblastic leukemia, hypothalamic tumor, pediatric medulloblastoma, empty sella, and idiopathic (all $n=1$).

Two of the malignancies were recorded as non-serious AEs (a renal cell carcinoma in a male patient with adult-onset MPHD naïve to rhGH treatment, a basal cell carcinoma occurring in patients with adult-onset MPHD who had received prior rhGH treatment); these were recorded as mild to moderate in severity and both were judged by the treating physician as not related to treatment. No changes to the Omnitrope® administration regimen were required and there was complete resolution in all cases.

Of the 38 malignancies recorded as serious AEs, only two were judged by the treating physician as possibly related to Omnitrope® treatment. The first was an ongoing case of basal cell carcinoma that occurred in a male patient with childhood-onset MPHD and naïve to rhGH treatment before study entry, who had received total body irradiation for acute lymphoblastic leukemia; this malignancy event was moderate in severity and did not require any changes to Omnitrope® administration. The second was a malignant melanoma in a female patient with childhood-onset MPHD as a result of pituitary gland tumor, who was naïve to rhGH treatment before study entry; this malignancy event was moderate in severity and resolved with sequelae, but required permanent discontinuation of Omnitrope® treatment. Fatal outcomes occurred in three patients with malignancies recorded as serious (a pancreatic carcinoma, brain stem glioma, and malignant lung neoplasm); none were suspected to be related to study treatment.

The mean IGF-I Standard Deviation Score (SDS) for patients with malignancies was –1.377 (±2.014), 0.341 (±0.927), 0.873 (±1.501), –0.279 (±1.297) at baseline, 1 year, 3 years, 5 years respectively. The mean IGF-I SDS in PATRO Adult patients was –1.190 (±2.289), –0.172 (±1.730), –0.011 (±1.689) and 0.045 (±1.569) at baseline, 1 year, 3 years and 5 years respectively.

Discussion

The purpose of the PATRO Adults post-marketing surveillance study is to describe the long-term safety of rhGH (Omnitrope®) treatment in adult patients with GHD in a real-life setting. The current analysis indicates that the safety profile of Omnitrope® treatment in adult patients is as expected; to date, there have been no reports of unexpected AEs with a possible causal relationship to Omnitrope® treatment in PATRO Adults.

The relationship between rhGH treatment and risk of cancer has long been (and continues to be) a subject of much debate and research.[14–16] Data from the current analysis of PATRO Adults indicate that rhGH treatment in the form of Omnitrope® might not increase the risk of *de novo* malignancies or tumor recurrence in adult GHD patients. These findings are in line with other published data. An observational prospective safety surveillance study in adult GHD patients compared AEs between those who were treated ($n=1988$) and not treated ($n=442$) with rhGH.[17] After a mean follow-up of 2.3 years, there was no significant difference between the groups in cancer rates. However, this study has several limitations; the mean follow-up period is short and its real life, observational design as well.

The German cohort of the observational Kabi Pharmacia International Metabolic Study (KIMS) was used to assess the long-term treatment effects of rhGH replacement therapy in 440 German adults with GHD. *De novo* neoplasia occurred in 2.5% of patients ($n=11$), and the incidence of AEs associated with rhGH treatment was low ($n=40/440$ patients).[18]

Of the 33 patients who developed an on-study malignancy, 30 had a previous malignancy or tumor recorded in their medical history; this indicates a putative increase in risk of second malignancies in the current study cohort compared with normal populations.[19] Again, similar findings have been previously reported. An analysis of the KIMS database found an increased risk of new neoplasm in childhood-onset cancer survivors, which was not the case in adult-onset cancer survivors (although the follow-up period may have been too restricted).[8] Basal cell carcinoma was the most common malignancy reported (consistent with the current analysis); radiotherapy was found to play a preponderant role in the occurrence of basal cell carcinomas, and to also be related to the development of a second malignant tumor. It is recognized that the risk of cancer in patients treated with rhGH may reflect the

underlying condition that leads to rhGH treatment being required, as well as non-rhGH treatments.[10] The PATRO Adults database does not hold complete information on other treatments received by participants, therefore explanation of the results in relation to specific confounding factors is not possible. A review of data from large-scale registry studies of patients receiving GH replacement therapy has been recently conducted.[20] The review found no evidence of an increased risk of new malignancy, leukemia, non-leukemic extracranial tumors or recurrence of intracranial malignancy in patients without risk factors. However, the risk of a second neoplasm was found to be increased, particularly in patients who have received radiation therapy for a central nervous system tumor.

A joint position statement from the European Society of Paediatric Endocrinology, the GH Research Society and the Pediatric Endocrine Society has provided an authoritative appraisal of rhGH safety in adults (and children).[21] For new primary cancers, the joint position statement noted that available data in adult rhGH recipients are reassuring. In addition, a systematic review found no evidence that long-term treatment increases the risk of recurrence of a previous primary cancer.[22] Similarly, this review found no increase in risk of second/subsequent cancers.[22] Available data on benign pituitary tumors in adults also indicate no increased risk of recurrence during long-term GH replacement.[21]

A number of different cancer types have been reported to date in the PATRO Adults study. The most common cancers to occur were basal cell carcinoma and prostate cancer; all other cancer types were diagnosed in three or fewer patients. Investigators assessed a suspected relationship to Omnitrope® treatment in only two patients; both were overweight, but other potential predisposing factors (such as high doses of rhGH, sex-steroid treatment, radiotherapy and smoking) could not be confirmed. One of these was a case of basal cell carcinoma in a patient who had previously received total body irradiation for acute lymphoblastic leukemia; basal cell carcinoma is common in patients who have received this type of radiation therapy. Across all of the patients who have so far developed a malignancy during the study, only a small number were considered to have high levels of IGF-I at malignancy onset; this suggests that rhGH-induced increase in IGF-I is not a major factor in cancer risk among adults with GHD.

As with any observational study, there are a number of limitations to be considered for the observational PATRO Adults study. These include the potential for selection bias (due to inclusion of selected clinics and enrollment of patients from only these clinics) and for information bias (due to incorrect or inexact recording of information). Also the absence of control group. Pertinent to the present analysis, malignancies may take a number of years to develop and therefore long-term follow-up of patients by the treating physicians outside of the study is necessary to confirm the low risk of malignancies associated with rhGH treatment. Nevertheless, the mean duration of rhGH treatment overall (including pre-Omnitrope® rhGH treatment) in this analysis was 10–11 years, and findings to date are reassuring in this regard.

Conclusion

Based on the latest data from PATRO Adults, Omnitrope® treatment is tolerated in adult patients with GHD in a real-life clinical practice setting. Our results do not support a carcinogenic effect of rhGH in adults with GHD, although the risk of second new malignancies in patients with previous cancer may be increased. Our findings are consistent with previously published data on the risk of malignancies in adult GHD patients receiving GH replacement therapy. PATRO Adults is ongoing and will continue to extend the safety database for rhGH in adults with GHD, as well as provide further long-term information on the risk of malignancies and tumor recurrence in this population.

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Author contribution(s)

Paolo Beck-Peccoz: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing-original draft; Writing-review & editing.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are not publicly available as the study is still ongoing, but are available from the corresponding author on reasonable request.

Conflict of interest statement

CH has acted as an investigator for Sandoz, Pfizer, and NovoNordisk; has received lecture fees from Sandoz, Pfizer, and NovoNordisk; and is a member of the global steering committee for the PATRO Adults study. RDM has received research funding from Sandoz, Ipsen, and Pfizer; has received lecture fees from Pfizer; and is a member of the global steering committee for the PATRO Adults study. PBP and SS are members of the global steering committee for the PATRO Adults study. GS has received honoraria for scientific advisory work and/or reimbursement of delegate fees for congresses/seminars and/or travel costs and/or research grants from the HRA, Ipsen, Lilly, Novartis, NovoNordisk, Pfizer, Sandoz, and Shire; and is a member of the global steering committee for the PATRO Adults study. HM and MZ are employees of Sandoz Biopharmaceutical/Hexal AG.

Ethics statement

The PATRO Adults study protocol was approved by the ethics review committee of participating centers in accordance with national laws and regulations. All procedures performed were in accordance with the ethical standards of these committees and with the 1964 Declaration of Helsinki and its later amendments.

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Informed consent

Written informed consent was obtained from all participating patients. As part of the informed consent process, all patients provided written consent for the publication of data collected in the study.

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