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ORIGINAL ARTICLE

Safety and effectiveness of Omnitrope® in patients with growth hormone deficiency: snapshot analysis of PATRO Adults study in the Italian population

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Abstract

Purpose PATRO adults is an ongoing, multicenter, observational, post-marketing surveillance study aimed at investigating the long-term safety (primary endpoint) and effectiveness (secondary endpoint) of the recombinant human growth hormone (rhGH) Omnitrope® during routine clinical practice. This report describes data from Italian participants in PATRO Adults with growth hormone deficiency (GHD), up to August 2017.

Methods Participants were adults (aged > 18 years) with GHD requiring rhGH therapy and were prescribed Omnitrope®, including those who had previously received another rhGH product. Adverse events (AEs) were evaluated in all study participants. Data were collected on insulin-like growth factor (IGF)-I levels and cardiovascular risk factors, including blood pressure, lipids, and anthropometric parameters.

Results From September 2007 to August 2017, 88 patients (mean age 48.9 years, 58.0% male) were enrolled at 8 sites in Italy. The mean treatment duration with Omnitrope® was 51.5 ± 37 months. AEs occurred in 54 patients; the most common were asthenia (20.5%), headache (14.8%), and arthralgia (13.6%). Serious AEs occurred in 22 patients (25%), including pneumonia ($n = 2$) and renal failure ($n = 2$). Neoplasms (2 benign and 1 malignant) developed in three patients, but none were considered to be drug-related. There were no significant changes in fasting glucose or glycosylated hemoglobin (HbA1c) during the study period. Long-term Omnitrope® therapy showed slight positive effects on lipid profile, while no significant changes were observed in body weight and BMI during the study.

Conclusion This snapshot analysis of Italian participants in PATRO Adults confirmed the long-term safety and effectiveness of Omnitrope® in adults with GHD.

Keywords Adults · Growth hormone deficiency · Omnitrope® · Recombinant human growth hormone · Safety

Introduction

Growth hormone deficiency (GHD) in adults is a well-defined syndrome characterized by clinical manifestations such as abnormal body composition, decreased physical performance, and impaired metabolism [1–3]. GHD can develop due to a variety of conditions and may present during childhood or adulthood. Adult-onset GHD (AGHD) can result from hypothalamic-pituitary disease and/or its treatment including neurosurgery and/or cranial irradiation, idiopathic causes, pituitary adenoma and other cranial tumors, traumatic brain injuries, lymphocytic hypophysitis, empty sella, apoplexia, infiltrative/granulomatous diseases (Langerhans cell histiocytosis, sarcoidosis, tuberculosis, hemochromatosis), subarachnoid hemorrhage, and stroke [4]. Health-related quality of life (QoL) in adult patients with GHD is compromised [5].

Patients with GHD are treated with recombinant human growth hormone (rhGH) replacement therapy [6–8]. Treatment with rhGH in AGHD is reported to reduce total and visceral fat mass, increase lean body mass, and bone mass, and improve exercise capacity and QoL [9–11]. However,

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long-term rhGH therapy may be associated with adverse events (AEs) such as arthralgia, myalgia, abdominal distension, and hypoesthesia [12]. In addition, alterations in glucose metabolism have been described and there has been a concern that GH replacement therapy could lead to the development or regrowth of malignancies. In contrast, the effects of GH replacement on several cardiovascular markers including lipids, markers of inflammation, endothelial function, and vascular disease are generally considered favorable, although some conflicting results do exist [12–17]. Monitoring of AEs during rhGH therapy is essential to ensure that long-term use of this product has a net favorable effect when weighed against the risk of AEs.

PAtients TReated with Omnitrope® (PATRO) Adults is a post-marketing non-interventional observational study that began in September 2007 and is designed to determine the long-term safety and effectiveness of Omnitrope® [12]. Omnitrope® is an rhGH recommended for the treatment of severe GHD in adults, including those with AGHD (adults who had GHD during adulthood as a result of acquired causes, such as structural hypothalamic/pituitary disease, surgery or irradiation in these areas, or head trauma) or childhood-onset GHD (adults who had GHD during childhood as a result of congenital, genetic, acquired, or idiopathic causes) [18]. A report of the long-term effectiveness and safety of Omnitrope® in Italian patients with GHD enrolled in the PATRO Adults study has already been published [12]. Our aim is to update the results of interim analysis of the PATRO Adults study in all patients enrolled in Italy during the first 10 years of the study between 2007 and 2017.

Patients and methods

Study design and treatment

PATRO Adults is a longitudinal, observational, multicenter, open-label study designed to determine the safety and effectiveness of Omnitrope® in routine clinical practice. The study is being conducted at several hospitals and specialized endocrinology clinics across Europe.

The rationale and detailed study design of PATRO Adults have been reported previously [19]. Briefly, adult patients (> 18 years old) with GHD, including those receiving other rhGH products before starting Omnitrope®, were included in the study. Treatment was given as per the recommendations within the Omnitrope® summary of product characteristics and/or prescribing information in respective countries [18].

The study was approved by each study site's Independent Ethics Committee or Institutional Review Board before initiation and was conducted in accordance with the Declaration of Helsinki. All patients included in the study provided written informed consent at enrolment.

Endpoints

The primary objective of the study was to determine the long-term safety of Omnitrope®. All AEs including serious adverse events (SAEs) and adverse drug reactions (ADRs) reported during the treatment were recorded using electronic case-report forms (eCRF), with emphasis on malignancies, fasting glucose levels, and risk of developing glucose intolerance or diabetes.

The secondary objective was to assess data on the effectiveness of Omnitrope® therapy in the treated patient population. Assessments included: measurement of insulin-like growth factor-1 (IGF-I) levels and anthropometric data [weight, waist and hip circumference, lean body mass, total fat mass, and body mass index (BMI)]. Effects on cardiovascular risk factors, such as blood pressure and lipid levels, were also examined.

Statistical analysis

All patients for whom either any visit date or the date of Omnitrope® treatment initiation was documented were included in the safety analysis set (SAF). SAF patients with a documented baseline visit and at least one further documented visit under Omnitrope® treatment were included in the effectiveness analysis set (EFF). Statistical calculations in this study were performed using the SAS software package, versions 9.3 and 9.4. Descriptive statistical parameters were calculated for continuous/quantitative variables, including the number of values available, number of values missing, arithmetic mean, standard deviation (SD), minimum, median, and maximum. Because this observational study is ongoing, the data used in this interim analysis were not fully cleaned, although data cleaning by plausibility checks and online queries was performed on an ongoing basis. Standard deviation score (SDS) values for IGF-I were calculated using the reference ranges for the Siemens IMMULITE® immunoassay system (Siemens Healthcare GmbH, Germany) as defined by Elmlinger and colleagues 2004 [20].

Results

Study population

As of August 2017, 88 patients (mean age ± SD 48.92 ± 14.19 years; 58% male; 75 [85%] with adult-onset GHD) were enrolled at eight sites across Italy; 31 patients (35.2%) had been pre-treated with other rhGH

products (Table 1). The mean ± SD dose of Omnitrope® at baseline was 0.24 ± 0.13 mg/day (range 0.10–0.69 mg/day) and the mean dose at year 5 was 0.27 ± 0.15 mg/day (range 0–0.70 mg/day). The lower bound of the range (0 mg) reflects missing data points, as all patients in the study received treatment with Omnitrope®. In patients with childhood onset of GHD, those aged < 25 years received a higher mean daily dose of Omitrope® (0.45 ± 0.07 mg/day, range 0.40–0.50 mg/day) at year 5 than patients aged 25–65 years (0.37 ± 0.35 mg/day, range 0–0.69 mg/day). In patients with AGHD, those aged 25–65 years received a higher mean daily dose of Omnitrope® (0.26 ± 0.14 mg/day, range 0.02–0.70 mg/day) at year 5 than those aged < 25 years (0.21 mg/day, only one patient was included in this group) and those aged > 65 years (0.17 ± 0.11 mg/day, range 0.09–0.35 mg/day). Both in patients with childhood- and adult-onset GHD, the mean daily dose of Omnitrope® at year 5 was higher in women (0.59 ± 0.13 mg/day, range 0.50–0.69 mg/day, and 0.29 ± 0.16 mg/day, range 0.06–0.70 mg/day, respectively) than in men (0.28 ± 0.24 mg/day, range 0–0.43 mg/day, and 0.22 ± 0.09 mg/day, range 0.02–0.40 mg/day, respectively). No dosage difference was observed according to weight (Figure S1). The overall duration of treatment was 51.5 ± 37.0 months or 4.3 ± 3.1 years [range 0–110 months (0–9.2 years)].

Table 1 Baseline characteristics of Italian patients enrolled in the study as of August 2017

Characteristic	*N* = 88
Gender, *n* (%)	
Male	51 (58)
Female	37 (42)
Age, years	48.92 ± 14.19
Age group, *n* (%)	
< 25 years	6 (6.8)
25–65 years	74 (84.1)
> 65 years	8 (9.1)
Weight, kg[a]	79.11 ± 20.00
BMI, kg/m^2[b]	28.57 ± 6.12
Height, cm[c]	165.88 ± 11.33
Hip circumference, cm[d]	108.75 ± 19.37
Waist circumference, cm[e]	95.52 ± 14.67
Diagnosis at presentation, *n* (%)	
Isolated GHD	16 (18.2)
Combined GHD	72 (81.8)
Onset of GHD, *n* (%)	
Childhood onset	13 (14.8)
Adulthood onset	75 (85.2)
Family history of diabetes, *n* (%)	
No	60 (68.2)
Yes	11 (12.5)
Unknown	17 (19.3)
Previous treatment status, *n* (%)	
Treatment naïve	57 (64.8)
Pre-treated	31 (35.2)
Omnitrope® dosing at baseline, mg/day[f]	0.242 ± 0.130
Duration of Omnitrope® treatment, months (years)	51.5 ± 37.0 (4.3 ± 3.1)

All values are presented as mean ± standard deviation unless otherwise stated

BMI body mass index, *GHD* growth hormone deficiency, *SD* standard deviation

[a] *N* = 66

[b] *N* = 65

[c] *N* = 68

[d] *N* = 6

[e] *N* = 21

[f] *N* = 83

Of the 88 enrolled patients, 67 patients (76.1%) are still actively participating and 21 (23.9%) have discontinued the study. Reasons for treatment discontinuation were: patients did not wish to continue (*n* = 6; 6.8%), AEs (*n* = 3; 3.4%), patient non-compliance (*n* = 2; 2.3%), patients lost to follow-up (*n* = 2; 2.3%), switch to other rhGH products (*n* = 1; 1.1%), and other reasons (*n* = 7; 8.0%). The SAF included all 88 patients enrolled during the study period, while the EFF included 76 patients.

Safety

A total of 287 AEs were reported in 54 patients during the study period (Table 2). SAEs were reported in 22 patients (25%); the only specific SAEs that occurred in more than one patient were pneumonia and renal failure, which were reported in two patients (2.3%) each.

Neoplasms (benign, malignant, or unspecified) were reported in three patients (3.4%), none of which was considered to be related to the study drug (Table 3). These neoplasms developed in three patients with AGHD, all of whom had a history of pituitary tumors. Concerning the nature of these neoplasms, two were benign (breast lump in a female patient and prostatic adenoma in a male patient) and one was malignant [basal cell carcinoma (BCC) in a male patient]. The patients with BCC and breast neoplasm also had a history of irradiation. In addition, a cerebral cavernoma (cluster of abnormal blood vessels in the brain) was reported in a 30-year-old female patient with childhood-onset GHD, but not considered to be related to the study drug. All patients with neoplasms or cerebral cavernoma had normal or low IGF-I levels at all timepoints throughout Omnitrope® treatment. Treatment with Omnitrope® was interrupted for approximately 5 weeks in the patient with a benign breast neoplasm, but none of the patients with neoplasms or cerebral cavernoma permanently discontinued

Table 2 Summary of adverse events in the safety analysis set ($n = 88$)

	Events, *n*	Patients, *n* (%)
Any AE	287	54 (61.4)
Relationship to the drug		
Not suspected	275	51 (58.0)
Intensity		
Mild	218	50 (56.8)
Moderate	65	31 (35.2)
Severe	4	4 (4.5)
Outcome		
Resolved completely	166	44 (50.0)
Resolved with sequelae	3	3 (3.4)
Ongoing	117	41 (46.6)
Missing	1	1 (1.1)
Medication given		
No	222	50 (56.8)
Yes	63	28 (31.8)
Missing	2	2 (2.3)
Changes to Omnitrope®		
Not changed	263	51 (58.0)
Reduced	9	5 (5.7)
Interrupted	5	4 (4.5)
Permanently discontinued	5	3 (3.4)
Missing	5	3 (3.4)
SAE		
Yes	33	22 (25.0)
No	253	53 (60.2)
Missing	1	1 (1.1)
AEs in ≥ 3 patients, *n* (%)		
Asthenia	–	18 (20.5)
Headache	–	13 (14.8)
Arthralgia	–	12 (13.6)
Insomnia	–	7 (8.0)
Somnolence	–	6 (6.8)
Paresthesia	–	5 (5.7)
Myalgia	–	5 (5.7)
Libido decreased	–	5 (5.7)
Amnesia	–	4 (4.5)
Back pain	–	4 (4.5)
Muscle spasms	–	4 (4.5)
Dyspepsia	–	4 (4.5)
Hypertension	–	4 (4.5)
Sleep apnea syndrome	–	4 (4.5)
Osteopenia	–	3 (3.4)
Vitamin D deficiency	–	3 (3.4)
Nephrolithiasis	–	3 (3.4)
Anemia	–	3 (3.4)
Hyperhidrosis	–	3 (3.4)
Vertigo	–	3 (3.4)

AEs adverse events, *SAE* serious adverse event

Omnitrope® treatment. As already reported in the previous paper, the BCC resolved after treatment [12], while the other neoplasms and cavernoma were ongoing at the time of data analysis.

Six patients (6.8%) reported ADRs during the study, none of which were severe (Table 4). The most common ADRs were myalgia and arthralgia (3 [3.4%] patient each). In most of the patients experiencing an ADR (4/6), the Omnitrope® dose was subsequently reduced. Most ADRs (6/7 events) resolved without sequelae. Overdose of rhGH was reported as an ADR in two patients (one of whom also experienced an ADR of arthralgia); IGF-1 levels at the time of or just prior to the overdose were above the normal range in both patients [419.6 µg/L (normal range 96–228 µg/L) and 232.7 µg/L (normal range 88–210 µg/L), respectively]. ADRs that resulted in treatment discontinuation included drug overdose in one patient and arthralgia, myalgia, and hypoesthesia in another patient.

Unrelated to the ADRs described above, one patient was reported to have an IGF-I level of 2016 µg/L at day 2501 (6.9 years) after the start of Omnitrope® treatment. IGF-I levels in this patient ranged between 135 and 188 ng/mL during eight other measurements taken between day 59 and day 2816. Therefore, the level reported at day 2501 was considered by the authors to be a transcription mistake.

The mean fasting glucose and glycosylated hemoglobin (HbA1c) levels of patients remained stable over the study period. In the entire patient population, the mean ± SD fasting glucose at baseline was 4.6 ± 0.7 mmol/L and 4.7 ± 0.5 mmol/L at Year 9 (last available observation). The mean HbA1c at baseline was 5.6 ± 0.4% and 5.7 ± 0.4% at Year 9 (last available observation). No significant differences between treatment-naïve and pre-treated patients were observed with available data.

Four patients (three females and one male) had a history of type 2 diabetes at enrolment. Of these patients, one female developed worsening type 2 diabetes during Omnitrope® treatment. A further two male patients developed de novo type 2 diabetes during Omnitrope® treatment. These type 2 diabetes events were not considered to be related to drug treatment by the attending physician and none resulted in Omnitrope® discontinuation (Table 5). Diabetes was rated as mild in all three patients.

Efficacy

Of the 76 patients in the EFF, baseline IGF-I levels were missing for 9 patients (11.8%); of 67 patients, 31 (40.8%) had an IGF-I level within the normal range and 36 (47.4%) had an IGF-I level below the normal range. IGF-I levels increased from a mean (± SD) of 98.3 ± 71.4 µg/L (median 80.1 µg/L) at baseline to 162.4 ± 70.5 µg/L (median 150.5 µg/L) at year 5 (Fig. 1a). The mean SDS

Table 3 Neoplasms that developed in patients receiving Omnitrope®

Patient	Type of GHD (onset)	Omnitrope® dose (mg/day)	Duration of Omnitrope® at neoplasm diagnosis, days	Type of neoplasm	Relationship to Omnitrope®	Effect on Omnitrope® treatment	Neoplasm treatment and outcome
Male, 63 years	Combined (adult)	0.25	498	BCC	Not suspected	Not changed	Resolved after treatment
Female, 53 years	Combined (adult)	0.257	514	Benign breast node	Not suspected	Interrupted	Ongoing
Male, 65 years	Combined (adult)	0.25	1668	Prostatic adenoma	Not suspected	Not changed	Ongoing

BCC basal cell carcinoma, *GHD* growth hormone deficiency

Table 4 ADRs that developed in patients receiving Omnitrope®

Patient	Type of GHD (onset)	Omnitrope® dose (mg/day)	Duration of Omnitrope® at ADR diagnosis, days	IGF-I level within ± 1 month	Type of ADR	Relationship to Omnitrope®	Effect on Omnitrope® treatment	ADR treatment and outcome
Female, 54 years	Isolated (adult)	0.35	82 547	63 mcg/L, low 29 mcg/L, low	Myalgia	Suspected	Reduced	None/resolved
Male, 60 years	Combined (adult)	0.3	708 1034	73 mcg/L, normal 51 mcg/L, low	Myalgia	Suspected	Interrupted	None/resolved
Male, 25 years	Combined (adult)	0.214	1795 2067	419.6 ng/mL, high NA	Overdose of rhGH	Suspected	Permanently discontinued	None/resolved
Female, 51 years	Combined (adult)	0.171	190	NA	Arthralgia, numbness, myalgia	Suspected	Permanently discontinued	None/ongoing
Male, 52 years	Combined (adult)	0.171	28 106	232.7 ng/mL, high NA	Bloated feeling, arthralgia	Suspected	Reduced	None/resolved
			41 81	232.7 ng/mL, high NA	Overdose of rhGH	Suspected	Reduced	None/resolved
Female, 52 years	Combined (adult)	0.342	73 78	NA NA	Arthralgia	Suspected	Reduced	None/resolved

ADR adverse drug reaction, *GHD* growth hormone deficiency, *IGF-I* insulin-like growth factor-I, *NA* not available, *rhGH* recombinant human growth hormone

Table 5 Confirmed cases of diabetes mellitus that developed in patients receiving Omnitrope®

Patient	Type of GHD (onset)	BMI at BL, kg/m^2	Omnitrope® dose (mg/day)	Duration of Omnitrope® at DM diagnosis, days	Fasting glucose, mmol/L	HbA1c, %	Relationship to Omnitrope®	Effect on Omnitrope® treatment	DM treatment and outcome
Female, 44 years	Combined (adult)	37.5	0.2	360	BL: 4.6 LAO: 5.7	BL: 6.3 LAO: 5.8	Not suspected	Not changed	None/ongoing
Male, 61 years	Combined (adult)	34.7	0.142	650	BL: 4.7 LAO: 5.6	BL: 6.0 LAO: 5.5	Not suspected	Not changed	None/resolved
Male, 67 years	Combined (adult)	30.0	0.357	1317	BL: 5.1 LAO: 5.2	BL: NA LAO: 6.2	Not suspected	Not changed	None/ongoing

BL baseline, *DM* diabetes mellitus, *GHD* growth hormone deficiency, *HbA1c* glycosylated hemoglobin, *LAO* last available observation

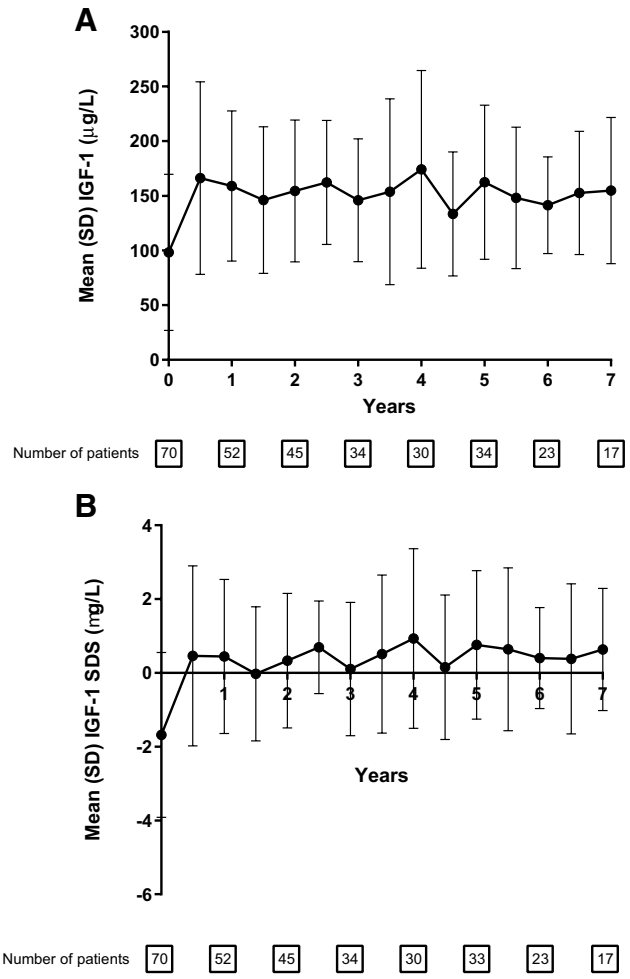

Fig. 1 Mean ± SD change in **a** IGF-I values and **b** IGF SDS in Italian patients during the study period

for IGF-I was − 1.68 ± 2.23 at baseline and 0.76 ± 2.01 at year 5 (Fig. 1b). When only patients for whom IGF-I values were available were considered, the proportion of patients with IGF-I SDS < − 2 decreased from 57.1% (n = 40/70) at baseline to 9.6% (n = 5/52) at Year 1, 6.1% (n = 2/33) at year 5 and 5.9% (n = 1/17) at year 7. Among patients with available IGF-I data, the proportion who had IGF-I levels within the normal range increased from 42.3% (n = 31/67) at baseline to 88.5% (n = 46/52) at Year 1, 88.5% (n = 27/33) at year 5 and 94.1% (n = 16/17) at year 7. Similarly, among patients with available data, the proportion of patients with IGF-1 SDS of – 2 to + 2 was 35.7% (n = 25/70) at baseline, 69.2% (n = 36/52) at Year 1, 75.8% (n = 25/33) at year 5, and 76.5% (n = 13/17) at year 7. Fewer than 4.2% of patients developed an IGF-I level above the normal range at any time during the first 7 years of treatment. It should be noted that IGF-I SDS data were missing for between 13.6% and 46.9% of patients at any given assessment between baseline and year 7.

There were no significant changes in body weight and BMI over the course of the study. Body weight and BMI were 79.1 ± 19.5 kg (n = 58) and 28.5 ± 6.0 kg/m^2 (n = 58) at baseline, and 79.8 ± 12.5 kg (n = 15) and 27.6 ± 4.4 kg/m2 (n = 12), respectively, at year 7. The number of patients for whom the data on other anthropometric parameters, such as waist circumference, hip circumference, and lean body mass, were available was too low to be informative. Of interest, the waist circumference did not change from baseline during the first year of therapy (95.5 ± 15.1 cm to 95.2 ± 4.6 cm, n = 20).

The lipid profile of patients showed a slight change over the study period. High-density lipoprotein (HDL) increased slightly over the treatment period, while low-density lipoprotein (LDL), total cholesterol, and LDL/HDL ratio showed a decrease (Fig. 2). The mean ± SD change from baseline in these parameters at year 5 was + 0.05 ± 0.36 mmol/L for HDL, − 0.21 ± 0.40 mmol/L for LDL, − 0.24 ± 1.24 mmol/L for total cholesterol, and − 0.06 ± 0.73 for the ratio of LDL/HDL.

Individual diastolic blood pressure (BP) readings ranged from 50 to 112 mmHg throughout the study, with a mean ± SD diastolic BP of between 75.8 ± 11.9 mmHg and 82.7 ± 10.4 mmHg during Omnitrope® treatment (i.e., between 0.5 and 9 years of treatment). Individual systolic BP recordings were between 95 and 220 mmHg, with the mean ± SD during treatment ranging from 120.0 ± 21.8 mmHg to 141.6 ± 29.1 mmHg.

Discussion

The present study was a snapshot analysis of data from Italian patients in the PATRO Adults study, and showed that Omnitrope® was safe and effective in Italian patients with GHD; these results are similar to and expand on the observations of the previous interim analysis of PATRO Adults [12].

As expected, IGF-I levels significantly increased after therapy. IGF-I is regarded as a reliable surrogate market of GH status [21]. Therefore, the fact that a non-negligible proportion of patients had IGF-I levels below the normal range or IGF-I SDS < − 2 indicates that either insufficient doses of Omnitrope® were used or that patients did not adhere to treatment. Treatment with Omnitrope® did not cause significant changes in fasting glucose or HbA1c during the study period, and there was minimal change in BP throughout the study. Conversely, HDL increased slightly over the treatment period, while LDL and LDL/HDL ratio showed a decrease. These data are in line with the previous studies [15, 22]. No marked changes in mean anthropometric parameters were noted over the course of Omnitrope® treatment, but data on these parameters were missing for a high proportion of patients, precluding meaningful interpretation. Similarly,

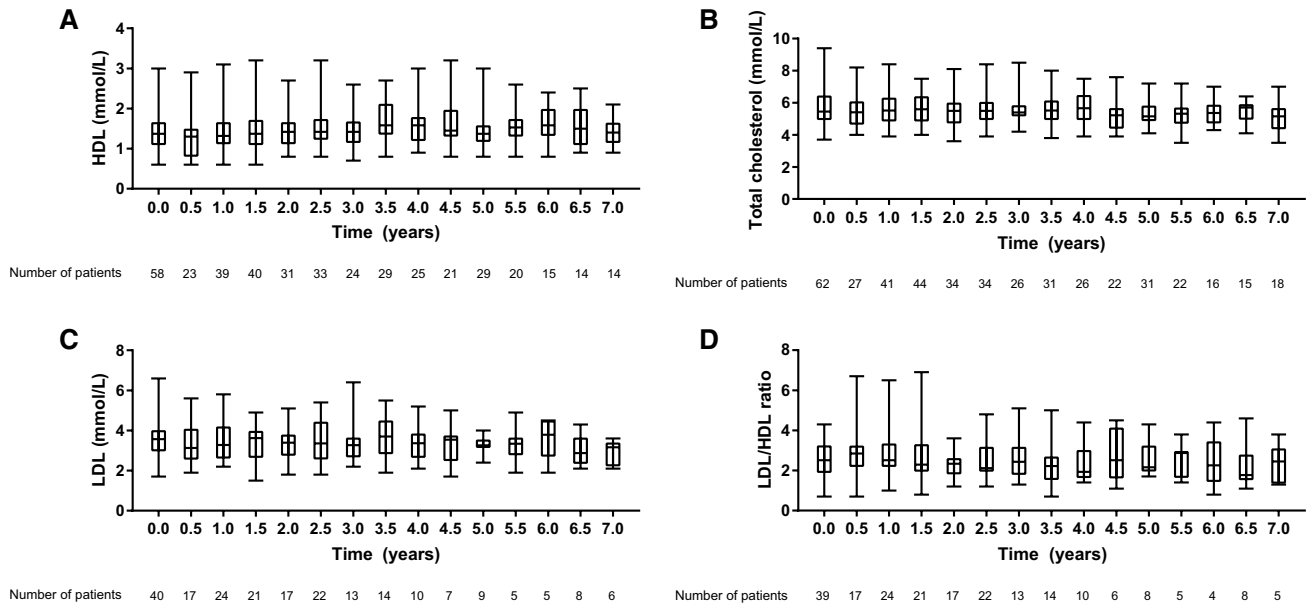

Fig. 2 Levels of **a** HDL, **b** total cholesterol, **c** LDL, and **d** LDL/HDL ratio in Italian patients during the study period, depicted as median, range, and interquartile range

there did not appear to be a relationship between anthropometric parameters and baseline IGF-I SDS or Omnitrope® dose.

In more detail, treatment with Omnitrope® did not result in severe ADRs in the present study, in line with the safety reports of Omnitrope® [23]. Moreover, no significant changes in glucose metabolism were recorded in the treated patients and the incidence of type 2 diabetes mellitus did not increase during the study. These data are in line with a study, showing that rhGH therapy did not increase the risk of diabetes [24]. However, there are conflicting reports regarding the effect of rhGH replacement on glucose metabolism and severe insulin resistance [25–27]. Insulin is known to significantly increase during the first year of treatment without further deterioration after long-term therapy, suggesting that long-term effects of therapy on body composition may overcome the negative influence of rhGH on glucose metabolism [28]. A combined registry analysis reported increased risk of type 2 diabetes mellitus with rhGH therapy in patients with pre-existing risk factors [29].

Despite the mitotic properties of GH and IGF-I, there is no clear evidence of malignancies caused by rhGH therapy [30, 31]. A recent analysis of data from a range of registries indicates that long-term rhGH treatment is not associated with an increased risk of cancer compared with cancer risk in the general population [29]. However, this analysis, along with data from the Pfizer International Metabolic Database (KIMS), suggests that people who have survived cancer and subsequently receive rhGH replacement may be at increased risk [29, 32]. The risk of a second malignancy seems to be greatest in patients who have received prior radiotherapy for cancer [29], or whose IGF-I levels fall outside of the normal range for their age [33]. In the current analysis, two of the four patients who developed a neoplasm while receiving Omnitrope® had a known history of cancer, and two had a known history of irradiation. Continuous monitoring for malignancies is recommended in patients on rhGH replacement therapy, with a particular vigilance recommended in those with a history of cancer, and rhGH therapy is contraindicated in patients with an active malignancy as it may worsen the condition [21].

There were no negative effects of long-term Omnitrope® therapy on the lipid profile of the treated patients. In fact, HDL values slightly improved and small decreases were observed in LDL, total cholesterol, and the LDL/HDL ratio during Omnitrope® therapy. Unfortunately, due to the observational design of the study, information on concomitant medications such as lipid- lowering therapy or antihypertensive treatment was not fully available. The previous studies have reported slight decreases in serum cholesterol and LDL levels and a modest increase in HDL levels with rhGH therapy [22, 34–37]. The results of the present study are similar to these reports and indicate that long-term rhGH therapy may not increase the risk of cardiovascular complications in this patient population, as no serious cardiovascular AEs occurred in Italian patients in the PATRO study during up to 9 years of treatment with Omnitrope®. However, the current guidelines suggest that therapy with rhGH in GHD adults improves several cardiovascular surrogate outcomes, including cholesterol, C-reactive protein levels, and visceral fat,

but tends to increase insulin resistance at least in the short term. Data are still not fully consistent across studies and may be influenced by other underlying factors, but, in general, cardiovascular outcomes seem to improve with rhGH replacement therapy [17].

Researchers from the KIMS registry have recently proposed a predictor of clinical response to rhGH replacement that includes waist circumference, total cholesterol levels, and QoL [38]. This is consistent with the other research, showing that IGF-I response to GH replacement in adults is correlated with first-year increases in lean body mass [39]. It has also been reported that GHD in adults results in a reduction in lean body mass and an increase in fat mass [40].

The overall effect of long-term rhGH treatment on cardiovascular risk in adults may be neutral. Data from the KIMS registry showed that the prevalence of metabolic syndrome does not change during long-term rhGH treatment, and that patients are just as likely to show a reversal in metabolic syndrome as they are to develop this condition de novo [41]. These data indicate that the beneficial effects of rhGH on waist circumference and HDL cholesterol may be offset by its negative effects on glucose metabolism. In addition, QoL of patients improved with GH replacement, irrespective of the presence or absence of metabolic syndrome [41].

Omnitrope® is reported to be bioequivalent to Genotropin® (a rhGH indicated for the treatment of adults with GHD) and considered therapeutically interchangeable [42]. Indeed, the safety and efficacy of Omnitrope® reported in the present study are comparable to those of Genotropin® [43]. Similar results were reported in a study comparing the safety and efficacy of Omnitrope® versus Genotropin®, with reduced overall cost of treatment [44].

The results of this snapshot analysis are comparable to the results of global PATRO Adults study. As of August 2017, 1199 patients have been enrolled (mean age 44.54 ± 16.72 years, 51.7% male) at 71 sites across Europe, of which 51.2% were pre-treated. Mean Omnitrope® dose at baseline was 0.291 ± 0.227 mg/day and the mean treatment duration was 34.0 ± 5.2 months. A total of 3045 AEs were reported in 752 patients during the study period; 7.1% of patients reported ADRs; ADRs of severe intensity included edema, skin ulcer, dyspnea, and lung disorder [45–47].

The main limitations of the present study were the small patient population and the lack of efficacy data in many patients due to reporting failures in this observational study. However, the study is ongoing and expected to enroll additional patients with GHD on Omnitrope® therapy. In addition, the patients are a real-world unselected patient group and each study center could manage patients according to their usual clinical practice. While this can introduce variation and selection bias, the results are reflective of real-world patients, unlike clinical studies which include a highly selected group of patients.

Another limitation of the present study is the fact that the proportion of patients with missing data for a number of outcomes was high and precluded meaningful interpretation. Missing data are often unavoidable in observational studies. Some results reported in this study require cautious interpretation, in particular the range (minimum–maximum) for the Omnitrope mean dose at 5 years and for treatment duration, which both had 0 as a minimum value. These results could be explained by patients who had temporarily interrupted treatment, missing data, or reporting failures.

The main strength of the PATRO Adults study is the long follow-up duration of patients on Omnitrope® therapy.

In conclusion, this snapshot analysis of the PATRO Adults study confirmed the safety and effectiveness of Omnitrope® in the treatment of Italian adult patients with GHD.

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Author contributions CG and MA contributed to the preparation of the manuscript; CG enrolled patients and conducted follow-up; GA, VG, and MRA enrolled patients, conducted follow-up, collected data, and critically revised various manuscript drafts; DF provided critical revision of the manuscript drafts and study coordination; RV enrolled patients, conducted follow-up, collected data, and read the manuscript drafts; PG, HZ, and PF contributed to the drafting of the manuscript, and critically revised the various drafts of the manuscript; EP critically revised the various drafts of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets generated/analyzed during the current study are not publicly available due to the fact that the data generated are issued from an ongoing global non-interventional study. Patient enrollment is still performed as per the objectives and the commitment with the European Medical Agency, but the data are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest MA, VG, CG, EP, RV, and DF declare that they have no conflicts of interest. GA has received lecture fees from Novartis and Otsuka, and consulting honoraria from HRA Pharma. MRA has received registration fees for scientific meetings from Ipsen, Novartis, Pfizer, and ItaPharma. PG and PF are employees of Sandoz S.p.A, Origgio (MI), Italy. HZ is an employee of Sandoz Biopharmaceutical c/o HEXAL AG, Holzkirchen, Germany.

Ethical approval The study was approved by each study site's Independent Ethics Committee or Institutional Review Board before initiation and was conducted in accordance with the Declaration of Helsinki.

Informed consent All patients included in the study provided written informed consent at enrolment.

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