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REVIEW

Long-term safety and effectiveness of a somatropin biosimilar (Omnitrope®) in children requiring growth hormone therapy: analysis of final data of Italian patients enrolled in the PATRO children study

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Abstract

Purpose Omnitrope® (a somatropin biosimilar), used to treat growth disturbances, is considered to have a good safety profile in children. Here, we present the analysis of final data of the Italian cohort of the PAtients TReated with Omnitrope® (PATRO) Children study.

Methods This multicenter, open-label, longitudinal, post-marketing surveillance study enrolled eligible children during 2010–2018. The primary objective was to assess the long-term safety of Omnitrope® by recording all adverse events (AEs), serious AEs, and adverse drug reactions (ADRs). A secondary objective was to evaluate the long-term effectiveness of Omnitrope® using height measurements.

Results A total of 375 patients were included in the Italian cohort of the PATRO Children study. After a mean ± standard deviation (SD) follow-up duration of 40.9 ± 24.6 months, 607 AEs were reported in 58.4% of patients, mostly of mild (52.5%) or moderate (15.7%) severity. The most common AEs were headache (11.7%), elevated insulin-like growth factor (IGF)-1 (4.8%), abdominal pain (4.3%), and pyrexia (3.7%). Sixty-seven ADRs occurred in 52 patients (13.9%); the most common ADRs were elevated IGF-1 (3.5%) and insulin resistance (2.9%). Mean ± SD height standard deviation scores in treatment-naïve patients increased from −2.5 ± 0.7 at baseline ($n = 318$) to −1.3 ± 0.7 at 5 years ($n = 56$) and to −0.8 ± 0.7 at 7.5 years ($n = 13$).

Conclusions This final analysis extends the interim analysis findings from the PATRO Children study and confirms the long-term safety and effectiveness of Omnitrope® in Italian pediatric patients with growth disturbances.

Keywords Adolescents · Children · Infants · Omnitrope® · Pediatric · Recombinant human growth hormone

Introduction

The recombinant human growth hormone (rhGH) Omnitrope® (a somatropin biosimilar) is approved in the United States (US) and Europe for pediatric patients with growth failure due to growth hormone deficiency (GHD), Prader–Willi syndrome, Turner syndrome, or in children who are small for gestational age (SGA) [1, 2]. Omnitrope® is also approved in pediatric patients with growth disturbances due to chronic renal insufficiency in Europe [1], and in the US for idiopathic short stature (ISS) [2].

Treatment with rhGH is considered to have a good safety record in children when used at the recommended dose for its approved indications; however, ongoing surveillance is important to ensure the long-term safety of growth hormone (GH)-treated patients [3]. Data from the long-term Safety and Appropriateness of Growth Hormone treatments in Europe (SAGhE) cohort study have indicated that rhGH treatment in childhood is not associated with an increased

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risk of cancer [4]. Pediatric patients who receive rhGH treatment may have a small increase in the risk of cardiovascular and cerebrovascular events in adulthood, as well as an increased risk of type 2 diabetes mellitus in the presence of other risk factors (e.g. family history, obesity, comorbidities, or a sedentary lifestyle) [5]; however, several studies temper these conclusions, and data on the safety of rhGH treatment in children and adolescents are largely reassuring [6–9].

As part of the European Medicines Agency's (EMA's) post-approval risk management plan, the PAtients TReated with Omnitrope® (PATRO) Children post-marketing surveillance study was conducted to evaluate the long-term safety and effectiveness of Omnitrope® in children with growth disturbances [10]. Interim analyses of PATRO Children have been previously reported for 10 European countries (as of September 2012) [10], the Italian cohort (as of August 2015 and August 2017) [11, 12], the US cohort (September 2018) [13], the Swedish cohort (January 2019) [14], and the full (global) study population (November 2017) [15]. Herein, we present the analysis of final data of the Italian cohort in the PATRO Children study.

Methods

Study design

The study design and rationale of PATRO Children have been described previously [10]. Briefly, PATRO Children was a multicenter, multinational, open-label, longitudinal, post-marketing surveillance study. The study complied with all national and international ethical recommendations and the ethical principles outlined in the Oviedo Human Rights Convention and the Helsinki Declaration of 1964, and its later amendments. The study was reviewed and approved by each study site's Independent Ethics Committee/Institutional Review Board. All patients (or their parents/legal guardians) provided written informed consent before study inclusion.

Treatment and outcomes

Omnitrope® was administered in accordance with the recommendations in the EMA's summary of product characteristics [1]. Treatment-naïve patients and patients who had previously received other rhGH treatments were eligible for inclusion in the study.

The primary objective of PATRO Children was to assess the long-term safety of Omnitrope® in routine clinical practice. All adverse events (AEs) and serious AEs (SAEs) were recorded irrespective of causality. Adverse drug reactions (ADRs) were defined as AEs with a suspected relationship to the study drug. Based on previous reports of AE incidences in rhGH recipients, benign intracranial hypertension, malignancies, scoliosis, slipped capital femoral epiphysis, and type 2 diabetes were identified as AEs of special interest [16, 17]. The development of type 2 diabetes was assessed according to World Health Organization (WHO) criteria [18, 19].

A secondary study objective was to assess the long-term effectiveness of Omnitrope® using height standard deviation scores (HtSDS) and height velocity SDS [20].

Data collection and verification

Data were collected at each routine visit during treatment, with the frequency of visits determined at the discretion of the treating physician. Laboratory tests were performed at baseline and subsequent visits as part of routine clinical practice.

Patient data were recorded and entered into an electronic case report form (eCRF) for capture into a centralized web-based electronic data collection system. Data were monitored by a data management team and managed by a contract research organization.

Statistical analysis

As described previously [7, 8], descriptive statistics were used to assess all endpoints. Safety was evaluated in the safety analysis set (SAS), which included all patients with a recorded visit date or Omnitrope treatment start date and who received at least one dose of Omnitrope® treatment during the study period. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 COVID-19 (Novartis).

Effectiveness was evaluated in the effectiveness analysis set (EAS), which included all treatment-naïve patients with a documented height measurement at baseline (start of Omnitrope® treatment) and at least one post-baseline height measurement ≥6 months after Omnitrope® initiation. Effectiveness was assessed separately in treatment-naïve patients with GHD and treatment-naïve pre-pubertal patients [21, 22] stratified by indication (all indications vs. GHD alone).

The 5-year analysis included all treatment-naïve patients and treatment-naïve pre-pubertal patients who completed ≥5 years of Omnitrope® treatment. All statistical analyses were performed using SAS® version 9.3 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Between February 2010 and February 2018, 375 patients (mean ± standard deviation [SD] age 9.9 ± 3.2 years; 58.1%

Table 1 Patient baseline characteristics and demographics

Characteristics	$N = 375$
Sex, *n* (%)	
Male	218 (58.1)
Female	157 (41.9)
Chronological age at start of Omnitrope®, mean ± SD, years	9.9 ± 3.2
Age group at start of Omnitrope®, *n* (%)	
<2 years	4 (1.1)
2 to <4 years	9 (2.4)
4 to <7 years	58 (15.5)
7 to <10 years	108 (28.8)
10 to <13 years	132 (35.2)
13 to <16 years	59 (15.7)
≥16 years	5 (1.3)
Pubertal status, *n* (%)	
Pre-pubertal	294 (78.4)
Pubertal	81 (21.6)
HtSDS, mean ± SD	–2.46 ± 0.71 (N_{miss} = 35)
BMI, mean ± SD, kg/m^2	16.8 ± 3.2 (N_{miss} = 42)
Chronological age at diagnosis, mean ± SD, years	9.3 ± 3.5[a]
Diagnosis at presentation, *n* (%)	
GHD	302 (80.5)
SGA	30 (8.0)
ISS	19 (5.1)
Prader–Willi syndrome	10 (2.7)
Turner syndrome	5 (1.3)
Chronic renal insufficiency	1 (0.3)
Other	8 (2.1)
Previous treatment status, *n* (%)	
Treatment naïve	362 (96.5)
Pre-treated	13 (3.5)
Omnitrope® dosing at baseline, mean ± SD, mg/kg/day	0.030 ± 0.006 (N_{miss} = 109)
GHD	0.030 ± 0.005
SGA	0.034 ± 0.007
ISS	0.031 ± 0.005
Prader–Willi syndrome	0.030 ± 0.006
Turner syndrome	0.044 ± 0.005

BMI body mass index, *GHD* growth hormone deficiency, *HtSDS* height standard deviation score, *ISS* idiopathic short stature, N_{miss} number of patients with data missing, *SD* standard deviation, *SGA* small for gestational age

[a] $n = 364$

male) from 20 sites in Italy started Omnitrope® treatment and were enrolled in the PATRO Children study (SAS; Table 1). The most common diagnoses at presentation were GHD in 302 patients (80.5%) and SGA in 30 patients (8.0%). Most patients (n = 362; 96.5%) were hormone treatment-naïve when they started Omnitrope®. At treatment initiation, 311 patients (82.9%) were aged <13 years, and 294 (78.4%) were pre-pubertal. The mean ± SD treatment duration was 40.9 ± 24.6 months.

Treatment discontinuation

Overall, 98 patients (26.1%) continued treatment with Omnitrope® through to study end (i.e., at the time of database lock in July 2020). The primary reasons for treatment discontinuation prior to study end were: attainment of final height/bone age maturation ($n = 65$; 17.3%); premature site closure (four centers closed ~3 years after study initiation; $n = 63$; 16.8%); patients reaching near final height ($n = 38$; 10.1%); patients switching to another rhGH product ($n = 26$; 6.9%); loss to follow-up ($n = 26$; 6.9%); AEs (n = 10; 2.7%); patient indication for Omnitrope® being no longer applicable ($n = 10$; 2.7%); patients reaching 18 years of age ($n = 8$; 2.1%); patients changing reference centers ($n = 7$; 1.9%); patients not wishing to continue injections ($n = 6$; 1.6%); patient non-compliance ($n = 4$; 1.1%); physician decision ($n = 4$; 1.1%); patient satisfied with height ($n = 3$; 0.8%); non-response to treatment ($n = 3$; 0.8%); and height velocity slowdown (< 1 cm/year; $n = 1$; 0.3%).

Adverse events

By 23 July 2020, 607 AEs were reported in 58.4% of patients in the SAS ($n = 219/375$). Most AEs were either mild ($n = 197$; 52.5%) or moderate ($n = 59$; 15.7%) in severity; 13 severe AEs occurred in eight patients (0.5%). The most common AEs (incidence of >10 per 1278.9 patient-years) were headache ($n = 44$; 11.7%), elevated (≥ 2 SDS) insulin-like growth factor-1 (IGF-1) ($n = 18$; 4.8%), abdominal pain ($n = 16$; 4.3%), and pyrexia ($n = 14$; 3.7%; Table 2).

In response to the occurrence of AEs, the Omnitrope® dose was increased in three patients (0.8%), reduced in eight (2.1%), interrupted in 20 (5.3%), and permanently discontinued in 10 patients (2.7%). Complete resolution was reported for 406 AEs ($n = 175$; 46.7%), while eight AEs ($n = 7$; 1.9%) resolved without sequelae; 191 AEs ($n = 113$; 30.1%) were ongoing at the time of database lock. One AE ($n = 1$; 0.3%) led to the death of a 10-year-old patient who had started Omnitrope® at 5.9 years of age; the cause of death was pneumonia/acute respiratory distress syndrome (ARDS) and was deemed unrelated to Omnitrope®.

Sixty-five SAEs occurred in 48 patients (12.8%); of these, eight SAEs in seven patients (1.9%) led to treatment interruption, and four SAEs in three patients (0.8%) led to permanent treatment discontinuation.

Table 2 Adverse events and adverse drug reactions with an incidence of >4 per 1278.9 patient years during Omnitrope® treatment

Event	Patients, *n* (%)	Incidence (per 1278.9 patient-years)
AEs	219 (58.4)	171.24
Headache	44 (11.7)	34.40
Elevated IGF-1	18 (4.8)	14.07
Abdominal pain	16 (4.3)	12.51
Pyrexia	14 (3.7)	10.95
Gastroenteritis	12 (3.2)	9.38
Arthralgia	12 (3.2)	9.38
Insulin resistance	12 (3.2)	9.38
Blood TSH increased	11 (2.9)	8.60
Pain in extremity	10 (2.7)	7.82
Gynecomastia	10 (2.7)	7.82
Scoliosis	9 (2.4)	7.04
Asthenia	9 (2.4)	7.04
HbA1c increased	6 (1.6)	4.69
Constipation	6 (1.6)	4.69
ADRs	52 (13.9)	40.66
Elevated IGF-1	13 (3.5)	10.16
Insulin resistance	11 (2.9)	8.60

ADR adverse drug reaction, *AE* adverse event, *HbA1c* glycosylated hemoglobin, *IGF-1* insulin-like growth factor-1, *TSH* thyroid-stimulating hormone

Adverse drug reactions

Seventy-six AEs in 52 patients (13.9%) were considered by the investigators as being ADRs. Of these, 45 patients (12.0%) had mild ADRs, and seven (1.9%) had moderate ADRs; there were no severe ADRs. The most common ADRs (incidence of >4 per 1278.9 patient-years; Table 2) were elevated IGF-1 ($n = 13$; 3.5%) and insulin resistance ($n = 11$; 2.9%).

Serious adverse events of special interest

SAEs of special interest occurred in six patients (1.6%), including hypothyroidism and gait disturbance in two patients (0.5%); the remaining four events occurred as isolated cases in four patients: generalized tonic-clonic seizures, neoplasm progression, elevated IGF-1, and an abnormal electroencephalogram. Gait disturbances were reported in an 8.6-year-old patient who started treatment at 7.9 years of age. The SAE was suspected of being treatment-related, but this could not be determined with full certainty; symptoms resolved completely after permanent discontinuation of treatment. Omnitrope® was also stopped following a single report of tonic-clonic seizures and an abnormal electroencephalogram in a 9-year-old patient; the seizures resolved without sequelae. At one study site, a 19-year-old patient who had been receiving Omnitrope® for 5 years experienced a minimal increase in a known residual of craniopharyngioma. Once detected, Omnitrope® treatment was halted, and the patient received substitutive therapies for the remaining hormonal deficiencies related to acquired hypopituitarism. After 4 months, the residual craniopharyngioma was deemed stable (via imaging) and Omnitrope® was restarted with no further events.

Scoliosis was reported in nine patients (2.4%; 7.04 per 1278.9 patient-years), four of whom had GHD, two had ISS, one patient each had Turner syndrome and Prader–Willi syndrome, and one patient was born SGA. Scoliosis developed during the fourth year of Omnitrope® treatment in one patient with ISS and was considered serious. None of the cases of scoliosis were considered to be related to Omnitrope®.

Glucose metabolism

Diabetes mellitus (according to WHO criteria) was confirmed in five patients (1.3%) after the beginning of Omnitrope® treatment. Four of these patients had GHD, and the indication for the remaining patient was classified as 'other.' Impaired glucose tolerance developed during treatment in nine patients (2.4%), of whom eight had GHD and one had Turner syndrome.

Of the 14 patients who developed glucose metabolism disorders, eight were considered to be treatment-related; insulin resistance was observed in six patients. Omnitrope® treatment was interrupted in four patients with insulin resistance, of whom three re-initiated treatment 2–3 months later after complete resolution of the AE.

Among the nine patients with high IGF-1 levels (i.e., above their sex and age-specific 'normal' range; 11 events), Omnitrope® dosage was reduced by a median of 5 µg/kg/day in 55.6% of cases ($n = 5$); thereafter, IGF-1 levels normalized within 3–6 months. In 22.2% of cases ($n = 2$), IGF-1 levels normalized after treatment had been discontinued for 12 months. Study treatment was discontinued for other reasons in the remaining 22.2% of cases, i.e., two patients achieved their final height and were either lost to follow-up or had low treatment adherence. Overall, 75.0% of events were suspected to be treatment related.

Effectiveness

A total of 318 patients were included in the EAS. Follow-up data for ≥5 years were available for 56 patients (5-year effectiveness analysis).

Height SDS

Pre-pubertal treatment-naïve patients across all indications showed a numerically similar increase in mean ± SD HtSDS from baseline (− 2.8 ± 0.5 [$n = 61$]) to 5 years (− 1.2 ± 0.6

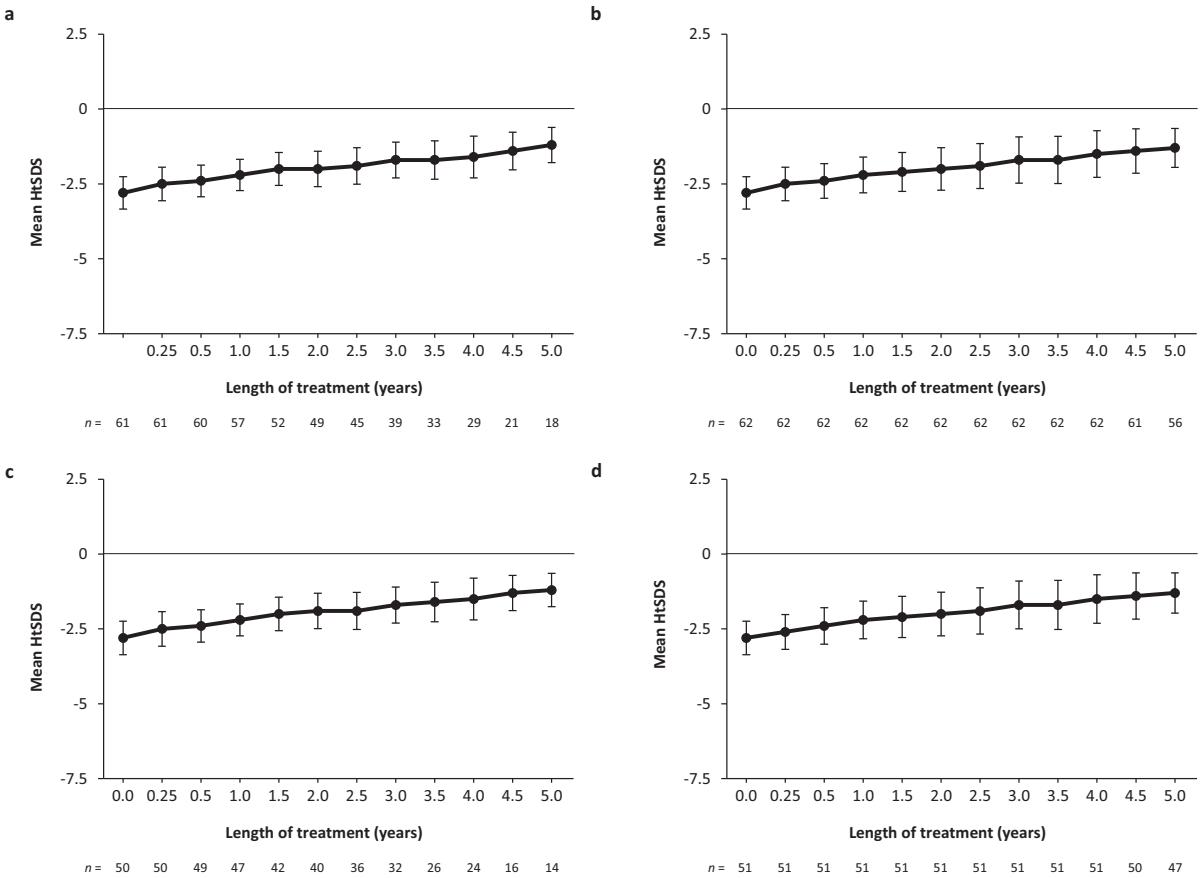

Fig. 1 Mean height standard deviation scores over 5 years of study duration across all indications in **a** pre-pubertal treatment-naïve patients, **b** all treatment-naïve patients, **c** pre-pubertal treatment-naïve patients with growth hormone deficiency, and **d** all treatment-naïve patients with growth hormone deficiency. Error bars represent standard deviation. *HtSDS* height standard deviation score

[$n = 18$]; Fig. 1a) compared with that observed in all treatment-naïve patients (from -2.8 ± 0.5 [$n = 62$] to -1.3 ± 0.7 [$n = 56$]; respectively; Fig. 1b). Likewise, the increase in mean HtSDS in pre-pubertal treatment-naïve patients with GHD (Fig. 1c) was numerically similar to that found in all treatment-naïve patients with GHD (Fig. 1d).

Among treatment-naïve patients in the EAS ($n = 318$), the mean ± SD HtSDS increased from -2.5 ± 0.7 at baseline to -1.3 ± 0.7 at 5 years ($n = 56$) and to -0.8 ± 0.7 at 7.5 years ($n = 13$) across all indications (Fig. 2a). In treatment-naïve patients with GHD ($n = 265$), the mean ± SD HtSDS also gradually increased over time, from -2.4 ± 0.7 at baseline to -1.3 ± 0.7 at 5 years ($n = 47$) and -0.8 ± 0.7 at 7.5 years ($n = 10$; Fig. 2b).

In total, 107 patients reached final height according to physician's opinion. The mean ± SD height SDS for these 107 patients was -1.49 ± 0.94.

Height velocity SDS

Height velocity SDS values peaked at 0.25 years and decreased thereafter in pre-pubertal treatment-naïve patients (Fig. 3a), in all treatment-naïve patients across all indications (Fig. 3b), and in patients with GHD (Fig. 3c, d). In pre-pubertal treatment-naïve patients, the mean ± SD height velocity SDS increased from -2.5 ± 1.3 at baseline ($n = 33$) to a peak of 3.7 ± 2.6 at 0.25 years ($n = 55$) and stabilized at 0.7 ± 1.0 at 2.5 years ($n = 45$). In pre-pubertal treatment-naïve patients with GHD, the mean ± SD height velocity SDS increased from -2.6 ± 1.0 at baseline ($n = 26$) to 3.9 ± 2.4 ($n = 46$) and stabilized at 0.7 ± 0.9 at 2.5 years ($n = 36$).

Discussion

The results of this analysis of Italian patients in the PATRO Children study are consistent with those of two previous interim analyses [11, 12], further confirming the long-term safety and effectiveness of the rhGH biosimilar Omnitrope® in pediatric patients with growth disturbances. These findings are consistent with those reported in previous interim analyses of the European [10], US [13], Swedish [14], and global [15] populations of PATRO Children.

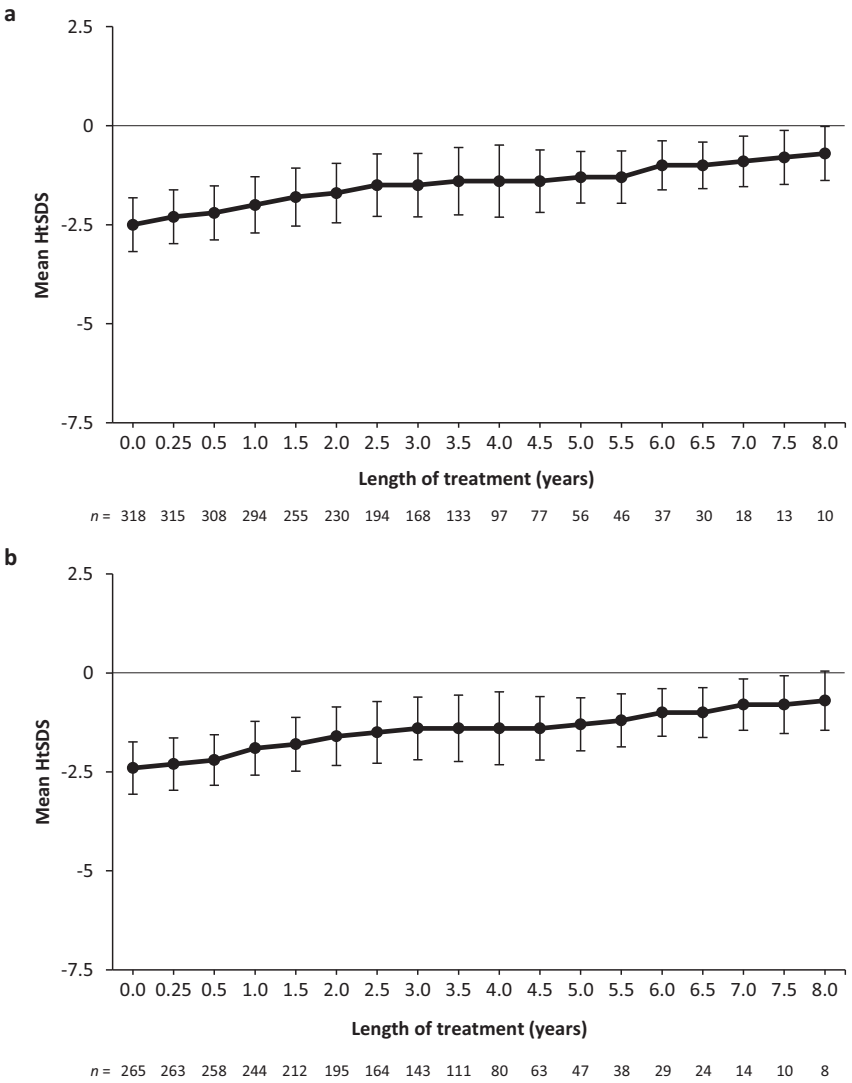

Fig. 2 Mean height standard deviation scores in treatment-naïve patients over 8 years of study duration **a** across all indications and **b** for those with growth hormone deficiency. Error bars represent standard deviation. *HtSDS* height standard deviation score

The baseline demographic and disease characteristics reported here differed slightly from the global PATRO Children study population. In the present analysis, 80.5% of patients were being treated for GHD and 8.0% were SGA, whereas, in the global population, 57.7% had GHD and 25.8% were SGA [15]. In addition, the proportion of patients who were rhGH treatment-naïve prior to starting Omnitrope® was higher in the present analysis (96.5%) than in the global study population (84.1%) [15]. These variations may reflect differences in treatment protocols or diagnostic criteria between Italy and other countries. Indeed, a previous study reported that the prevalence of SGA in Italy was under-reported due to improper identification or misdiagnoses [23]. Alternatively, based on an author's experience, it may be related to endocrinologists' preferences to maintain treatment continuity with the same medication or device, given that changes in treatments can cause disruption and increase treatment noncompliance.

The incidence rates of AEs and ADRs in a previous interim analysis of the global PATRO Children study population were 152.3 and 21.9 per 1000 patient-years, respectively [15]. In comparison with the global population, the current analysis showed a lower AE incidence rate (171.24 per 1278.9 patient-years or 133.9 per 1000 patient-years) and a higher ADR incidence rate (40.66 per 1278.9 or 31.79 per 1000 patient-years). An even lower AE incidence rate (94.2 per 1000 patient-years) was reported for Genotropin® (originator of somatropin) in the Pfizer International Growth Database (KIGS) study [8] than the above-mentioned rates for PATRO Children. However, direct comparisons between PATRO Children and other observational studies should be made with caution due to variations in observational time periods and in safety data collection methods [15]. Since AEs in the KIGS study were not recorded over a long treatment period, it is likely that some AE data were not reported by investigators [8].

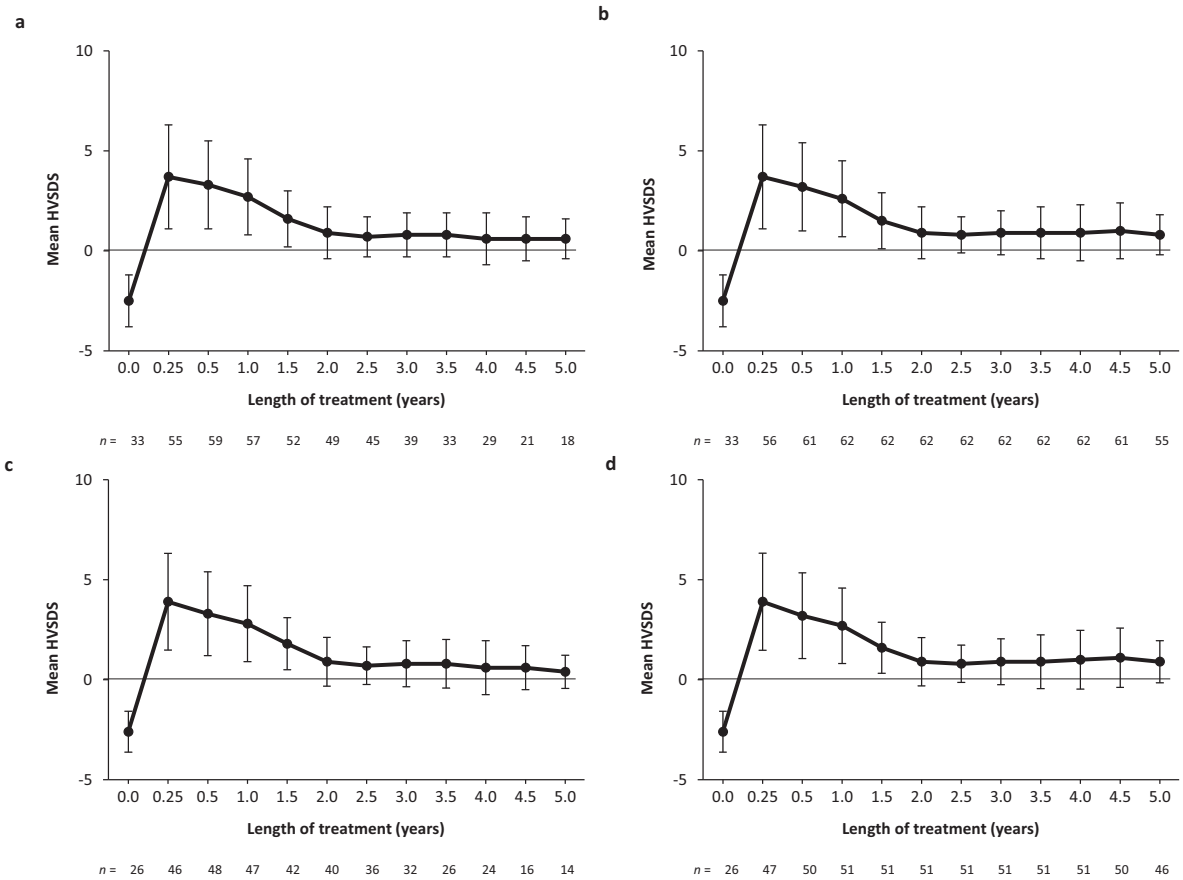

Fig. 3 Mean height velocity standard deviation score over 5 years of study duration across all indications in **a** pre-pubertal treatment-naïve patients, **b** all treatment-naïve patients, **c** pre-pubertal treatment-naïve patients with growth hormone deficiency, and **d** all treatment-naïve patients with growth hormone deficiency. Error bars represent standard deviation. *HVSDS* height velocity standard deviation score

The PATRO Children study also examined the potential for the development of malignancies during rhGH therapy. Treatment-related neoplasm progression was reported in one patient in the Italian cohort. In a previous interim analysis of the global PATRO cohort, treatment-related neoplasm development was reported in four patients, and treatment-related progression of pre-existing craniopharyngioma was reported in two patients (one of whom was the above-mentioned patient in the Italian cohort) [15]. Taken together with data from the SAGhE cohort study [4] and a report from the Pediatric Endocrine Society Drug and Therapeutics Committee [24], these results indicate there is no increase in the risk of malignancies with Omnitrope® treatment.

Musculoskeletal AEs may occur during rhGH therapy. Although nine patients developed scoliosis during Omnitrope® treatment in the current study (one of whom had serious scoliosis), none were considered treatment related. The scoliosis did not progress further in any of the patients in the current study. However, as scoliosis has been associated with GH therapy previously, it should be monitored at routine clinic visits as a precaution [25]. One patient developed a treatment-related gait disturbance; whether or not this was a symptom of slipped capital femoral epiphysis, which is a known adverse effect of GH treatment [25], was not reported. Another study also reported that a pediatric patient developed gait changes after the administration of rhGH, which, similar to this study, normalized without further sequelae after treatment was discontinued [26]. Various components of the GH-IGF-1 axis are known to impact the development, function, and regeneration of certain portions of the central nervous system, including the spinal cord [27].

Because of concerns regarding a potential association between the development of diabetes and rhGH therapy [28], the PATRO Children study specifically examined the risk for diabetes during Omnitrope® treatment [10]. In the Italian cohort of PATRO Children, five patients developed diabetes mellitus, and nine developed impaired glucose tolerance after starting Omnitrope®. The global interim analysis of PATRO Children (to November 2017) reported only one case of type 1 diabetes mellitus and seven cases of impaired glucose tolerance that were considered treatment-related among 6009 patients [15]. The current results

confirm the limited risk of inducing insulin resistance with rhGH treatment.

GH therapy can also increase IGF-1 levels intrinsically without the risk of impairing glucose metabolism [26]. In the current study, nine patients had elevated IGF-1 levels. The management of these patients indicates that in instances where IGF-1 levels increase over the normal range and/or glucose metabolism impairment arises, physicians should assess treatment correlation and subsequently reduce or temporarily interrupt drug administration until such parameters normalize. This approach produces positive safety outcomes within a few months, allowing for treatment continuation when the patient's age and therapeutic window remain favorable.

The final analyses of PATRO Children effectiveness data are in line with those reported in previous interim analyses in Italian pediatric patients [11, 12]. In all treatment-naïve patients and in those with GHD, Omnitrope® was associated with increased HtSDS, while height velocity peaked within the first 3 months of treatment and stabilized thereafter. These findings are also consistent with the efficacy results of previous phase 3 clinical studies of Omnitrope® in pre-pubertal children with GHD [29, 30]. Further, Omnitrope® has bioequivalent pharmacokinetics and pharmacodynamics [31] and similar efficacy [32] to that of the reference medicine Genotropin®.

In the 12-month interim analysis of the Italian cohort, pre-pubertal treatment-naïve patients with GHD or SGA had a greater increase in HtSDS with Omnitrope® than the overall population of treatment-naïve patients [12]. After 5 years, Omnitrope® was similarly effective in pre-pubertal treatment-naïve patients, all treatment-naïve patients across all indications, and those with GHD [12]. Patient age at the initiation of rhGH therapy has previously been reported to have a negative correlation with increases in HtSDS [33]. The difference in growth response between pre-pubertal patients and the overall population may not be as apparent in the current analysis, as most patients (78.4%) were pre-pubertal at treatment onset.

This study was limited by its observational design and, as such, may include confounding variables that could not be measured or controlled. There is also a risk of bias due to missing or erroneous data collection (e.g., baseline AE and height velocity data were not available for all or some of the EAS, respectively). In addition, the results may not be representative of all indications for rhGH therapy, as the majority of enrolled patients had GHD.

Conclusions

The analysis of final data of the PATRO Children study confirmed the long-term safety and effectiveness of Omnitrope® in Italian pediatric patients with growth disturbances in routine clinical practice. These data are consistent with those observed in randomized clinical studies and extend the findings of previous interim analyses of the PATRO Children study in Italian patients.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Author contributions Conceptualization: LI, LL and SZ; Methodology: LI and SZ; Formal analysis: LI, LL and SZ; Formal investigation: FA, CG, SB, TA, LG, MES, EMG, LP, GP, LR, SS, GT, CZ, CM and SZ F; Writing - review and editing: GT, MES, TA, CG, LP and LL; Supervision: LI and SZ. All authors read and approved the final manuscript for publication.

Compliance with ethical standards

Conflict of interest **Lorenzo Iughetti** has received fees for participation on advisory boards from Sandoz. **Franco Antoniazzi** has received research funding from Merck Serono and Sandoz, and fees for participation on advisory boards from BioMarin. **Tommaso Aversa** has consulted for Pfizer and Sandoz. Luca Persani has received fees for participation on advisory boards from Sandoz. **Gabriella Pozzobon** has received consulting fees and for participation on advisory boards from Sandoz, Merck Serono and Novo Nordisk. **Emiliano Zecchi, Paolo Fedeli** and **Markus Zabransky** are part of Sandoz Company Organization. **Claudia Giavoli, Simonetta Bellone, Laura Guazzarotti, Maria Elisabeth Street, Emanuele Miraglia del Giudice, Stefano Stagi, Gianluca Tornese**, **Chiara Mameli, Laura Lucaccioni, Letizia Ragusa, Clara Zecchino, and Stefano Zucchini** have no relevant financial or non-financial interests to disclose.

Ethics approval The study was reviewed and approved by each study site's Independent Ethics Committee/Institutional Review Board.

Research involving human participants All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committees, with the 1964 Helsinki Declaration and its later amendments, and with the ethical principles outlined in the Oviedo Human Rights Convention.

Consent to participate All patients (or their parents/legal guardians) provided written informed consent before study inclusion.

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