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ORIGINAL ARTICLE

Safety and effectiveness of a somatropin biosimilar in children requiring growth hormone treatment: second analysis of the PATRO Children study Italian cohort

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Abstract

Purpose To investigate the long-term safety (primary endpoint) and effectiveness (secondary endpoint) of the somatropin biosimilar Omnitrope®.

Methods PATRO Children is an ongoing, multicenter, observational, post-marketing surveillance study. Children who received Omnitrope® for any indication were included. Adverse events (AEs) were evaluated in all study participants. Auxological data, including height standard deviation scores (HSDS) and height velocity standard deviation scores (HVSDS), were used to assess effectiveness. In this snapshot analysis, data from the Italian subpopulation up to August 2017 were reported.

Results A total of 291 patients (mean age 10.0 years, 56.0% male) were enrolled at 19 sites in Italy. The mean duration of Omnitrope® treatment was 33.1 ± 21.7 months. There were 48 AEs with a suspected relationship to the study drug (as reported by the investigator) that occurred in 35 (12.0%) patients, most commonly headache, pyrexia, arthralgia, insulin-like growth factor above normal range, abdominal pain, pain in extremity and acute gastroenteritis. There were no confirmed cases of type 1 or type 2 diabetes; however, two patients (0.7%) had impaired glucose tolerance that was considered Omnitrope® related. The mean HSDS increased from − 2.41 ± 0.73 at baseline ($n = 238$) to − 0.91 ± 0.68 at 6.5 years ($n = 10$). The mean HVSDS increased from − 1.77 ± 1.38 at baseline ($n = 136$) to 0.96 ± 1.13 at 6.5 years ($n = 10$).

Conclusions In this sub-analysis of PATRO Children, Omnitrope® appeared to have acceptable safety and effectiveness in the treatment of in Italian children, which was consistent with the earlier findings from controlled clinical trials.

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

Background

Recombinant human growth hormones (rhGH) have been established as safe and effective for the treatment of various growth disorders in children, with several rhGH products now licensed [1–3].

Omnitrope® (Sandoz GmbH, Kundl, Austria) is a somatropin developed as the biosimilar medicinal product to the originator Genotropin® (Pfizer Limited, Sandwich, UK). In 2006, Omnitrope® was the first product to be approved by the European Medicines Agency (EMA) via the European regulatory pathway for biosimilars. Omnitrope® is licensed for use in treating infants, children, and adolescents with growth hormone deficiency (GHD), those born small for gestational age (SGA) and those with conditions that can affect growth such as Turner syndrome (TS), chronic renal insufficiency (CRI) and Prader–Willi syndrome (PWS) [4]. Omnitrope® is also approved for the treatment of patients with idiopathic short stature (ISS) in the USA, Canada, and Brazil. Pivotal phase III clinical trials demonstrated that Omnitrope® is safe and efficacious for the treatment of GHD in infants, children, and adolescents [5, 6].

The PAtients TReated with Omnitrope® (PATRO) Children post-marketing surveillance study was initiated to complement the phase III clinical trial data as part of an EMA post-approval Risk Management Plan. The PATRO Children is an ongoing international, multicenter, longitudinal,

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non-interventional study that is investigating the long-term safety and efficacy of Omnitrope® in children with growth disturbances [7]. As of August 2017, 5797 patients have been recruited from 297 sites across 14 different countries (Austria, Canada, Czech Republic, France, Germany, Italy, Poland, Romania, Slovenia, Spain, Sweden, Taiwan, UK, USA) to participate in the study.

Interim 1-year results of all patients recruited up to September 2012 ($n = 1837$) have previously been reported [7], with annual updates presented at international meetings [8, 9]. In addition, a snapshot analysis of patients enrolled at Italian sites since the beginning of the study up to August 2015 has previously been published [10]. Herein we report the results of a second snapshot analysis of patients ($n = 291$) in the PATRO Children study recruited at 19 Italian sites up to August 2017.

Methods

Study design

The design of the PATRO Children study has been previously published in detail [7]. Briefly, PATRO Children was a multicenter, open-label, longitudinal post-marketing surveillance study conducted at 297 children's hospitals and specialist endocrinology clinics in 15 countries where Omnitrope® is available. Nineteen centers in Italy participated. Patients eligible for PATRO Children were infants, children, and adolescents receiving treatment with Omnitrope® for any diagnosis. Both hormone treatment-naïve patients and patients who had previously been treated with another rhGH product before starting Omnitrope® were eligible for inclusion. All patients were required to provide written informed consent (or have consent provided by a parent or legal guardian). The study was reviewed and approved by each study site's Independent Ethics Committee/Institutional Review Board, and was conducted in accordance with the Oviedo Human Rights Convention and the Declaration of Helsinki.

Treatment and outcomes

Patients participating in the PATRO Children study received Omnitrope® treatment in accordance with the recommendations in the European Medicines Agency Summary of Product Characteristics [4] and/or the prescribing information of the respective countries.

The primary objective of the study was to assess the long-term safety of Omnitrope® in infants, children, and adolescents treated in routine clinical practice, including in patients with PWS. All adverse events (AEs) and serious AEs (SAEs) were recorded irrespective of causality. AEs of special interest were the development of diabetes or malignancies. The development and clinical implications of antibodies to rhGH were also investigated.

A secondary objective of the study was to assess the long-term effectiveness of Omnitrope® treatment. Height measurements were used to determine height standard deviation scores (HSDS) and height velocity standard deviation scores (HVSDS) [11, 12].

Data collection and verification

Data were collected at each routine visit during treatment with Omnitrope®, with the frequency of visits determined at the discretion of the treating physician. No additional visits were scheduled as part of the protocol. Patient data were recorded and entered into an electronic case report form (eCRF) at least once a year during the study, along with any other available clinical information (e.g., findings from examinations [pubertal stage, bone age, vital signs, body composition, and body mass index (BMI)], concomitant medications, AEs). Laboratory tests performed at baseline were hematology, blood chemistry, glucose metabolism parameters [including oral glucose tolerance test (OGTT)], fasting lipid profile, urinalysis, hormones (thyroid, gonadal and adrenal), levels of insulin-like growth factor 3 (IGF-3) and insulin-like growth factor-binding protein 3 (IGFBP-3), and anti-rHGH antibodies. Laboratory tests conducted at subsequent visits were those performed as part of routine clinical practice.

All eCRFs were entered into a centralized web-based electronic data collection system, and were monitored by a contract research organization (CRO). The system includes automatic plausibility checks such that any entered data point that is outside the expected range generates an automatic query. Complete data cleaning will be performed by the CRO on completion of the study.

Statistical analysis

Statistical calculations in this analysis were performed using the software package SAS version 9.3 as described previously [10]. The statistical parameters calculated for continuous/quantitative variables were descriptive and included the number of data values available, the number of data values missing, arithmetic mean, standard deviation, minimum, median, and maximum. The incidence of AEs was calculated per patient-year, where a patient-year was defined as the total sum of the number of years that each child has been under observation in this study and calculated as follows: (date of last documented visit − baseline date)/365.25. Because this post-marketing surveillance is ongoing, any data used in this snapshot analysis were not fully cleaned,

although data quality was checked by plausibility checks and online queries on an ongoing basis.

Results

The majority (95.5%) of patients in this analysis were naïve to hormone therapy at enrolment, with Omnitrope® prescribed as their first therapy. As of August 2017, 291 patients (mean age 10.0 years, 56.0% male) had been enrolled at 19 sites in Italy (Table 1) and had received Omnitrope® treatment for a mean duration of 33.1 ± 21.7 months (2.8 ± 1.8 years). Mean age at diagnosis was 9.4 ± 3.5 years and mean age at the start of treatment was 10.0 ± 3.3 years.

Treatment was discontinued in 140 of the 291 patients (48.1%) at the time of the analysis. Reasons for discontinuation listed in the eCRFs included patient reached final height/bone age maturation ($n = 46$; 32.9% of patients); switch to other growth hormone product ($n = 21$; 15.0%); lost to follow-up ($n = 19$; 13.6%); reached near final height ($n = 7$; 5.0%); non-responder ($n = 4$; 2.9%); AE ($n = 3$; 2.1%); patient non-compliance ($n = 2$; 1.4%); a slowdown of height velocity (patients grew < 1 cm/year; $n = 1$; 0.7%); patient satisfied with height ($n = 1$; 0.7%); patient did not wish to continue the injections ($n = 1$; 0.7%); referral to adult endocrinologist ($n = 1$; 0.7%); other reason ($n = 34$; 24.3%). Among the patients who discontinued because of AEs, only one event was considered related to Omnitrope® (described below).

Safety

Up until August 2017, 344 AEs occurred in 138 (47.4%) of the 291 patients in the Italian safety analysis set over a mean treatment duration of 33.1 ± 21.7 months. There were 48 AEs with a suspected relationship to the study drug (as reported by the investigators), occurring in 35 (12.0%) patients. Of these, 43 AEs ($n = 31$; 10.7%) were mild and 5 AEs ($n = 4$; 1.4%) were moderate in intensity. Complete resolution was reported for 34 AEs ($n = 25$; 8.6%), while 1 AE [obstructive apnea ($n = 1$); 0.3%] resolved with sequelae after treatment interruption and 13 AEs ($n = 12$; 4.1%) were ongoing at the time of analysis. As a result of drug-related AEs, the dose of Omnitrope® was increased in two patients (0.7%), one who had received a lower-than-prescribed dose and one with hyperinsulinism, and reduced in six patients (2.1%), four with elevated levels of insulin-like growth factor-1 (IGF-1), one with hyperglycemia, and one with both elevated IGF-1 and insulin resistance. All but one of these AEs had resolved completely by the time of reporting; one 14-year-old girl had ongoing high IGF-1 (in the 97th percentile for age and sex). Omnitrope® treatment was interrupted due to AEs in nine patients (3.1%) and permanently discontinued in one patient (0.3%). Reasons for treatment interruption were elevated levels of IGF-1 ($n = 3$), headache ($n = 1$), gait disorder ($n = 1$), minimal regrowth of a craniopharyngioma ($n = 1$), abnormal glucose ($n = 1$), asthenia ($n = 1$), and obstructive apnea ($n = 1$). All but the latter resolved completely after treatment interruption. The patient who permanently discontinued Omnitrope® was an 11-year-old female with TS who developed an elevated IGF-1 level

Table 1 Baseline characteristics and demographics of patients enrolled at sites in Italy in the PATRO Children study as of August 2017

Characteristic	$N = 291$
Gender, *n* (%)	
Male	163 (56.0)
Female	128 (44.0)
Chronological age at the start of treatment, years	10.0 ± 3.25
Pubertal status, *n* (%)	
Prepubertal	225 (77.3)
Pubertal	66 (22.7)
HSDS	− 2.40 ± 0.74 ($N_{miss} = 35$)
Height velocity, cm/year	3.6 ± 1.6 ($N_{miss} = 143$)
BMI, kg/m^2	16.8 ± 3.2 ($N_{miss} = 40$)
Age at diagnosis, years	9.4 ± 3.5
Diagnosis at presentation, *n* (%)	
Growth hormone deficiency	245 (84.2)
Isolated	232
Combined	9
Neurosecretory dysfunction	3 ($N_{miss} = 1$)
Small for gestational age	18 (6.2)
Prader–Willi syndrome	7 (2.4)
Idiopathic short stature	7 (2.4)
Turner Syndrome	3 (1.0)
Chronic renal insufficiency	1 (0.3)
Other	10 (3.4)
Growth hormone deficiency etiology, *n*	
Unknown	222
Malformation	9
Other	8
Brain tumor	3 ($N_{miss} = 2$)
Previous treatment status, *n* (%)	
Treatment-naïve	278 (95.5)
Pre-treated	13 (4.5)
Omnitrope® dosing at baseline, mg/kg/day	0.031 ± 0.005 ($N_{miss} = 95$)

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

BMI body mass index, HSDS Height Standard Deviation Scores, N_{miss} number of patients with data missing

(722.5 ng/mL) after 4.25 years of treatment. The elevated IGF-1 level resolved after treatment discontinuation.

The most common AEs reported (incidence > 10 over 822.0 patient-years) were headache (25 patients; 8.6%), pyrexia (13 patients; 4.5%), arthralgia (11 patients; 3.8%), IGF-1 level above normal range (10 patients; 3.4%), abdominal pain (9 patients; 3.1%), pain in extremity (9 patients; 3.1%) and acute gastroenteritis (9 patients; 3.1%) (Table 2). Of the ten patients who had higher than normal levels of IGF-1, only one had another AE (headache).

Headache was reported as an AE 31 times in 25 patients (16 females and 9 males). All headaches were either mild (26 headaches) or moderate (5 headaches) in severity. Only three headaches (two mild and one moderate) were suspected to be related to Omnitrope®. Two patients with headache had Omnitrope® interrupted, but in only one of these cases (a moderate headache) was Omnitrope® suspected to be the cause of the headache. In all other patients, Omnitrope® was continued without change.

A total of 35 SAEs were reported in 21 (7.2%) patients. Among these, two SAEs in two patients were suspected of being related to Omnitrope® treatment, and included one patient with gait disturbance and a worsening of walking difficulties and one patient with a minimal increase in a known residual craniopharyngioma [10]. However, it is possible that the regrowth of the craniopharyngioma was spontaneous and unrelated to treatment since a high proportion (3–50%) of craniopharyngiomas recur some time after partial removal. The patient with craniopharyngioma was a 19-year-old male who had been receiving Omnitrope® treatment at 0.005 mg/kg/day for 5 months. Omnitrope® treatment was interrupted for safety reasons and then restarted 4 months later; there was no increase in the size of the craniopharyngioma after restarting Omnitrope®. The patient with gait difficulties was an 8-year-old boy with isolated GHD and a history of psychomotor delay, epilepsy, and hypothyroidism. After 5 months of treatment with Omnitrope® (dose 0.032 mg/kg/day), his walking difficulties worsened. Treatment was interrupted and the gait disturbance resolved, but investigators considered that it was not possible to assess the relationship with Omnitrope®. Both of these SAEs developed within the first 2 years of Omnitrope® treatment, and have been reported previously [10]. No new SAEs were reported and the incidence of each of these SAEs was 1.2 per 1000 patient-years.

To date, there have been no confirmed cases of type 1 or type 2 diabetes with Omnitrope® treatment among patients in the Italian safety analysis set although risk factors for diabetes have been reported as drug-related AEs (Table 2); in this analysis, one case of hyperglycemia suspected of being drug related was reported. In addition, two patients (0.7%) had impaired glucose tolerance; BMI information was available for one of them (aged 13.4 years) and was 24.97 kg/m^2 (1.67 SDS, 97th percentile according to World Health Organization charts). Both patients had isolated GHD of unknown etiology and were treatment naïve. In both patients, impaired glucose tolerance was considered related to Omnitrope®. Impaired glucose tolerance did not lead to changes in Omnitrope® treatment and patients received treatment for 37 and 45 months, respectively, before discontinuing because the center closed or they had reached their final height/bone age.

Scoliosis was reported in three patients (1.0%, 3.65 per 1000 patient-years), all of whom were treatment naïve at the time of starting Omnitrope®. Mild scoliosis was reported in one patient with GHD 7–12 months after the start of GH therapy and in one patient with ISS during the fourth year of GH therapy. Moderate scoliosis was reported in one patient with PWS during the second year of GH therapy. In the patient with ISS, scoliosis was considered serious. Scoliosis was not considered to be related to Omnitrope® in any of these patients.

Efficacy

Omnitrope® treatment was associated with increases in both HSDS and HVSDS; this was consistent with

Table 2 Most common drug-related AEs and AEs of interest in the Italian safety analysis set ($n = 291$)

Adverse events[a]	Patients, *n* (%)	Incidence (patient-years[b] = 822.0)
Insulin-like growth factor above normal range	10 (3.4)	12.17
Insulin above normal range	5 (1.7)	6.08
Blood creatine phosphokinase increased	4 (1.4)	4.87
Scoliosis	3 (1.0)	3.65
Impaired glucose tolerance	2 (0.7)	2.43
Headache	2 (0.7)	2.43

[a]Preferred term/MedDRA dictionary

[b]Until cut-off date

previously reported sub-analyses of the PATRO Children study [7, 9, 10].

The mean HSDS increased from a baseline value of − 2.41 ± 0.73 (n = 238) to − 1.30 ± 0.94 at 4 years (n = 53) and to − 0.91 ± 0.68 at 6.5 years (n = 10) (Fig. 1). Mean HVSDS increased from a baseline value of − 1.77 ± 1.38 (n = 136) to a peak mean of 2.43 ± 2.31 at 0.5 years (n = 229) and stabilized to 1.00 ± 1.69 at 4.0 years (n = 53) and 0.96 ± 1.13 at 6.5 years (n = 10) (Fig. 2). HSDS and HVSDS appeared to increase from 6.5 to 8.5 years of treatment; however, as the number of Italian patients over this time was low (< 10 patients), no formal analysis was conducted.

Pre-pubertal treatment-naïve patients with GHD (from − 2.49 ± 0.73 to − 1.92 ± 0.70) and SGA (from − 3.02 ± 0.39 to − 2.54 ± 0.39) had the largest increase in HSDS at 12 months compared with the overall population of patients who received pre-treatment [from − 1.67 ± 0.83 to − 1.36 ± 0.74 (GHD) and from − 2.64 ± 0.27 to − 2.23 ± 0.27 (SGA), respectively] and the overall population of treatment-naïve patients [from − 2.43 ± 0.69 to − 1.90 ± 0.68 (GHD) and from − 3.02 ± 0.39 to − 2.64 ± 0.46 (SGA); Fig. 3a].

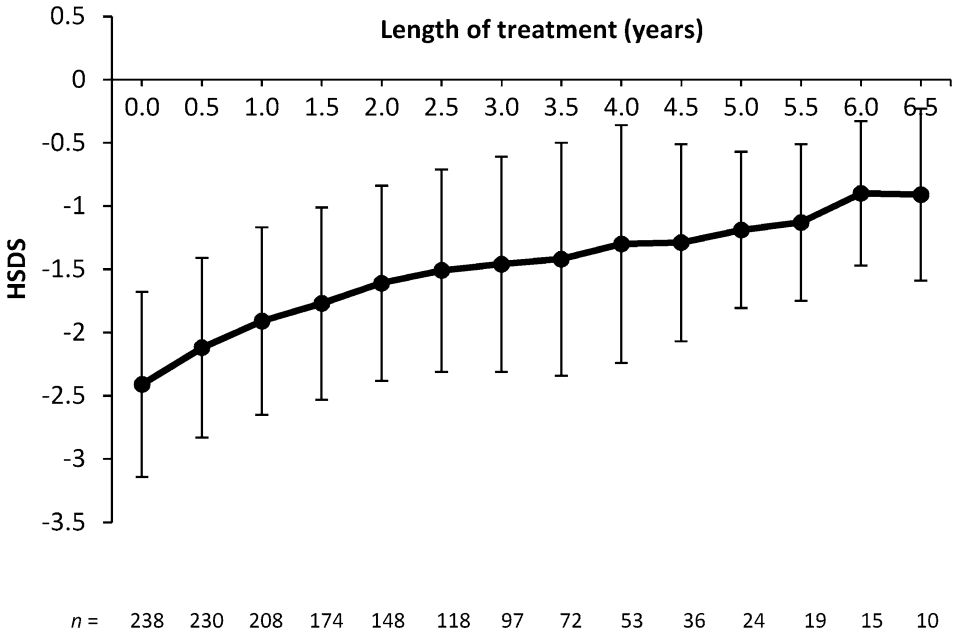


Fig. 1 Change in Height Standard Deviation Scores (HSDS) in the Italian total efficacy analysis set (n = 238) over 6.5 years of the study duration

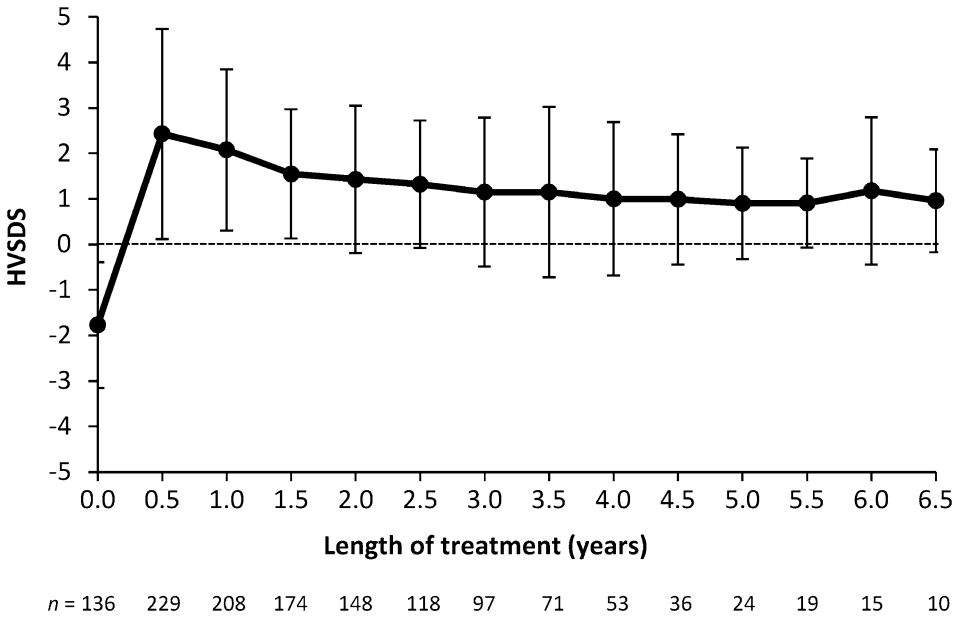


Fig. 2 Change in Height Velocity Standard Deviation Scores (HVSDS) in the Italian total efficacy analysis set over 6.5 years of the study duration

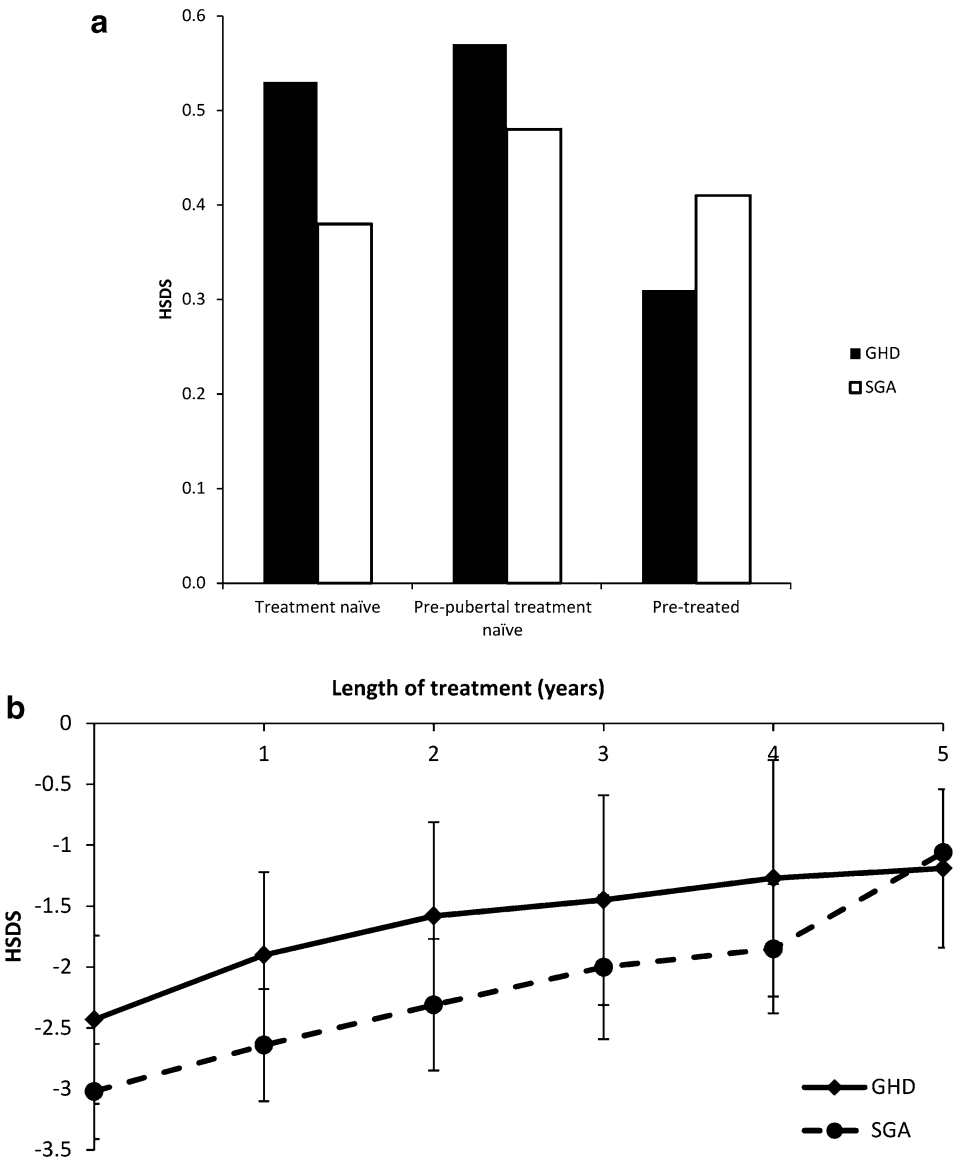


Fig. 3 Change in Height Standard Deviation Scores (HSDS) in **a** Italian patients with growth hormone deficiency (GHD) and patients that were small for gestational age (SGA) at 12 months and **b** treatment-naïve Italian patients with GHD and SGA

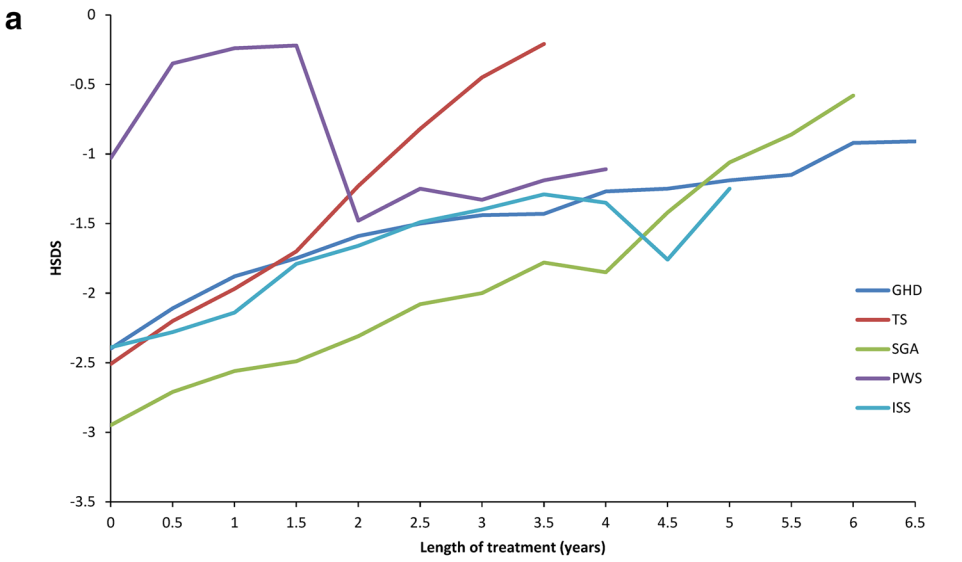
For treatment-naïve patients, the mean HSDS increased from a baseline of − 2.43 ± 0.69 (GHD) and − 3.02 ± 0.39 (SGA) to − 1.19 ± 0.65 (GHD) and − 1.06 (SGA) in 5 years (Fig. 3b).

HSDS and HVSDS by indication are presented in Fig. 4a, b, respectively. At 3.0 years, patients with TS had the highest HSDS and HVSDS; however, no further data for patients with this indication are available. At 6.0 years, patients with SGA had higher HSDS and HVSDS compared with patients who had GHD [− 0.92 ± 0.59 vs − 0.58 (SD not available) and 1.09 ± 1.65 vs 2.36 (SD not available), respectively].

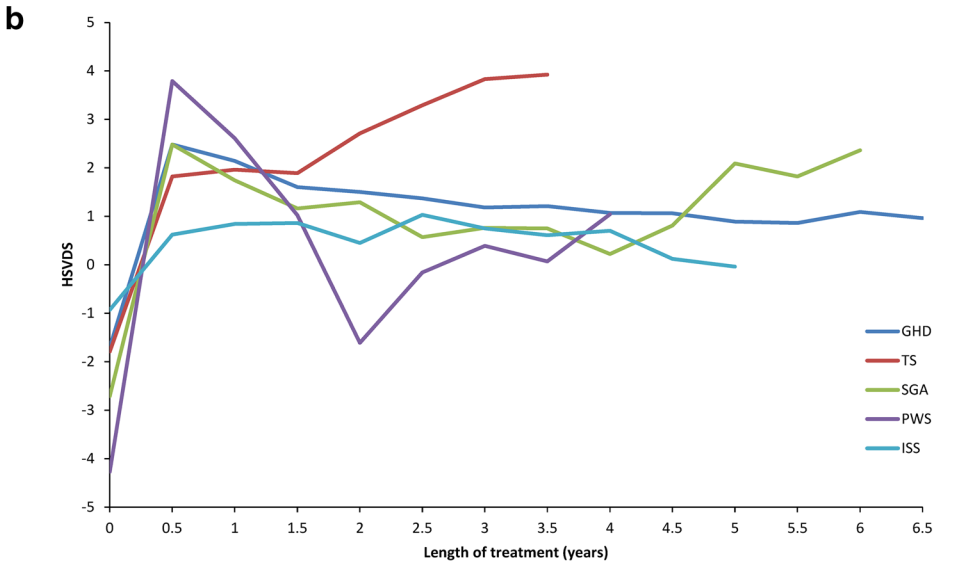
HSDS and HVSDS by sex are presented in Fig. 5a, b, respectively. HSDS was lower in males than in females at 3.0 years (− 1.48 ± 0.97 vs − 1.43 ± 0.68) and 6.0 years (− 0.95 ± 0.66 vs − 0.85 ± 0.52), but HVSDS was higher in males than in females at 3.0 years (1.19 ± 1.84 vs 1.11 ± 1.39) and 6.0 years (1.44 ± 1.25 vs 0.94 ± 1.95).

Discussion

The results of this analysis support and extend the findings of an earlier sub-analysis in Italian patients in the PATRO Children study [10] and provide further evidence that Omnitrope® treatment is effective and well tolerated over the longer term, with no new safety concerns becoming apparent during treatment for up to 8.5 years. Of note, no new SAEs suspected to be related to Omnitrope® treatment were reported in the 2-year period between the first and second snapshot analyses. In addition, the findings in the Italian subgroup are generally consistent with those reported for



	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5
GHD n=	213	207	185	156	135	106	85	61	45	32	22	18	14	10
TS n=	2	2	2	2	1	1	1	1						
SGA n=	12	11	11	9	6	5	5	4	3	2	1	1	1	
PWS n=	4	3	3	3	2	2	2	2	2					
ISS n=	7	7	7	4	4	4	4	4	3	2	1			

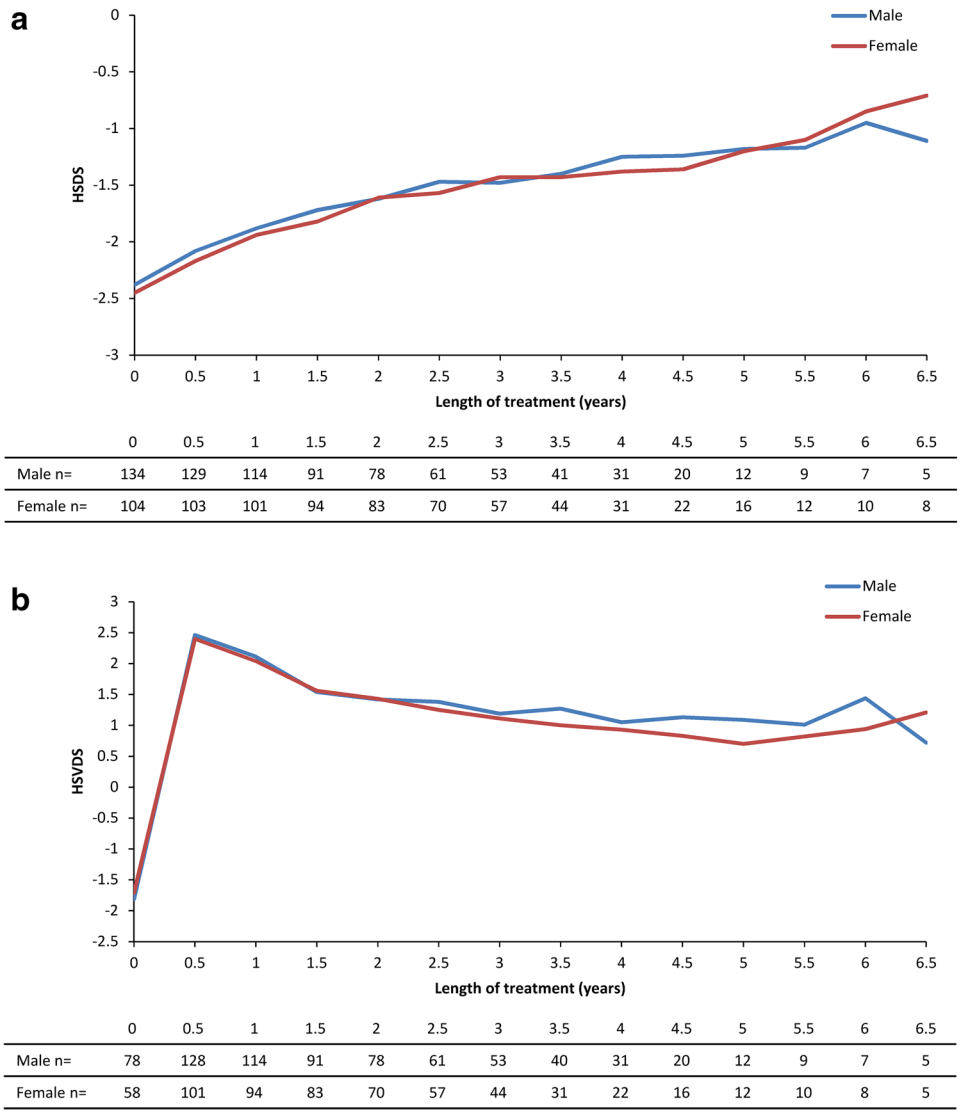


	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5
GHD n=	120	206	185	156	135	106	85	60	45	32	22	18	14	10
TS n=	1	2	2	2	1	1	1	1						
SGA n=	8	11	11	9	6	5	5	4	3	2	1	1	1	
PWS n=	2	3	3	3	2	2	2	2	2					
ISS n=	5	7	7	4	4	4	4	4	3	2	1			

Fig. 4 Effectiveness outcomes by indication. **a** Height Standard Deviation Scores (HSDS) and **b** height velocity standard deviation scores (HVSDS)

the full (global) study population [7–9]. Similarly, safety findings from this sub-analysis were also consistent with published data for Genotropin®, in which the rate of total AEs per patient-year was 0.849 [6].

Given concerns about a potential link between rhGH treatment and the development of diabetes [13], the PATRO Children study objectives included a particular focus on investigating the diabetogenic potential of Omnitrope® [7].



	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5
Male n=	134	129	114	91	78	61	53	41	31	20	12	9	7	5
Female n=	104	103	101	94	83	70	57	44	31	22	16	12	10	8

	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5
Male n=	78	128	114	91	78	61	53	40	31	20	12	9	7	5
Female n=	58	101	94	83	70	57	44	31	22	16	12	10	8	5

Fig. 5 Effectiveness outcomes by sex. **a** Height Standard Deviation Scores (HSDS) and **b** Height Velocity Standard Deviation Scores (HVSDS)

There have been no confirmed cases of type 1 or type 2 diabetes with Omnitrope® treatment among patients in the Italian safety analysis set, and just one adverse drug reaction of diabetes reported to date in the full study population ($n > 5000$) [9].

The investigation of the occurrences of malignancies in Omnitrope®-treated patients was also a key objective of the PATRO Children study [7]. The current analysis, together with the global data [9], showed no evidence of an increased risk of malignancies associated with Omnitrope® treatment.

Treatment with rhGH may be associated with musculoskeletal AEs. In the present study, scoliosis was reported in three patients and was considered serious in one. This patient had ISS. Scoliosis is reported in approximately 0.2% of patients with GHD and occurs as a result of rapid growth and not as a direct effect of GH therapy [3]. Gait disturbance was reported in one patient in the present study (incidence 1.2 per 1000 patient-years). This AE was considered serious and related to Omnitrope® therapy. In patients with GHD, the incidence of slipped capital femoral epiphysis has been reported to be 73 per 100,000 patient-years [3].

The efficacy data of the current analysis support previous results showing a positive effect of Omnitrope® treatment on HSDS and HVSDS in pediatric Italian patients with growth hormone disorders, confirming outcomes of previous phase 3 studies [5, 6]. The efficacy of Omnitrope® was also shown to be similar to its reference medicine, Genotropin®. This was consistent with the published literature, which found Omnitrope® and Genotropin® were bioequivalent in their efficacy, pharmacokinetics, and pharmacodynamics [14, 15].

Interestingly, analysis of the Kabi Pharmacia International Growth Study (KIGS) database found that age at rhGH treatment start is inversely correlated with the growth response [16]. In the present analysis, the mean age of patients at baseline was 10.0 ± 3.25 years (10.5 years for males, and 9.3 years for females) and patients were generally

older at enrolment for every indication; in the global study population, the mean age was 9.1 years [9]. However, treatment-naïve patients had a mean age (9.5 years) that was closer to the age of patients in the global study. Furthermore, treatment-naïve patients who initiated treatment before the onset of puberty had a greater response in HSDS increase for both GHD and SGA indications, compared with older treatment-naïve patients. Given the importance of initiating rhGH treatment before pubertal onset [16], the potential to achieve greater benefit by starting treatment earlier should be considered.

As expected, hormone treatment-naïve patients had a lower baseline HSDS (-2.43 ± 0.69 for GHD and -3.02 ± 0.39 for SGA), compared with the total Italian population (-2.41 ± 0.73). However, growth responses followed a similar trend for both populations.

There were some differences between the demographic and disease characteristics of the patients in the full analysis of the PATRO Children study and the present analysis of Italian patients. In the global study population, 57.0% of enrolled patients had GHD and 45.5% of the patients were born SGA [9]. In the present analysis, 84.2% of patients had GHD and 6.2% of patients were born SGA. This may be an indication of different diagnosis and/or treatment protocols in Italian children compared with other countries [10].

While the results of this current analysis are supportive of the long-term interventional trials of Omnitrope®, there are some limitations to the interpretation of these findings. As mentioned above, the patients included in this analysis were predominantly diagnosed as having GHD, and this sample is not representative of all the different indications of rhGH treatment. Furthermore, the observational study design and the interim nature of this analysis can only provide a snapshot of treatment in these patients, and ongoing data from the study are required to confirm our results. The discontinuation rate in the study was high, as expected for a pediatric population who may discontinue rhGH treatment on reaching final height or bone age. The mean age of patients at the start of treatment is consistent with these results and explains the small number of patients with 6.5 years of continuous treatment. Finally, the data in this snapshot analysis have not been fully cleaned, although we can be confident in the quality based on the plausibility checks and online queries undertaken regularly throughout the data collection process. However, this study retains the advantage of reflecting real-world clinical practice in Italy in this context.

Conclusions

The results from the longitudinal post-marketing surveillance study of Omnitrope® were consistent with those observed in controlled clinical trials. The reported analysis supports and extends earlier findings of the PATRO Children study and provides further evidence that Omnitrope® is safe, well tolerated, and effective in the treatment of a range of pediatric growth disorders.

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Author contributions LP, LP, and NAG enrolled patients, and read and approved the manuscript drafts. SZ and LI contributed to study design, enrolled patients, and critically revised the manuscript.FA, GB, TA, LG, RM, GP, LR, SS, GT, PG, HZ, PF, and CZ contributed to the drafting of the manuscript, critically revised the various drafts of the manuscript, read and approved the final version before submission. CG enrolled patients, critically revised the various drafts of the manuscript, and read and approved the final version before submission.

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Data availability The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request**.**

Compliance with ethical standards

Conflict of interest LI has participated in Advisory Boards for Eli Lilly, Italy and Novo Nordisk, Italy; FA has received honoraria from Eli Lilly, Novo Nordisk and Ipsen and research funding from Merck Serono; CG, TA, NAG, LG, RM, L Perrone, LR, SS, and GT have no conflict of interest to declare; L Persani has been an invited speaker for Sandoz and Merck-Serono, and has received unconditional research funds from Novartis, IBSA and Merck-Serono; GB has received honoraria from Ferring, Novo, Serono, Lilly, Sandoz; CZ has received honoraria from Sandoz, Novo, Medtronic; HZ is an employee of Sandoz Biopharmaceutical c/o HEXAL AG, Germany; PG and PF are employees of Sandoz S.p.A, Milan, Italy; SZ has been a member of expert committees for Eli Lilly Diabetes, Italy, and Roche Diagnostics.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Comitato Etico Indipendente dell'Azienda Ospedaliero-Universitaria di Bologna, Policlinico S. Orsola-Malpighi, n°120/2007/O/Oss) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the parents or legal guardians of all individual participants included in the study.

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