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PATRO children, a multi-center, non-interventional study of the safety and effectiveness of Omnitrope® (somatropin) treatment in children: update on the United States cohort

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Abstract

Objectives: Omnitrope® (somatropin, Sandoz Inc.) is one of several recombinant human growth hormones (rhGH) approved in the United States (US) for use in pediatric indications, including growth hormone deficiency (GHD) and idiopathic short stature (ISS). We report data on the effectiveness and safety of Omnitrope® in the US cohort of the PATRO Children (international, longitudinal, non-interventional) study.

Methods: All visits and assessments are carried out according to routine clinical practice, and doses of Omnitrope® are given according to country-specific prescribing information.

Results: By September 2018, 294 US patients were recruited; the two largest groups were GHD (n=193) and ISS (n=62). Across all indications, HSDS improvement (Δ HSDS) from baseline at three years was +1.0 (rhGH-naïve, +1.2; pre-treated, +0.7). In pre-pubertal patients, Δ HSDS from baseline at three years was +0.94 (rhGH-naïve, +1.3; pre-treated, +0.7). Following three years of treatment, Δ HSDS from baseline was +1.3 in rhGH-naïve GHD patients and +1.1

in rhGH-naïve ISS patients. In pre-pubertal rhGH-naïve patients, Δ HSDS from baseline was +1.3 and +1.2 in GHD and ISS patients, respectively. Overall, 194 patients (66.0%) experienced adverse events (AEs; n=886 events); most were of mild-moderate intensity. Five patients (1.7%) had AEs that were suspected to be treatment-related (n=5 events). All reported neoplasms were benign, non-serious, and considered unrelated to rhGH therapy. No AEs of diabetes mellitus or hyperglycemia were reported.

Conclusions: Omnitrope® appears to be well tolerated and effective in the majority of patients, without evidence of an increased risk of developing unexpected AEs, diabetes mellitus, or new malignancies during treatment.

Keywords: growth hormone; growth hormone deficiency; idiopathic short stature; Omnitrope®; pediatrics.

Introduction

Omnitrope® (somatropin, Sandoz Inc.) is a recombinant human growth hormone (rhGH) approved by the United States Food and Drug Administration (US FDA) in 2006. A rhGH was first approved in 1985 to treat children with growth failure caused by inadequate secretion of endogenous growth hormone (growth hormone deficiency; GHD) [1, 2]. rhGH therapy was subsequently approved in the US for use in various other pediatric indications, including Turner syndrome (TS) in 1996, Prader–Willi syndrome (PWS) in 2000, children born small for gestational age (SGA) in 2001, and children with idiopathic short stature (ISS) in 2003 [2]. TS, SGA, and ISS are not characterized by a deficiency in endogenous GH; nevertheless, rhGH treatment has been shown to improve linear growth and adult height in patients with these conditions [3].

Although rhGH has been used for many years to treat growth disorders in children, some concerns have been raised about its safety, particularly in relation to its

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diabetogenic risk and potential cancer-causing effects (both *de novo* and recurrent malignancy) [4]. The PATRO Children study is a post-marketing surveillance program for Omnitrope[®], which began in 2006 [5]. We report effectiveness and safety results from an analysis (September 2018) of patients enrolled in the PATRO Children study in the US.

Materials and methods

Study design and patient population

PATRO Children is an international, longitudinal, non-interventional study conducted in hospitals and specialized endocrinology clinics across 14 different countries (Germany, France, Romania, Italy, USA, UK, Czech Republic, Sweden, Canada, Spain, Poland, Austria, Taiwan, and Slovenia). The study design has been reported in detail elsewhere [5]. Briefly, infants, children, and adolescents who require rhGH treatment and receive at least one dose of Omnitrope[®] are eligible for enrollment. All diagnoses were made by treating physicians (investigators); no diagnostic criteria were specified in the protocol. Patients previously treated with another rhGH medicine before switching to Omnitrope[®] are also eligible for inclusion. All visits and assessments are carried out according to routine clinical practice, and doses of Omnitrope[®] are given according to country-specific prescribing information. In the US, the recommended Omnitrope[®] dose is 0.16–0.24 mg/kg/week (divided into six to seven daily injections) for GHD patients. The corresponding weekly doses (also divided into six to seven daily injections) for patients with PWS, TS, ISS, and patients born SGA are 0.24 mg/kg, 0.33 mg/kg, up to 0.47 mg/kg, and up to 0.48 mg/kg, respectively [1].

The PATRO Children study protocol was approved by the ethics review committee of participating centers in accordance with national laws and regulations. The study was conducted according to the ethical principles of the Declaration of Helsinki (1964) and its later amendments. All patients (and/or their parents/guardians) provide written informed consent. Patients are permitted to withdraw their informed consent at any time or discontinue Omnitrope[®] treatment for any reason.

Safety and effectiveness assessments

Auxological data are recorded at each visit, including height velocity (HV, cm/year), height standard deviation score (HSDS), HVSDS, and body mass index (BMI) SDS, and are derived from height and weight measurements and country-specific reference tables [6, 7].

All adverse events (AEs) are monitored and recorded for the complete duration of Omnitrope[®] treatment. Particular emphasis is placed on new onset or reoccurrence of malignancies, and the development of glucose intolerance or diabetes mellitus. The relationship between AEs and Omnitrope[®] treatment is independently evaluated by investigator and sponsor, and classified according to the worse case. Reasons for treatment discontinuation are also recorded.

Laboratory values (including glucose metabolism testing) are measured at least once a year. Circulating insulin-like growth factor

(IGF)-I is obtained according to routine clinical practice and measured locally at each participating center.

Data collection and statistical analysis

Patient data are entered into an electronic case report form (eCRF) at each visit. The eCRFs are reviewed by data management and on-site monitoring is performed by a contract research organization to ensure data quality.

The safety population includes all patients enrolled before the analysis cut-off date (September 2018). Patients without a recorded visit date or Omnitrope[®] treatment start date are excluded from the safety population. The effectiveness population is a subset of the safety population and includes all patients with a documented height measurement at the start of Omnitrope[®] treatment (baseline) and at least one height measurement during Omnitrope[®] treatment (at least 60 days after baseline). The three-year analysis population comprises patients who have completed at least three years of Omnitrope[®] therapy.

Standard descriptive statistics (mean, standard deviation [SD], and frequency) are used to describe continuous parameters (e.g. age, height, weight) and categorical parameters (e.g. gender).

Results

Patients and treatment

As of September 2018, 294 patients had been recruited from 14 sites in the US and included in the safety population. The two largest groups in the US cohort were GHD (n=193; n=181 with isolated GHD, n=9 with multiple pituitary hormone deficiencies, n=3 other/missing) and ISS (n=62) (Table 1). Baseline characteristics for the overall population, GHD patients, and ISS patients are shown in Table 2. In the overall cohort, the mean ($\pm$ SD) age at enrollment was 10.44 ± 3.64 years and 72.8% of patients were male. Overall, 53.1% of patients were naïve to rhGH upon entry into the study.

The mean (SD) treatment duration of Omnitrope[®] was 40.24 (17.39) months (approx. 3.4 years). In total, 177 patients (60.2%) in the safety population completed at least three years of treatment and were included in the three year analysis cohort, including 117 GHD patients and 36 ISS patients.

In the entire US cohort, the mean (SD) prescribed Omnitrope[®] dose was 0.047 (0.014) mg/kg/day at baseline, and 0.054 (0.029) mg/kg/day at three years. In patients with GHD, the mean (SD) dose was 0.047 (0.014) mg/kg/day at baseline and 0.055 (0.033) mg/kg/day at three years. In rhGH-naïve patients with GHD, the corresponding doses were 0.045 (0.008) mg/kg/day at baseline and 0.059 (0.042) mg/kg/day at three years. In patients with ISS, the

Table 1: Recruitment per indication (safety population).

Indication	Patients	
	n	%
GHD	193	65.6
Isolated	181	61.6
Multiple pituitary hormone deficiency	9	3.1
Other/missing	3	1.0
SGA	8	2.7
TS	9	3.1
PWS	2	0.7
ISS	62	21.1
Other	20	6.8
Panhypopituitarism	3	1.0
Russell-Silver syndrome	3	1.0
Congenital adrenal hyperplasia	2	0.7
Idiopathic IGF-I deficiency	2	0.7
Neurosecretory GH insufficiency	2	0.7
Precocious puberty	2	0.7
SHOX gene deficiency	2	0.7
Abnormal pituitary	1	0.3
Hurler's syndrome	1	0.3
Noonan syndrome	1	0.3
Unclear ^a	1	0.3
Total	294	100.0

^aPatient seen for short stature; growth hormone stimulation test done at this visit. GH, growth hormone; GHD, growth hormone deficiency; IGF, insulin-like growth factor; ISS, idiopathic short stature; PWS, Prader-Willi syndrome; SGA, small for gestational age; TS, Turner syndrome.

mean (SD) Omnitrope[®] dose was 0.050 (0.017) mg/kg/day at baseline and 0.051 (0.014) mg/kg/day at three years. In rhGH-naïve ISS patients, the corresponding doses were 0.044 (0.005) mg/kg/day at baseline and 0.050 (0.012) mg/kg/day at three years.

Effectiveness

A total of 146 patients completed at least three years of treatment and were included in the three year analysis

cohort (effectiveness population). This included 107 GHD patients (n=54 rhGH-naïve) and 31 ISS patients (n=16 rhGH-naïve). Twenty-three GHD patients reached adult height (patients who discontinued treatment due to 'Patient reached final height/bone age maturation' or 'reached near-final height'). In this group, mean (SD) adult height SDS was -0.85 (1.17) across all patients, -1.10 (1.36) in the rhGH-naïve patients (n=14), and -0.47 (0.71) in the pre-treated patients (n=9).

Across all indications, HSDS improvement (Δ HSDS) from baseline at three years was +1.0 (rhGH naïve, +1.2; pre-treated, +0.7). In pre-pubertal patients, Δ HSDS from baseline at three years was +0.94 (rhGH naïve, +1.3; pre-treated, +0.7). Following three years of treatment, Δ HSDS from baseline was +1.3 in rhGH-naïve GHD patients and +1.1 in rhGH-naïve ISS patients (Figure 1A). In pre-pubertal rhGH-naïve patients, Δ HSDS from baseline was +1.3 and +1.2 in GHD and ISS patients, respectively (Figure 1B).

As summarized in Figure 2A, following three years of treatment, the improvement from baseline in mean HVSDS was +6.5 and +7.6 in rhGH-naïve GHD and ISS patients, respectively. Following three years of treatment, mean HVSDS improved from baseline by +5.7 and +6.7 in pre-pubertal rhGH-naïve GHD and ISS patients, respectively (Figure 2B).

Figure 3A, B shows the effect of Omnitrope[®] treatment on BMI SDS in GHD and ISS patients. Generally, BMI SDS remained stable over a three year treatment duration, except for a possible upward trend in pre-pubertal, pre-treated patients.

Safety

As of September 2018, 230 patients (78.2%) from the safety population had discontinued the study; primary reasons for discontinuation are found in Table 3. AEs were the primary reason for discontinuation in only three patients (1.3% of discontinued patients).

Table 2: Patient baseline characteristics (safety population).

Indication	Total, n	Male/female, %	Mean age, years (range)	Mean BMI SDS, SD	Mean HSDS, SD	Mean HV, cm/year, SD	Mean PC HVSDS, SD
All indications	294	72.8/27.2	10.44 (0.5–18.2)	-0.17 (1.18)	-1.62 (1.01)	4.62 (2.66)	-1.72 (3.26)
GHD Naïve	106	80.2/19.8	11.41 (1.0–16.8)	-0.27 (1.30)	-1.91 (0.75)	3.56 (2.56)	-3.26 (3.22)
Pre-treated	87	70.1/29.9	10.48 (1.1–18.2)	-0.16 (1.02)	-1.20 (1.12)	5.12 (2.26)	-0.91 (2.58)
ISS Naïve	32	75.0/25.0	9.85 (2.9–13.9)	-0.04 (1.30)	-2.16 (0.94)	2.78 (1.58)	-4.13 (2.61)
Pre-treated	30	73.3/26.7	10.27 (2.8–15.4)	-0.28 (0.78)	-1.58 (0.92)	5.59 (2.78)	-0.06 (3.98)

BMI, body mass index; GHD, growth hormone deficiency; HV, height velocity; ISS, idiopathic short stature; PC, peak-centered; SD(S), standard deviation (score).

A

	Time (months)							
	Baseline	3	6	12	18	24	30	36
Patients (n)								
GHD naïve	54	54	54	54	54	52	52	52
ISS naïve	16	16	16	16	16	16	15	15
GHD pre-treated	53	53	52	53	53	53	53	46
ISS pre-treated	15	15	15	15	15	15	15	15

B

	Time (months)							
	Baseline	3	6	12	18	24	30	36
Patients (n)								
GHD naïve	43	40	37	29	24	19	14	12
ISS naïve	11	11	11	11	11	7	7	7
GHD pre-treated	40	39	37	36	28	26	21	18
ISS pre-treated	13	13	11	10	10	9	8	5

Figure 1: (A) Height SDS for GHD patients and ISS patients over three years of Omnitrope® treatment (three year effectiveness population). (B) Height SDS for pre-pubertal GHD patients and ISS patients over three years of Omnitrope® treatment (three year effectiveness population). GHD, growth hormone deficiency; HSDS, height standard deviation score; ISS, idiopathic short stature; SD(S), standard deviation (score).

A summary of AEs is provided in Table 4. Overall, 194 patients (66.0%) experienced AEs (n=886 events), most of which were of mild or moderate intensity. Five patients (1.7%) had AEs that were suspected to be treatment-related (n=5 events). There were 14 patients (4.8%) who experienced serious AEs (SAEs; n=19 events). Pneumonia was the only SAE to occur in more than one patient (reported in

three patients). One patient (0.3%) had an SAE that was considered to be drug-related (MedDRA preferred term *kypnosis*); all other SAEs were deemed unrelated to rhGH therapy.

Neoplasms were recorded in the medical history of six patients (0.2%) as a past illness and as a current or chronic illness in five patients (1.7%). During rhGH therapy, a total

Figure 2: (A) Peak-centered height velocity SDS for GHD and ISS patients over three years of Omnitrope® treatment (three year effectiveness population). (B) Peak-centered height velocity SDS for pre-pubertal GHD and ISS patients over three years of Omnitrope® treatment (three year effectiveness population). GHD, growth hormone deficiency; HVSDS, height velocity standard deviation score; ISS, idiopathic short stature; SD(S), standard deviation (score).

of six patients (2.0%) reported neoplasms; melanocytic naevus (n=2 patients); adenoma (n=1 patient); fibroma (n=1 patient); osteochondroma (n=1 patient), and pituitary microadenoma (n=1 patient). All neoplasms reported during the study were benign, and considered non-serious and unrelated to rhGH therapy. Two neoplasms occurred in

patients who had previously received rhGH treatment (osteochondroma, one case of melanocytic naevus). rhGH treatment was changed (interrupted) in one case (osteochondroma). No patients had diabetes mellitus recorded in their medical history as a pre-existing condition. No AEs of diabetes mellitus or hyperglycemia were reported during

A

	Baseline	3	6	12	18	24	30	36
Patients (n)								
GHD naïve	54	52	53	53	50	49	48	51
ISS naïve	16	16	16	16	16	15	15	14
GHD pre-treated	53	50	50	52	51	51	52	43
ISS pre-treated	15	15	15	13	13	14	15	15

B

	Baseline	3	6	12	18	24	30	36
Patients (n)								
GHD naïve	43	39	36	28	22	17	13	12
ISS naïve	11	11	11	11	11	6	7	7
GHD pre-treated	40	37	35	36	28	25	21	16
ISS pre-treated	13	13	11	9	9	8	8	5

Figure 3: (A) BMI SDS for GHD and ISS patients over three years of Omnitrope® treatment (three-year effectiveness population). (B) BMI SDS for pre-pubertal GHD and ISS patients over three years of Omnitrope® treatment (three year effectiveness population). BMI, body mass index; GHD, growth hormone deficiency; ISS, idiopathic short stature; SD(S), standard deviation (score).

the study. Two patients developed impaired fasting glucose, with fasting glucose concentrations of 7.00 mmol/L (126 mg/dL) and 7.17 mmol/L (129 mg/dL) reported on a single occasion. Their hemoglobin A1c values were 5.3 and 5.4%, respectively, indicating that these patients most likely had GH-induced insulin resistance.

To date, no clinically relevant (growth attenuating) positive anti-hGH antibody titers have been detected after

the start of rhGH therapy, but only two patients in the US cohort had been tested as of September 2018.

The change in IGF-I over three years of rhGH treatment is shown in Figure 4A and Figure 4B for GHD and ISS patients, respectively. At each timepoint, a proportion of patients in the overall GHD and ISS groups had an IGF-I concentration that was above the normal reported range for the assay used (4.1–14.8% for GHD, 3.2–16.1% for ISS);

Table 3: Primary reasons for study discontinuation (safety population).

Reason	Patients	
	n	%
Patient reached adult height/bone age maturation	23	10.0
Reached near final height	9	3.9
Patient satisfied with current height	18	7.8
Switch to other rhGH medicine	63	27.4
Miscellaneous reasons ^a	64	27.8
Lost to follow-up	25	10.9
Patient stopped rhGH treatment as did not wish to continue the injections	17	7.4
Site closure	3	1.3
Investigator decision due to lack of response to therapy	3	1.3
Adverse event	3	1.3
Insurance reasons	2	0.9
Total	230	100.0

^aMiscellaneous reasons include patient non-adherence (n=1), referral to adult endocrinologist (n=1), unknown reason (n=1), and other reasons (n=61; n=45 where investigators stopped participating in the study).

however, a substantial proportion of patients had missing IGF-I data at each timepoint.

Discussion

Based on this analysis of the PATRO Children study, treatment with Omnitrope[®] is well tolerated and effective in the majority of pediatric patients from the US cohort. These findings are in line with data from the overall PATRO Children cohort [5, 8, 9], and also with results from other registries of rhGH therapy [10–14].

Concerns have previously been raised about the long-term safety of rhGH therapy in children. A potential link between rhGH treatment and premature death has been suggested, based on results from a retrospective evaluation of over 6,000 rhGH-treated patients with GHD, ISS, or born SGA [15]. An increased risk of mortality related to cardiovascular causes was observed in patients treated with doses of rhGH above 50 µg/kg/day (0.05 mg/kg/day) [15]. Following this initial report, an increased risk of stroke in rhGH-treated GHD, ISS, and SGA patients was also reported based on results from the same patient cohort [16]. However, subsequent reports, both from the same cohort (SAGhE) and other registries, did not corroborate these concerns [17–21]. In 2016, the European Society for Paediatric Endocrinology (ESPE), the Growth Hormone Research

Table 4: Summary of adverse events (safety population).

	All patients (n=294)	
	n ^a	%
Any AE	194	66.0
Relationship to study drug		
Not suspected	192	65.3
Suspected	5	1.7
Intensity		
Mild	145	49.3
Moderate	55	18.7
Severe	13	4.4
Missing	130	44.2
Changes to rhGH treatment		
Not changed	145	49.3
Increased	14	4.8
Reduced	6	2.0
Interrupted	11	3.7
Permanently discontinued	3	1.0
Missing	128	43.5
Treatment-related AEs, by MedDRA preferred term (intensity)		
Arthralgia (mild)	1	0.3
Heart rate increased (mild)	1	0.3
Kyphosis (severe)	1	0.3
Overdose (mild)	1	0.3
Swelling face (moderate)	1	0.3
SAEs		
No	191	65.0
Yes	14	4.8
SAE relationship to study drug		
Not suspected	13	4.4
Suspected	1	0.3
Treatment-related SAEs, by MedDRA preferred term		
Kyphosis	1	0.3
SAEs, by MedDRA preferred term		
Pneumonia	3	1.0
Appendicitis	1	0.3
Bronchitis	1	0.3
Mastoiditis	1	0.3
Respiratory tract infection	1	0.3
Tracheitis	1	0.3
Upper respiratory tract infection	1	0.3
Viral infection	1	0.3
Food poisoning	1	0.3
Hematochezia	1	0.3
Mallory–Weiss syndrome	1	0.3
Vomiting	1	0.3
Kyphosis	1	0.3
Synovitis	1	0.3
Arnold–Chiari malformation	1	0.3
Dehydration	1	0.3

^aAs patients can report multiple AEs, categories in this column are not mutually exclusive. AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; rhGH, recombinant growth hormone; SAE, serious adverse event.

Figure 4: IGF-I for (A) GHD and (B) ISS patients over three years of Omnitrope® treatment (safety population). GHD, growth hormone deficiency; IGF, insulin-like growth factor; ISS, idiopathic short stature; SD, standard deviation.

Society (GRS), and the Pediatric Endocrine Society (PES) published a joint position statement on the safety of rhGH treatment [22]. The group concluded that rhGH has a reliable safety record when used for approved indications and at recommended doses, but affirmed the importance of continued surveillance both during and after treatment. Most recently, mortality data based on long-term follow-up of the whole SAGhE cohort (n=24,232) has been reported [23]. All-cause mortality was shown to be associated with

underlying diagnosis and, in patients with isolated GHD and ISS, rhGH treatment was not associated with all-cause mortality. However, mortality from certain causes was increased, highlighting the need for continued surveillance [23]. Across the pediatric indications for rhGH treatment in the current analysis, there was no evidence of an increased risk of developing unexpected AEs, diabetes, or *de novo* malignancies. IGF-I concentrations above the reference range were reported in some children at certain times during rhGH treatment; however, this was not associated with AEs. This emphasizes the lack of evidence for a threshold IGF-I concentration above which AEs will occur [24]. It remains prudent, though, to target IGF-I concentrations in the normal range unless there is evidence of IGF-I resistance.

Our results demonstrate that rhGH therapy over three years improved linear growth, without any noticeable impact on BMI. As expected, greater growth improvements were observed in children who were rhGH-naïve at study entry. While the benefit of rhGH for improving height in children with GHD is well accepted, its use in children with ISS has not been universally adopted [23]. Guidelines from the PES suggest that the decision to treat ISS children with rhGH should be made on a case-by-case basis after assessment of physical and psychological burdens and risk/benefit consideration [23]. Our analysis indicates that rhGH therapy in patients with ISS, treated over three years in real-life clinical practice, increases both HVSDS and HSDS.

The PES guidelines recommend an initial dose of 0.022–0.035 mg/kg/day in GHD patients and 0.034–0.067 mg/kg/day in ISS patients [23]. In the current analysis, the mean baseline dose was 0.045 mg/kg/day in rhGH-naïve GHD patients and 0.044 mg/kg/day in rhGH-naïve ISS patients. These doses are consistent with previous studies in the US and reflect the range of doses approved by the US FDA for the treatment of children with GHD and ISS.

There were a small number of patients enrolled into the study with “other” indications, for example Russell-Silver syndrome (n=3) and Noonan syndrome (n=1). A small proportion of these patients reported AEs during the study; however, conclusions about the safety and effectiveness of rhGH therapy in this group are precluded given the low patient numbers.

The PATRO Children study does have limitations, many of which are common to all observational studies. Firstly, as data are collected according to routine clinical practice, there is a risk of inaccuracies due to missing or erroneous data. However, on-site data monitoring is performed to minimize this risk. It is also conceivable that AEs

are under-reported as patient visits occur at the discretion of the treating physician rather than by a standardized protocol. The relatively short observation period (mean treatment duration 3.4 years) may hinder interpretation of some data, for example, the emergence of rare events such as malignancies. Such events may develop over a number of years and continued long-term follow-up of patients is therefore required. As this report focuses on a relatively small number of patients from the US cohort of PATRO Children, the amount of data available for some assessments is low. The interpretation of some data is also impacted by the observational nature of the study. For example, a range of different assays are likely to have been used in the collection of IGF-I measurements, and IGF-I values expressed as SD scores are not available; nevertheless, the availability of mean IGF-I concentrations is a useful indicator of the trend over time. Also, data on adherence to treatment, which can influence safety and effectiveness, were not collected as part of the study. Finally, as ISS patients constitute a heterogeneous group, a larger cohort and further stratification of these patients could provide additional insight into the effects of rhGH treatment in this indication.

In summary, on the basis of this analysis of the US cohort from the PATRO Children study, Omnitrope® treatment appears to be well tolerated and effective in the majority of patients. Across the pediatric indications examined, there was no evidence of an increased risk of developing unexpected AEs, diabetes mellitus, or new malignancies during rhGH treatment. PATRO Children is providing meaningful additional data on the safety and effectiveness of Omnitrope®, as well as adding information to the safety profile for all rhGH medicines.

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Competing interests: PB is a member of the PATRO Children Study Global Steering Committee. BM, RL, and KM are investigators in the PATRO Children study. HZ, MZ, and KC are employees of Sandoz Biopharmaceutical/HEXAL AG. The study funder was involved in the study design, in the

collection, analysis, and interpretation of data, and in the decision to submit the article for publication.

Informed consent: All patients (and/or their parents/guardians) provide written informed consent. Patients are permitted to withdraw their informed consent at any time or discontinue Omnitrope® treatment for any reason.

Ethical approval: The PATRO Children study protocol was approved by the ethics review committee of participating centers in accordance with national laws and regulations. The study was conducted according to the ethical principles of the Declaration of Helsinki (1964) and its later amendments.

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