Safety and Effectiveness of Omnitrope[®], a Biosimilar Recombinant Human Growth Hormone: More Than 10 Years' Experience from the PATRO Children Study

Roland Pfäffle^a Martin Bidlingmaier^b Ilonka Kreitschmann-Andermahr^c
Christof Land^d Carl Joachim Partsch^e Karl Otfried Schwab^f Heide Sommer^g
Philippe Backeljauw^h Shankar Kanumakalaⁱ Sandro Loche^j Hichem Zouater^k
Christian J. Strasburger^l

^aDepartment of Pediatrics, Leipzig University, Leipzig, Germany; ^bMedizinische Klinik und Poliklinik IV, Klinikum der Universität München, Munich, Germany; ^cDepartment of Neurosurgery, University Medicine Essen, Essen, Germany; ^dPraxis für Kinder-Endokrinologie und Diabetologie, Gauting, Germany; ^eDepartment of Paediatric Endocrinology, Endokrinologikum Hamburg, Hamburg, Germany; ^fDepartment of Pediatrics, University Hospital Freiburg, Freiburg, Germany; ^gSandoz Germany c/o HEXAL AG, Holzkirchen, Germany; ^hCincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA; ⁱRoyal Alexandra Children's Hospital, Brighton and Sussex University Hospitals NHS Trust, Brighton, UK; ^jSSD Endocrinologia Pediatrica e Centro Screening Neonatali Ospedale Pediatrico Microcitemico "A. Cao," AO Brotzu, Cagliari, Italy; ^kSandoz Biopharmaceutical c/o HEXAL AG, Holzkirchen, Germany; ^lDepartment of Medicine for Endocrinology, Charité – Universitätsmedizin Berlin, Berlin, Germany

Keywords

Childhood · Growth hormone deficiency · Long-term treatment · Recombinant human growth hormone · Small for gestational age · Turner syndrome

Abstract

Introduction: Omnitrope[®] was approved as a biosimilar recombinant human growth hormone (rhGH) in 2006. **Objective:** The purpose of this work was to evaluate the long-term safety and effectiveness of Omnitrope[®] in PATRO Children – an ongoing, international, longitudinal, non-interventional study in children who require rhGH treatment. **Methods:** The study population includes infants, children, and adolescents receiving Omnitrope[®]. Adverse events (AEs) are monitored for safety and rhGH effectiveness is evaluated by calculation of the height standard deviation score (HSDS), height velocity (HV), and HVS DS using height measurements and country-specific references. **Results:** As of

November 2017, 6,009 patients from 298 centers across 14 countries were enrolled in PATRO Children. Overall, 57.7% of patients had growth hormone deficiency (GHD), 25.8% were born small for gestational age (SGA), and 4.8% had Turner syndrome (TS). In total, 84.1% were rhGH treatment naïve at study entry. The mean duration of Omnitrope[®] treatment in the study was 36.1 months (range 0–133.7). Overall, 10,360 AEs were reported in 2,750 patients (45.8%). Treatment-related AEs were reported in 396 patients (6.6%; 550 events), and serious AEs (SAE) in 636 patients (10.6%; 1,191 events); 50 SAEs in 37 patients (0.6%) were considered treatment related. Following 5 years of therapy in patients who were rhGH treatment naïve at study entry, improvement from baseline in mean HSDS was +1.85 in GHD, +1.76 in SGA, and +1.0 in TS patients. In total, 912 (17.9%) patients reached adult height ($n = 577$ GHD, $n = 236$ SGA, $n = 62$ TS). **Conclusions:** This analysis of PATRO Children indicates that biosimilar rhGH is well tolerated and effective in real-world clinical practice.

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Introduction

Growth hormone (GH) is involved in the regulation of lipid, carbohydrate, and protein metabolism. In children who have an endogenous GH deficiency (GHD), the use of GH replacement therapy stimulates linear growth and increases growth rate [1]. Human GH (hGH) therapy has been used since the 1950s in children with GHD [2] when it was produced by extraction from cadaveric human pituitaries. However, following the occurrence of prion-induced Creutzfeldt-Jakob disease in patients treated with contaminated batches of hGH, in 1985 this treatment was halted worldwide [3].

Recombinant hGH (rhGH) was first approved in 1985 for children with GHD [3]. Following the development of Creutzfeldt-Jakob disease in patients treated with cadaveric hGH, health authorities requested prolonged post-marketing surveillance of patients treated with the newly developed rhGH. In the years that followed, rhGH treatment was approved for use in various other conditions, including children with chronic renal insufficiency (CRI) in 1993, Turner syndrome (TS) in 1996, Prader-Willi syndrome (PWS) in 2000, short children born small for gestational age (SGA) in 2001, and children with idiopathic short stature (ISS; USA and Canada only) in 2003 [3].

In 2005, the European Medicines Agency (EMA) was the first regulatory agency to introduce a legal framework and regulatory approval pathway for similar biological medicinal products, also known as biosimilars [4]. Guidelines for biosimilar approval were subsequently adopted by other regulatory authorities around the world. Biosimilar rhGH (Omnitrope[®], Sandoz GmbH, Kundl, Austria) was the first medicine to be approved via the EMA biosimilar approval pathway in 2006, granted on the basis that it matches the reference medicine (Genotropin[®], Pfizer Limited, Sandwich, UK) in terms of safety, efficacy, and quality [5]. Since the EMA approval of Omnitrope[®], numerous other biosimilar medicines have been approved and used in clinical practice, confirming the usefulness of the EMA biosimilar regulatory framework.

The clinical efficacy of Omnitrope[®] was demonstrated in clinical development studies; however, some concerns remain about the long-term safety of this and all rhGH medicines. The Patients Treated with Omnitrope[®] (PATRO) Children study was set up in 2006 as part of the post-approval pharmacovigilance requirements and risk management plan for biosimilar rhGH [6]. Here, we report safety and effectiveness results from an interim analysis of the PATRO Children study carried out in November 2017.

Fig. 1. Patient enrollment by indication (safety population). CRI, chronic renal insufficiency; GHD, growth hormone deficiency; ISS, idiopathic short stature; PWS, Prader-Willi syndrome; SGA, small for gestational age; TS, Turner syndrome.

Materials and Methods

Study Design and Patient Population

PATRO Children is an ongoing, multicenter, open-label, longitudinal, non-interventional study. The primary objective of the study is to evaluate the long-term safety of Omnitrope[®]. Particular emphasis is placed on the diabetogenic potential of rhGH treatment in children born SGA, the risk of malignancies in all indications, and adverse events (AEs) with a possible causal relationship to Omnitrope[®] treatment and that are unexpected and/or unique to patients with PWS. The long-term effectiveness of rhGH is assessed as a secondary objective of the study.

The PATRO Children study is conducted in hospitals and specialized endocrinology clinics across 14 countries (Austria, Canada, Czech Republic, France, Germany, Italy, Poland, Romania, Slovenia, Spain, Sweden, Taiwan, the UK, and the USA). The study design has been described in detail previously [6]. Briefly, eligible patients are infants, children, and adolescents (male or female) who are receiving Omnitrope[®] treatment and who have provided informed consent. Patients previously treated with another rhGH medicine before starting Omnitrope[®] are also eligible for inclusion. All visits and assessments are carried out as per routine clinical practice, and doses of Omnitrope[®] are given according to country-specific prescribing information.

Safety and Effectiveness Assessments

All AEs are recorded for the complete duration of Omnitrope[®] treatment. The relationship between AEs and Omnitrope[®] treatment is independently evaluated by investigator and sponsor assessment and classified according to the worse case. Laboratory assessments (including glucose metabolism) and vital signs are requested to be documented at least once a year, according to routine clinical practice. Reasons for treatment discontinuation are also collected.

Auxological data can be recorded at each visit and are requested to be documented at least annually. Height velocity (HV;

Table 1. Patient baseline characteristics (safety population)

Indication	Total, <i>n</i>	Male/ female, %	Age, years median (range)	BMI SDS	HSDS	HV, cm/year	PC HVSDS
All indications							
Naïve	5,051	59.0/41.0	8.7 (0.1–22.5)	−0.4 (1.4)	−2.7 (1.0)	3.8 (2.2)	−2.9 (2.4)
Pre-treated	918	60.1/39.9	10.9 (0.5–22.2)	0.0 (1.3)	−1.5 (1.2)	4.9 (2.3)	−0.7 (3.2)
GHD							
Naïve	2,930	67.3/32.7	9.4 (0.1–19.0)	−0.2 (1.3)	−2.5 (0.9)	3.6 (1.8)	−3.1 (2.5)
Pre-treated	524	65.6/34.4	11.3 (1.1–22.2)	−0.1 (1.3)	−1.4 (1.2)	5.1 (2.3)	−0.4 (3.3)
SGA							
Naïve	1,323	51.9/48.1	7.8 (0.9–17.3)	−0.9 (1.4)	−2.9 (0.8)	4.0 (1.9)	−2.8 (2.2)
Pre-treated	224	60.3/39.7	10.3 (3.3–16.5)	−0.3 (1.3)	−1.6 (1.2)	4.8 (2.0)	−1.0 (2.9)
TS							
Naïve	229	0/100	8.7 (0.7–17.9)	0.2 (1.2)	−3.0 (1.0)	3.4 (1.8)	−3.1 (2.0)
Pre-treated	61	1.6*/98.4	11.1 (2.9–18.0)	0.8 (1.1)	−1.8 (1.1)	3.9 (2.0)	−1.3 (2.9)

Data are presented as indicated, the median (range), or mean (SD). BMI, body mass index; GHD, growth hormone deficiency; HV, height velocity; HSDS, height standard deviation score; HVSDS, height velocity standard deviation score; PC, peak-centered; SD, standard deviation; SDS, standard deviation score; SGA, small for gestational age; TS, Turner syndrome.

^a The diagnosis of this male patient was documented as TS in error, and was subsequently corrected in the database to “other indication” (verbatim entry SHO/X/XY/X0/XY).

cm/year), height standard deviation score (HSDS), and HVSDS are derived from height measurements and country-specific reference tables. IGF-1 (insulin-like growth factor 1) and IGFBP-3 (insulin-like growth factor binding protein 3) are recorded according to routine clinical practice; levels are categorized as low, normal, or high according to local laboratory reference ranges.

Patients are considered to have reached adult height (AH) if the investigator agrees with one of the following reasons for patient discontinuation: reaching AH/bone age maturation, or reaching near AH (investigator assessment method). A second method of defining AH utilizes a decision tree based on a number of stringent criteria, regardless of study discontinuation (decision tree method).

Data Collection and Statistical Analysis

Patient data are entered into an electronic case report form (eCRF) at each routine visit. All study visits entered into the eCRF and visit-independent eCRF forms are reviewed and signed by the responsible physician or any of his/her authorized delegates. The eCRFs are reviewed by data management and onsite monitoring is performed by a contract research organization to assure data quality. In addition, plausibility checks were carried out by the data management group to identify outliers or any data that were obviously incorrect, which were subsequently excluded from the analysis.

Standard descriptive statistics are used to describe categorical parameters (e.g., sex) and continuous parameters (e.g., age, height, weight). If rhGH treatment duration during the study was not assessable or recorded as lower than 0, treatment duration was reported as 0 months. Treatment duration during the study is also documented to be 0 if data from the baseline visit are available, but no post-baseline visit is yet recorded.

The safety population includes all patients documented in the eCRF before the interim analysis cutoff date. Patients who do not have 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 measurement of height during Omnitrope® treatment (at least 60 days after baseline). The 5-year analysis cohort comprises patients who have completed at least 5 years of Omnitrope® therapy. Auxological data of patients with GHD, born SGA, and with TS included in the 5-year cohort (effectiveness population) are analyzed in this current evaluation of Omnitrope® treatment effectiveness. The current interim analysis was performed in November 2017 for a clinical study report, which was submitted to the EMA in September 2018 as part of the post-authorization commitments for Omnitrope®.

Results

Patient Characteristics (Safety Population)

As of November 2017, 6,009 patients from 298 centers across 14 countries were enrolled into the study and included in the safety population. The most common treatment indication was GHD ($n = 3,468$; 57.7%), followed by children born SGA ($n = 1,552$; 25.8%). Further indications included TS, PWS, ISS, CRI, and others (Fig. 1).

Patient baseline characteristics are provided in Table 1 for the total population and for patients with GHD, born SGA, and with TS. Overall, 84.1% of patients ($n = 5,051$) were rhGH treatment naïve at study entry and 15.3% of patients ($n = 918$) had received prior rhGH therapy. Pre-treatment information was missing in the remaining

Table 2. Reasons for treatment discontinuation (safety population)

Total	2,286 (100)
Patient reached AH/bone age maturation	581 (25.4)
Lost to follow-up	327 (14.3)
Patient did not wish to continue the injections	239 (10.5)
Reached near AH	225 (9.8)
Switch to other rhGH medicine	148 (6.5)
Patient satisfied with current height	124 (5.4)
Non-responder	100 (4.4)
AE	90 (3.9)
Patient non-compliant	64 (2.8)
Site closure	41 (1.8)
Referral to adult endocrinologist	22 (1.0)
HV slowdown (HV <1 cm/year)	16 (0.7)
Withdrawal of informed consent	11 (0.5)
Miscellaneous reasons ^a	298 (13.0)

Data are presented as *n* (%). AE, adverse event; AH, adult height; HV, height velocity; rhGH, recombinant human growth hormone.

^a Miscellaneous reasons include: other reasons (*n* = 287), reason unknown (*n* = 5), insurance reasons (*n* = 2), and indication for rhGH no longer applicable (*n* = 4).

0.7% of patients (*n* = 40). The rhGH most commonly received prior to study entry was Genotropin[®] (*n* = 292), followed by Norditropin[®] (Novo Nordisk Limited, Crawley, UK; *n* = 183). Omnitrope[®] was received prior to study entry in 99 patients.

At baseline, the mean patient age was 8.5 years (range 0.4–21.8) in females and 9.4 years (range 0.1–22.5) in males. The mean baseline age was 8.7 years (range 0.1–22.5) in treatment-naïve patients and 10.9 years (range 0.5–22.5) in pre-treated patients.

The mean duration of treatment with Omnitrope[®] was 36.1 months (range 0–133.7) (approx. 3 years) and the mean dose of Omnitrope[®] at baseline was 0.033 mg/kg/day (range 0.002–0.145). In total, 1,125 (18.7%) patients in the safety population completed at least 5 years of treatment and were included in the 5-year analysis cohort (including 633 patients with GHD, 327 born SGA, and 49 with TS).

Safety (Safety Population)

At the time of the current analysis, 2,286 patients (38.0%) had discontinued Omnitrope[®] treatment (Table 2). The most commonly reported reason for discontinuation was the patient reaching AH/bone age maturation (*n* = 581; 25.4%). In total, 124 patients (5.4%) discontinued because they were satisfied with their current height

Table 3. Summary of AEs (safety population; total patients, *n* = 6,007)

	Patients, <i>n</i> (%)	Events, <i>n</i>
Any AE	2,750 (45.8)	10,360
Relationship to study drug		
Not suspected	2,650 (44.1)	9,802
Suspected	396 (6.6)	550
Missing	7 (0.1)	7
Not assessable	1 (0.0)	1
Intensity		
Mild	2,101 (35.0)	5,678
Moderate	1,222 (20.3)	2,840
Severe	263 (4.4)	430
Missing	522 (8.7)	1,412
Change to rhGH treatment		
Not changed	2,576 (42.9)	9,467
Increased	104 (1.7)	185
Reduced	64 (1.1)	79
Interrupted	167 (2.8)	227
Permanently discontinued	90 (1.5)	114
Missing	145 (2.4)	288
SAEs		
No	2,616 (43.5)	9,160
Yes	636 (10.6)	1,191
Missing	7 (0.1)	9
SAE relationship to study drug		
Not suspected	610 (10.2)	1,141
Suspected	37 (0.6)	50

AE, adverse event; rhGH, recombinant human growth hormone; SAE, serious adverse event.

and 225 (9.8%) discontinued due to reaching near AH. Overall, 90 patients (3.9%) discontinued treatment due to an AE, which was treatment-related in 44 patients (1.9%).

In total, 10,360 AEs were reported in 2,750 patients (45.8%; incidence of 152.3 per 1,000 patient-years). The majority of AEs were mild to moderate in intensity and did not result in any change to Omnitrope[®] treatment (Table 3). Treatment-related AEs were reported in 396 patients (6.6%; incidence of 21.9 per 1,000 patient-years). Headache was the most commonly reported treatment-related AE (*n* = 95 patients; 1.6%), followed by injection-site pain (*n* = 42 patients; 0.7%), and injection-site hematoma (*n* = 35; 0.6%). Overall, 1,191 serious AEs (SAEs) were reported in 636 patients (10.6%; incidence of 35.2 per 1,000 patient-years). Of the reported SAEs, 50 events in 37 patients (0.6%) were considered treatment related (incidence of 2.1 per 1,000 patient-years). In 19 patients, treatment-related SAEs led to the interruption or discontinuation of Omnitrope[®] treatment (Table 4).

Table 4. Drug-related SAEs resulting in treatment disruption

Indication	Sex; age, years	SAE (preferred term)	Action taken with treatment	Outcome
GHD	Female; 6	Intracranial pressure increased	Interrupted	Resolved
	Male; 8	Gait disturbance	Interrupted	Resolved
	Male; 19	Neoplasm progression	Interrupted	Resolved
	Male; 7	Respiratory syncytial virus bronchiolitis	Permanently discontinued	Resolved
	Male; 7	Muscle spasms	Permanently discontinued	Resolved
	Female; 13	Germ cell cancer	Permanently discontinued	Ongoing
		Hemianopia		
	Female; 6	Pituitary enlargement		
SGA		Osteochondrosis	Dose reduced	Ongoing
		Osteonecrosis		
	Male; 4	Intracranial pressure increased	Permanently discontinued	Resolved
	Male; 5	Transaminases increased	Permanently discontinued	Ongoing
	Male; 14	Heart injury	Permanently discontinued	Resolved
		Pulmonary artery atresia		
	Male; 11	Ocular hypertension	Interrupted	Ongoing
	Female; 14	Type 1 diabetes mellitus	Permanently discontinued	Ongoing
PWS	Male; 8	Osteochondrosis	Permanently discontinued	Ongoing
	Male; 10	Upper airway resistance syndrome	Interrupted	Ongoing
	Male; 4	Sleep apnea syndrome	Interrupted	Ongoing
	Male; 9	Insulin-like growth factor increased	Interrupted	Resolved
ISS	Male; 16	Kyphosis	Permanently discontinued	Ongoing
TS	Female; 11	Benign intracranial hypertension	Interrupted	Ongoing
Other	Female; 18	Astrocytoma	Interrupted	Resolved with sequelae

GHD, growth hormone deficiency; ISS, idiopathic short stature; PWS, Prader-Willi syndrome; SAE, serious adverse event; SGA, small for gestational age; TS, Turner syndrome.

Neoplasms were reported in 94 patients (1.6%), of which around half were patients with GHD ($n = 48$). There were 4 patients (0.1%) with neoplasms that developed de novo during treatment and were considered possibly related to treatment. The first event was malignant germ cell cancer in a female patient with GHD aged 13 years. The patient discontinued rhGH treatment and the event was ongoing at the time of the interim analysis. The second case was benign fibroma in a male patient with GHD aged 10 years, the third case was benign melanocytic nevus in a male patient born SGA aged 3 years, and the final case was a hair follicle tumor (benign) in a male patient aged 5 years with suspected biologically inactive GH. In these 3 cases, there was no change to rhGH treatment and the event was still ongoing at the time of the current analysis.

Treatment-related progression of a pre-existing craniopharyngioma was reported in 2 patients. The first case

was in a male patient with GHD aged 19 years; rhGH treatment was interrupted and the event had resolved completely at the time of the interim analysis. The second case (verbatim report “recurrence of craniopharyngioma with mild hydrocephalus”) was reported in a female patient with combined GHD with an etiology of brain tumor and pituitary disorder. The patient was aged 6 years at the time of the event and there was no change to rhGH treatment. The patient underwent a repeat resection of the craniopharyngioma, after which she recovered completely and the event was considered resolved.

Type 1 diabetes mellitus suspected to be related to rhGH treatment was reported in a female patient born SGA. The patient was treatment naïve at study entry and was receiving ongoing treatment with oral levothyroxine for primary hypothyroidism. The patient was 14 years old at the SAE onset. The SAE occurred after approximately

Fig. 2. HSDS for rhGH treatment-naïve GHD, SGA, and TS patients over 5 years of Omnitrope® treatment (5-year effectiveness population).

10 months of therapy, was considered to be of moderate intensity, and was accompanied by polyuria, polydipsia, and weight loss. The laboratory values for fasting glucose were out of range (475.6 mg/dL) and considered clinically significant. The dose of rhGH at the SAE onset was 0.026 mg/kg/day and IGF-1 was within the normal range. rhGH treatment was subsequently discontinued and the patient started insulin treatment shortly after. The event was ongoing at the time of analysis.

Seven patients developed impaired glucose tolerance that was suspected to be related to study treatment. rhGH treatment remained unchanged in 3 of these patients, was interrupted in 1 patient, reduced in 1 patient, and discontinued in 2 patients.

In total, 7 patients died during the observational period; 6 patients had GHD and 1 was born SGA. None of the reported deaths were considered to be related to rhGH treatment. The AEs with fatal outcomes were: peritoneum metastases, neuroendocrine tumor, and liver metastases (GHD patient); status epilepticus and device malfunction (ventriculoperitoneal shunt malfunction; GHD patient); cardiorespiratory arrest (GHD patient); cystic fibrosis (GHD patient); pneumonia (GHD patient); cardiac failure and congestive cardiomyopathy (GHD patient), and congenital heart disease (patient born SGA).

Overall, the following anti-rhGH antibody assessments were performed: 31 assessments prior to baseline ($n = 31$ patients), 112 assessments at baseline ($n = 111$ patients), and 106 assessments post-baseline ($n = 69$ pa-

tients). Positive anti-rhGH antibody test results were recorded in 2 of 31 patients tested prior to baseline, and in 6 of 111 patients tested at baseline. All patients with positive test results were rhGH treatment naïve. One of the patients with a positive test result was re-tested at a later time point; no positive anti-hGH antibody titer was detected. None of the post-baseline anti-rhGH antibody assessments showed a positive test result. At the time of the current analysis, 22 anti-rhGH assessments ($n = 19$ patients) were carried out beyond 2 years of Omnitrope® treatment and no positive anti-hGH antibody titers were detected in these patients.

Efficacy

Improvements in Growth Parameters (5-Year Cohort, Effectiveness Population)

Overall, 1,017 patients from the effectiveness population completed at least 5 years of treatment and were included in the 5-year cohort. This included 591 patients with GHD ($n = 514$ treatment naïve, $n = 77$ pre-treated), 312 patients born SGA ($n = 270$ treatment naïve, $n = 42$ pre-treated), and 45 patients with TS ($n = 29$ treatment naïve, $n = 16$ pre-treated).

The improvement in HSDS over 5 years for treatment-naïve GHD, SGA, and TS patients is shown in Figure 2. At 5 years, the mean (SD) improvement from baseline HSDS was +1.85 (0.94) in rhGH treatment-naïve patients with GHD, +1.76 (0.68) in those born SGA, and +1.0 (0.57) in those with TS. In pre-treated patients, the change from baseline in mean HSDS at 5 years was +0.81 (1.02)

Fig. 3. Peak-centered (PC) HVSDS for rhGH treatment-naïve GHD, SGA, and TS patients over 5 years of Omnitrope® treatment (5-year effectiveness population).

in patients with GHD, +0.71 (0.75) in patients born SGA, and −0.42 (0.86) in patients with TS.

The improvement in HVSDS over 5 years for rhGH treatment-naïve GHD, SGA, and TS patients is shown in Figure 3. At year 1, the mean (SD) improvement in HVSDS from baseline was +7.47 (3.80), +7.10 (2.83), and +5.43 (3.67) in treatment-naïve GHD, SGA, and TS patients, respectively. As expected, treatment-naïve patients had a greater improvement in peak-centered HVSDS at year 1 compared with pre-treated patients. In pre-treated patients, the mean (SD) change from baseline at year 1 was +2.27 (4.49), +4.09 (3.20), and −0.35 (2.52) in GHD, SGA, and TS patients, respectively.

Adult Height (Effectiveness Population)

Overall, 147 (2.9%) patients in the effectiveness population reached AH according to the decision tree method (*n* = 82 treatment naïve, *n* = 65 pre-treated); further data from this subgroup are not presented. In total, 912 (17.9%) patients in the effectiveness population reached AH according to investigator assessment (*n* = 675 treatment naïve, *n* = 237 pre-treated). Of the patients who reached AH according to investigator assessment, 577 patients had GHD, 236 patients were born SGA, and 62 patients had TS.

The mean patient age at AH (according to investigator assessment) was 16.3 years (range 8.2–24.8) in patients

with GHD, 15.8 years (range 7.2–20.6) in patients born SGA, and 16.5 years (range 13.1–21.3) in patients with TS. The mean HSDS at AH was −1.29 (range −6.2 to 2.7) in patients with GHD, −2.09 (range −8.6 to 1.3) in patients born SGA, and −2.07 (range −5.8 to −0.3) in patients with TS. At AH, the mean difference between adult HSDS and target HSDS was −0.90 (range −6.4 to 2.2) in patients with GHD, −1.46 (range −7.5 to 0.7) in patients born SGA, and −1.94 (range −4.9 to 0) in patients with TS.

Discussion

Results from the current interim analysis indicate that Omnitrope® is well tolerated and effective in children requiring rhGH therapy. These findings are generally consistent with those from other observational studies of pediatric rhGH treatment [7–15]. However, direct comparisons between the PATRO Children study and other observational registries are difficult due to differences in observational time periods and differences in safety data collection.

The safety profile of biosimilar rhGH treatment reported in the current interim analysis is consistent with reports from other observational studies of long-term rhGH therapy [7, 9, 10, 13–17]. Most of the AEs reported in PATRO Children were mild (54.8% of events) or moderate (27.4%) in nature. The most frequent treatment-re-

lated AEs were headache, injection-site pain, and injection-site hematoma. None of these events were unexpected as they represent well-known and commonly occurring side effects of rhGH therapy.

The incidence rate of AEs reported in the current analysis was 152.3 per 1,000 patient-years. Similar incidence rates have been reported in other observational studies that, like PATRO Children, report all AEs, regardless of causality (175.3 treatment-emergent AEs per 1,000 patient-years in the Genetics and Neuroendocrinology of Short Stature International Study; GeNeSIS [9]). The Pfizer International Growth Database (KIGS) study (which also collects all AEs) reported a slightly lower incidence rate of 96.9 AEs per 1,000 patient-years. However, the authors acknowledged that a large number of AEs were probably not reported by investigators, as the majority of patients in the study had no AEs recorded over a long treatment period [18].

A direct comparison with other observational studies is difficult because of differences in the safety data collected. For example, the National Cooperative Growth Study (NCGS) only reports events suspected to be rhGH treatment related and unrelated events of special interest [7]. Similarly, only adverse drug reactions (ADRs), serious ADRs, and SAEs are reported in the NordiNet® study [13]. As could be expected, the event incidence rates reported from these studies are lower (SAE and ADR incidence rate of 5.6 per 1,000 patient-years in NordiNet® and ADR incidence rate of 20.9 per 1,000 patient-years in NCGS) [7, 13]. The incidence of treatment-related AEs in the current analysis was 21.9 per 1,000 patient-years, similar to that reported in the NCGS. The varying incidence rates reported may also be influenced by the different observational time periods in each study.

Some concerns have previously been raised about the long-term safety of rhGH therapy. A retrospective evaluation of 6,928 rhGH-treated patients with GHD, ISS, or born SGA from the French Safety and Appropriateness of Growth Hormone Treatments in Europe (SAGhE) study suggested a link between rhGH treatment and premature death (standard mortality ratio of 13) when patients were treated with doses above 50 µg/kg/day [19]. This finding was mainly due to an increased risk of mortality due to circulatory system causes. The mean follow-up time from the start of treatment to last follow-up or study end in this cohort was approximately 17 years [19]. A later publication from the same patient cohort showed an increased risk of stroke, particularly hemorrhagic stroke, among patients diagnosed with GHD, ISS, or born SGA [20]. However, these findings could not be reproduced in oth-

er studies and reviews [21–24], or in subsequent reports from the same cohort [14, 16, 17]. In this context, it is important to note that no patients in PATRO Children died of classic cardiovascular complications, although further follow-up will be helpful in clarifying the cardiovascular safety of rhGH.

The first efficacy data for biosimilar rhGH came from a phase III study that compared Omnitrope® with the reference medicine in 89 patients with GHD. Omnitrope® was shown to have comparable efficacy to the reference medicine in terms of height increase and improvement in HV [25]. It has subsequently been demonstrated that switching from another rhGH medicine to Omnitrope® does not change the growth trajectories of patients diagnosed with GHD, TS, ISS, or born SGA [26]. Results from the current PATRO Children analysis demonstrate a slightly less pronounced increase in HVSDS in rhGH-treated patients with GHD, compared with results from the phase III study [25]. This difference may be partly explained by the younger average patient age at therapy initiation in the phase III study compared with PATRO Children (7.6 vs. 9.4 years) [25], in addition to the observational nature of PATRO Children. However, data from the current analysis indicate that Omnitrope® induces comparable improvements in patients with GHD in a real-life clinical setting.

Results from the current interim analysis of Omnitrope® effectiveness in patients with GHD are consistent with those from observational studies of other approved rhGH medicines [8, 11, 12]. As expected, growth responses in the current study were dependent on whether the patient was treatment naïve at study entry or had been previously treated with rhGH. The differences in growth response may be attributed, at least in part, to the older age of pre-treated patients at study entry (i.e., for patients with GHD, 11.3 years pre-treated vs. 9.4 years treatment naïve). Age at onset of rhGH therapy has been demonstrated to be negatively correlated with change in HSDS and the AH outcome of the patient [11]. Although the effect of age at rhGH treatment initiation is well known, the average patient age at treatment start does not appear to have significantly decreased over the past decade of rhGH therapy, although exceptions in Czech Republic and Germany have been reported [27].

Some of the patients who reached AH were surprisingly young; the minimum age reported at AH was 8.2 and 7.2 years in GHD and SGA patients, respectively. It is likely that in some cases investigators may have incorrectly documented that patients discontinued treatment due to reaching AH/bone age maturation or reaching near AH. The decision tree method of confirming AH includes more stringent criteria, such as

HV, bone age, chronological age, and pubertal status. As could be expected, patients were older (at least 11 years old) at AH when the decision tree method was used to confirm AH.

The PATRO Children study has some limitations, which are found in all observational studies. First, as data are collected according to routine clinical practice (as opposed to standardized protocols in controlled clinical trials), there is a risk of bias due to missing or erroneous data collection. As a consequence, some assessments in the current analysis are based on a relatively small amount of data, for example anti-rhGH antibody assessments. Furthermore, the interpretation of some data may be limited as the mean duration of Omnitrope® treatment in the study is approximately 3 years. For instance, rare events such as malignancies may take several years to develop and therefore continued follow-up of patients is required. Due to the observational nature of the study, a few discrepancies were reported in the data. For example, a small number of patients in PATRO Children were aged over 18 years ($n = 13$ patients in the safety population). These patients were permitted to remain in the study after reaching 18 years old as they remained under the care of a pediatric endocrinologist. In addition, treatment duration during the study was not assessable or recorded as lower than 0 for some patients, resulting in a reported duration of 0 months. Furthermore, there was 1 TS patient in the study who was reported to be male, which was later confirmed to be a data entry error; the patient diagnosis was corrected to “other indication” (verbatim entry SHOX/YYY/X0/XY) after the interim analysis. Finally, the maximum Omnitrope® dose recorded was very high (0.145 mg/kg), which may be a data entry error.

Conclusion

This analysis from the PATRO Children study describes the use of Omnitrope®, the first biosimilar approved by the EMA, in real-life clinical practice. All available data indicate that Omnitrope® does not differ from other rhGH medicines with regard to its effectiveness and safety profile in approved indications. Ten years after the initiation of the PATRO Children study, the average treatment duration is approximately 3 years, which is considered relatively short. To address previously raised concerns about rhGH treatment, long-term observation of children receiving rhGH therapy by their physician is needed in the future.

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Statement of Ethics

All patients (and/or their parents/guardians where the patient was a minor) gave their written informed consent to participate in the study. The PATRO Children study protocol was approved by the ethics review committee of all participating centers in accordance with national laws and regulations. All procedures performed were in accordance with the ethical standards of these committees and with the 1964 Declaration of Helsinki and its later amendments.

Conflict of Interest Statement

C.L. has received consultancy and speaker fees from Pfizer, Novo Nordisk, Ipsen, Merck Serono, and Sandoz, and serves on the German PATRO Children study board. M.B. has received research support, lecture fees, and/or consultancy honoraria from Antisense, Chiasma, DiaSorin, Genexine, GeneScience, IDS, Ionis, Ipsen, Midatech, Novartis, ONO, OPKO, Pfizer, Roche, Sandoz, and Strongbridge, and serves on the German PATRO Children study board. I.K.-A. has received travel grants, speaker fees, consulting fees, and/or research grants from Ipsen Pharma, Novartis, Pfizer, and Sandoz/Hexal, and serves on the German PATRO Children study board. C.J.P. has received travel grants, speaker fees, and consulting fees from Pfizer, Novartis, Sandoz/Hexal, Merck, Ferring, Kyowa Kirin, and Ipsen Pharma, and serves on the German PATRO Children study board. K.O.S. serves on the German PATRO Children study board and the PATRO Children Global Steering Committee, and has received honoraria and grants from Alexion, Ipsen, Merck Serono, Novo Nordisk, Pfizer, Sandoz, and VitaFlo. C.J.S. has received consultancy and speaker fees from Aeterna Zentaris, Ascendis Pharma, Chiasma, Crinetics, Ipsen, Merck-Serono, Novartis, Novo Nordisk, Pfizer, Sandoz, Strongbridge, and Tiburio, and serves on the German PATRO Children study board. P.B. has received research funding from Ipsen, Novo Nordisk, and Opko, has functioned in an advisory role for Endo Pharmaceuticals, Ipsen, Novo Nordisk, and Sandoz, and is a member of the PATRO Children Global Steering Committee. S.K. has received speaker fees from Sandoz, is a member of the Global Steering Committee for PATRO Children study, and has received financial assistance to attend scientific meetings from Ferring, Novo Nordisk, and Sandoz. S.L. has received research support, consultancy fees, and lecture fees from Eli Lilly, Ipsen, Merck Serono, and Sandoz, and is a member of the PATRO Children Global Steering Committee. H.S. is an employee of Sandoz Germany c/o HEXAL AG, Holzkirchen, Germany. H.Z. is an employee of Sandoz Biopharmaceutical c/o HEXAL AG, Holzkirchen, Germany. R.P. has received consultancy and speaker fees from Ferring, Merck Serono, Novo Nordisk, and Sandoz, and serves on the German PATRO Board (Sandoz).

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Author Contributions

All authors had full access to the study data, contributed to data analysis, data interpretation, writing, and critical review of the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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