Latest results from PATROchildren®, a multi-centre, non-interventional study of the long-term safety and efficacy of Omnitrope® in children requiring growth hormone treatment

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Kanumakala S,[1] Pfäffle R,[2] Höybye C,[3] Kriström B,[4] Battelino T,[5] Zabransky M,[6] Zouater H[6]

[1]Department of Paediatrics, Royal Alexandra Children's Hospital, Brighton & Sussex University Hospitals NHS Trust, Brighton, UK; [2]Department of Paediatric Endocrinology, University of Leipzig Medical School, Leipzig, Germany; [3]Patient Area Endocrinology and Nephrology, Inflammation and Infection Theme, Karolinska University Hospital, Sweden; [4]Department of Clinical Science/Paediatrics, Umeå University, Sweden; [5]Department of Endocrinology, Diabetes and Metabolic Diseases, University Children's Hospital, Ljubljana, Slovenia; [6]Sandoz GmbH, Holzkirchen, Germany.

Introduction

- Omnitrope® is a recombinant human growth hormone (rhGH, somatropin) approved by the European Medicines Agency in 2006, with approval granted on the basis of comparable quality, safety and efficacy to the reference medicine (Genotropin®, Pfizer).
- rhGH replacement therapy stimulates linear growth and increases growth rate in children with growth hormone deficiency (GHD).[1]
- rhGH therapy is also approved for paediatric use in other indications, such as short children with Turner Syndrome (TS) and Prader-Willi Syndrome (PWS), children born small for gestational age (SGA), and children with chronic renal insufficiency (CRI).[1] GH therapy is also approved for the treatment of idiopathic short stature (ISS) in the United States, Canada and Brazil.
- Although rhGH has been used for many years to treat growth disorders in children, some concerns remain about its long-term safety.[2]
- The PAtients TReated with Omnitrope® (PATRO) children® study is an ongoing, long-term, post-marketing surveillance programme for Omnitrope®.

Objectives

- The main objective is to assess the long-term safety of rhGH, particularly in terms of diabetogenic potential and risk of malignancies in all indications, and all potential risks in PWS patients.
- The long-term effectiveness of rhGH is analysed as a secondary objective by evaluation of changes in growth parameters.
- Here we present safety and effectiveness data from a snapshot analysis carried out in May 2018.

Methods

- PATROchildren® is an international, longitudinal, non-interventional study, currently being conducted in hospitals and specialised endocrinology clinics across 14 different countries.[3]
- In brief, infants, children and adolescents who require rhGH treatment and receive at least one dose of Omnitrope® are enrolled. Patients previously treated with another rhGH medicine are also included.
- Omnitrope® is administered as per standard clinical practice and doses are given according to country-specific prescribing information.

Safety assessments

- All adverse events (AEs) are monitored and recorded for the complete duration of Omnitrope® treatment. Particular emphasis is placed on: long-term safety; re-occurrence or new onset of malignancies; and the development of glucose intolerance or diabetes.
- Laboratory values (including glucose metabolism and anti-hGH antibodies) are requested at least once a year.

Efficacy assessments

- Auxological data may be recorded at each visit. Height velocity (HV, cm/year), height standard deviation score (HSDS), HVSDS and BMI SDS are derived from height and weight measurements and country-specific reference tables.

Results

Patients and treatment

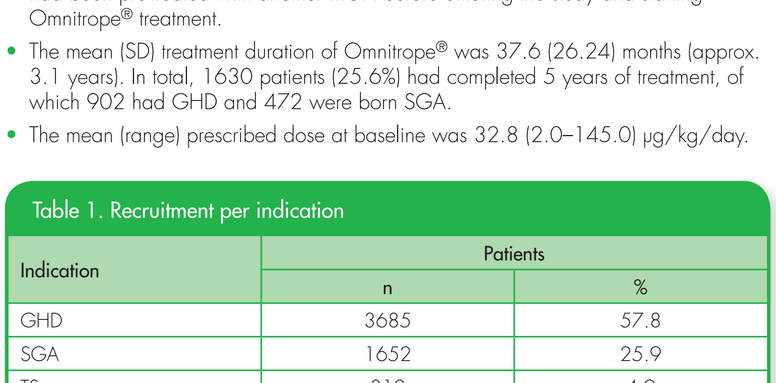
- As of May 2018, 6371 patients had been enrolled from 299 centres across 14 countries (Table 1 and Figure 1).
- Baseline characteristics are shown in Table 2. In total, 948 patients (14.9%) had been pre-treated with another rhGH before entering the study and starting Omnitrope® treatment.
- The mean (SD) treatment duration of Omnitrope® was 37.6 (26.24) months (approx. 3.1 years). In total, 1630 patients (25.6%) had completed 5 years of treatment, of which 902 had GHD and 472 were born SGA.
- The mean (range) prescribed dose at baseline was 32.8 (2.0–145.0) µg/kg/day.

Table 1. Recruitment per indication

Indication	Patients	
	n	%
GHD	3685	57.8
SGA	1652	25.9
TS	312	4.9
PWS	210	3.3
ISS*	196	3.1
CRI	60	0.9
Other	243	3.8
Unknown	13	0.2
Total	6371	100.0

*Omnitrope® is approved for ISS patients in US, Canada and Brazil
CRI, chronic renal insufficiency; GHD, growth hormone deficiency; ISS, idiopathic short stature; PWS, Prader-Willi syndrome; SGA, small for gestational age; TS, Turner syndrome

Figure 1. Patient enrolment by country (safety set)



'Other' refers to Spain (n=80), Poland (n=52), Austria (n=21), Taiwan (n=20) and Slovenia (n=12)

Table 3. Primary reasons for study discontinuation

Total (n=2651)	Patients	
	n	%
Patient reached final height/bone age maturation	637	24.0
Reached near final height	301	11.4
Patient satisfied with current height	132	5.0
Lost to follow-up	386	14.6
Patient does not wish to continue the injections	272	10.3
Switch to other rhGH medicine	158	6.0
Non-responder	113	4.3
Adverse event	104	3.9
Patient non-compliant	77	2.9
Referral to adult endocrinologist	30	1.1
Height velocity slowdown (HV <1 cm/year)	16	0.6
Withdrawal of informed consent	13	0.5
Unknown	9	0.3
Miscellaneous reasons	403	15.2

rhGH, recombinant human growth hormone; HV, height velocity. Miscellaneous reasons include; site closure, insurance reasons, indication for rhGH no longer applicable, and other reasons

Safety

- To date, a total of 2651 patients (41.6%) have discontinued the study (Table 3). Of the 104 (3.9%) patients who discontinued due to an AE, the AEs were suspected to be treatment-related in 55 (2.1%) patients.
- Overall, 3040 patients (47.7%) experienced AEs, most of which were mild or moderate; 438 (6.9%) patients reported drug-related AEs (Table 4).
- Of the 741 patients (11.6%) who experienced serious AEs (SAE), only 50 (0.8%) had SAEs that were considered to be possibly related to treatment. Of these, rhGH treatment was disrupted in 25 patients.
- Drug-related SAEs relating to malignancies or diabetes mellitus are provided in Table 5.
- In total, 154 samples from 77 patients were assessed for anti-hGH antibodies. Only one positive anti-hGH antibody titre occurred transiently in a treatment-naïve patient at baseline prior to rhGH treatment; all subsequent results for this patient were negative.
- So far, 19 patients have been tested for anti-hGH antibodies following two years of Omnitrope® treatment; no clinically relevant positive anti-hGH antibody titres or neutralising antibodies have been reported in these patients.

Efficacy

- After 5 years of Omnitrope® treatment, improvements were observed in most growth parameters across all indications, irrespective of gender or pre-treatment status.
- Greater height gains at 5 years were observed amongst treatment-naïve patients compared with pre-treated patients.
  - Improvements in mean HSDS and HVSDS over 5 years for treatment-naïve and pre-treated GHD and SGA patients are shown in Figures 2 and 3.
- Mean HV (SD) at 5 years was 6.2 (1.5) cm/year in naïve pre-pubertal GHD patients (n=291) and 6.0 (1.7) cm/year in naïve pre-pubertal SGA patients (n=178).

Table 4. Summary of patients with AEs

	Total number of patients n=6371	Patients n	Patients %
	Any AE	3040	47.7
Relationship to study drug	Not suspected	2942	46.2
	Suspected	438	6.9
	Missing	9	0.1
	Not assessable	1	0.0
Intensity	Mild	2341	36.7
	Moderate	1332	20.9
	Severe	286	4.5
	Missing	587	9.2
Changes to rhGH treatment	Not changed	2865	45.0
	Increased	118	1.9
	Reduced	73	1.1
	Interrupted	178	2.8
	Permanently discontinued	106	1.7
	Missing	147	2.3
SAEs	No	2894	45.4
	Yes	741	11.6
	Missing	5	0.1
SAE relationship to study drug	Not suspected	701	11.0
	Suspected	50	0.8
	Missing	1	0.0
Treatment-related AEs (>15 patients), by MedDRA preferred term	Headache	103	1.6
	Injection site pain	50	0.8
	Injection site haematoma	37	0.6
	Arthralgia	27	0.4
	Hypothyroidism	19	0.3
	Insulin-like growth factor increased	18	0.3
	Sleep apnoea syndrome	17	0.3

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; rhGH, recombinant human growth hormone; SAE, serious AE

Table 5. Treatment-related SAEs relating to malignancies or diabetes mellitus

MedDRA preferred term	Indication	Age[a], sex	Time to SAE onset (years)[b]	Intensity	Outcome	Action taken with Omnitrope®	Relevant medical history
Type 1 diabetes mellitus	SGA	14, female	0.8	Moderate	Ongoing	Permanently discontinued	None
Glucose tolerance impaired	SGA	8, male	2.1	Moderate	Ongoing	Permanently discontinued	None
Germ cell cancer	GHD	13, female	3.0[c]	Severe	Ongoing	Permanently discontinued	None
Neoplasm progression	GHD	19, male	5.1	Moderate	Resolved completely	Interrupted	GHD aetiology: brain tumour
Malignant astrocytoma	Other	18, female	2.3	Severe	Resolved with sequelae	Interrupted	Past illness: astrocytoma

[a]Age at SAE onset. [b]Time to SAE onset after start of Omnitrope® treatment. [c]SAE occurred after discontinuation of Omnitrope® treatment
Assessment of seriousness and relationship to rhGH treatment according to Investigator and Sponsor (worst case). All patients were naïve to rhGH therapy
GHD, growth hormone deficiency; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SGA, small for gestational age

Figure 2. Height SDS for pre-treated and growth hormone-naïve GHD and SGA patients following 5 years of Omnitrope® treatment (efficacy set*)

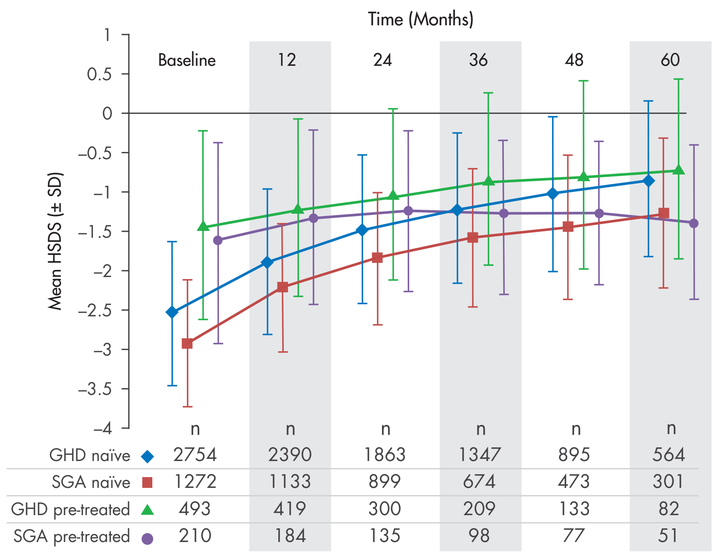
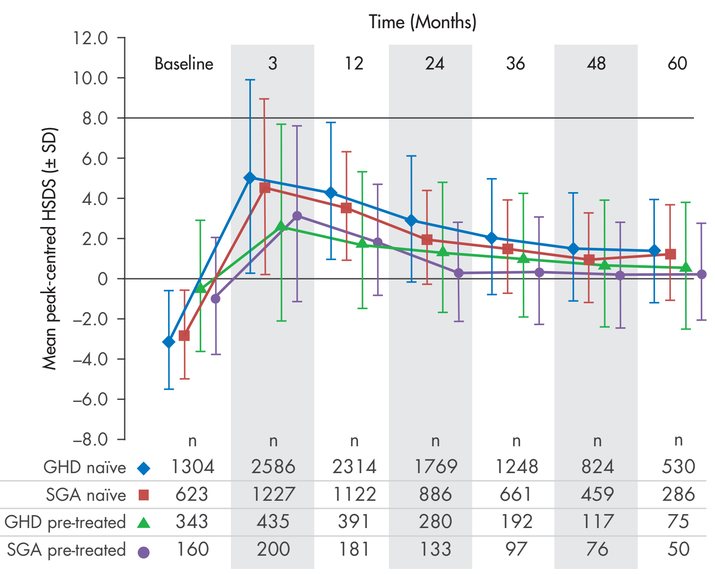


Figure 3. Peak-centred height velocity SDS for pre-treated and growth hormone-naïve GHD and SGA patients following 5 years of Omnitrope® treatment (efficacy set*)



*Efficacy set: all patients with documented height measurement at baseline (start of Omnitrope® treatment) and at least one measurement of height under Omnitrope® treatment before the cut-off date
GHD, growth hormone deficiency; HSDS, height SDS; HVSDS, height velocity SDS; SD, standard deviation; SDS, standard deviation score; SGA, small for gestational age

Conclusions

- The results of this snapshot analysis demonstrate that rhGH therapy is effective and well-tolerated in the majority of rhGH-treated children.
- Across the paediatric indications examined, the data available on patients to date show no evidence of an increased risk of developing unexpected AEs, diabetes or new malignancies during rhGH treatment.
- The ongoing PATROchildren® study will continue to provide valuable data on the long-term safety and efficacy of Omnitrope®, as well as contributing to the safety profile for all rhGH medicines.

Table 2. Patient baseline characteristics

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		6371	59.3/40.7	9.0 (0.1–22.5)	–0.3 (1.4)	–2.5 (1.1)	4.1 (2.3)	–2.4 (2.8)
GHD	Naïve	3129	67.6/32.4	9.4 (0.1–19.0)	–0.2 (1.3)	–2.5 (0.9)	3.6 (1.8)	–3.1 (2.5)
	Pre-treated	546	65.2/34.8	11.3 (1.1–22.2)	–0.1 (1.3)	–1.4 (1.2)	5.1 (2.3)	–0.4 (3.3)
SGA	Naïve	1419	52.3/47.7	7.8 (0.9–17.3)	–0.8 (1.4)	–2.9 (0.8)	4.0 (1.9)	–2.8 (2.2)
	Pre-treated	229	60.3/39.7	10.3 (3.3–16.5)	–0.3 (1.2)	–1.6 (1.3)	4.9 (2.0)	–0.9 (2.9)

BMI, body mass index; GHD, growth hormone deficiency; HV, height velocity; HSDS, height standard deviation score; SD, standard deviation; HVSDS, HV standard deviation score; SGA, small for gestational age; PC, peak-centred

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