Results up to 3 years from PATRO Children, a multi-centre, non-interventional study of the long-term safety and efficacy of Omnitrope® in children requiring growth hormone treatment

Pfäffle R,[1] Kanumakala S,[2] Höybye C,[3] Kriström B,[4] Schuck E,[5] Zabransky M,[5] Battelino T,[6] Colle M[7]

[1]Department of Paediatric Endocrinology, University of Leipzig Medical School, Leipzig, Germany; [2]Department of Paediatrics, Royal Alexandra Children's Hospital, Brighton, UK; [3]Department of Endocrinology, Metabolism and Diabetology, Karolinska University Hospital, Stockholm, Sweden; [4]Department of Clinical Science/Paediatrics, Umeå University, Umeå, Sweden; [5]Sandoz International GmbH, Holzkirchen, Germany; [6]Department of Endocrinology, Diabetes and Metabolic Diseases, University Children's Hospital, Llubljana, Slovenia; [7]25 rue Boudet, Bordeaux, France

Introduction

- Recombinant human growth hormone (rhGH, somatropin) has been used for many years to treat growth disorders in children, but some concerns remain about its long-term safety.[1]
- Omnitrope® is a rhGH approved by the European Medicines Agency in 2006, with approval granted on the basis of comparable quality, safety and efficacy to the reference product (Genotropin®, Pfizer).[2]
- Omnitrope® has been approved in the following indications:[2]
  - growth hormone deficiency (GHD)
  - Turner syndrome (TS)
  - chronic renal insufficiency (CRI)
  - born small for gestational age (SGA)
  - Prader-Willi syndrome (PWS)
  - idiopathic short stature (ISS; USA only).
- The PAtients TReated with Omnitrope® (PATRO) Children study is an ongoing, long-term, post-marketing surveillance programme for Omnitrope®.[3]

Objectives

- The main objective of PATRO Children is to assess the long-term safety of Omnitrope®, particularly in terms of the diabetogenic potential of rhGH therapy, the risk of malignancies and potential risks of rhGH in children with PWS.
- The long-term efficacy of Omnitrope® is analysed as a secondary objective through changes in height parameters.
- Here, we present an interim analysis of safety and efficacy data up to 3 years after the start of treatment with Omnitrope®.

Methods

- International, observational, longitudinal, non-interventional study, currently being conducted across 14 different countries (Study EP00-501).[3]
- In brief, infants, children and adolescents who require rhGH treatment and receive at least one dose of Omnitrope® are enrolled. Patients who have been previously treated with another somatropin product can also be included.
- Omnitrope® is administered as part of usual clinical practice in the centres involved and doses are given according to country-specific prescribing information. All patient data are captured in an electronic case report form.

Safety assessments

- All adverse events (AEs) are recorded at each visit for the complete duration of rhGH treatment.
- Fasting plasma glucose, 2-hour oral glucose tolerance tests (OGTT), insulin levels, glycosylated haemoglobin (HbA_{1c}) and anti-GH antibodies are requested to be documented according to routine clinical practice.

Efficacy assessments

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

Results

Patients and treatment

- To date, 4397 patients have been enrolled; all patients have been included in the safety set.
- The baseline characteristics of all of these patients are presented in Table 1. The mean age for the total population is 9.2 years and there were slightly more males (58.8%) than females (TS patients included).
- In total, 775 patients (17.6%) had been pre-treated with another rhGH before study entry and were transferred to Omnitrope® (Table 1).
- The mean (SD) treatment duration of Omnitrope® was 28.6 (21.0) months. The mean (SD) daily dose of Omnitrope® was 0.034 (0.014) mg/kg/day.

Safety

- A total of 1278 patients have discontinued treatment. The most common reason for patients discontinuing treatment was reaching final height/bone maturation (27.4%), with very few (2.9%) discontinuing due to AEs (Table 2). The reason for discontinuation was unknown or not documented in 11.4% of patients
- Overall, 1475 patients (33.5%) experienced AEs, most of which were mild to moderate in intensity (Table 3).
- rhGH treatment was interrupted in 94 patients (2.1%) and the rhGH dose was reduced in 28 patients (0.6%).
- In total, 191 patients (4.3%) have reported drug-related AEs, with headache being the most common (52 patients, 1.2%) (Table 3).

Table 2. Reasons for treatment discontinuation

	n	%
Patient reached final height/bone age maturation	350	27.4
Height velocity slowdown (HV <1 cm/year)	48	3.8
Patient satisfied with current height	56	4.4
Patient does not wish to continue the injections	139	10.9
Adverse event	37	2.9
Patient non-compliant	38	3.0
Switch to other GH product	105	8.2
Reached near final height	30	2.3
Non-responder	17	1.3
Lost to follow-up	154	12.1
Other reason	158	12.4
Unknown	146	11.4
Total	**1278**	**100.0**

GH=growth hormone; HV=height velocity

Table 3. Summary of AEs

	Total number of subjects n=4397	n	%
	Any AE	**1475**	**33.5**
Relationship to study drug	Not suspected	1403	31.9
	Suspected	191	4.3
	Missing	18	0.4
Intensity	Mild	1136	25.8
	Moderate	664	15.1
	Severe	125	2.8
	Missing	120	2.7
Changes to Omnitrope® treatment	Not changed	1375	31.3
	Increased	53	1.2
	Reduced	28	0.6
	Interrupted	94	2.1
	Permanently discontinued	37	0.8
	Missing	20	0.5
SAEs	No	1415	32.2
	Yes	168	3.8
	Missing	10	0.2
Treatment-related AEs (>5 patients), by MedDRA preferred term	Headache	52	1.2
	Hypothyroidism	13	0.3
	Arthralgia	12	0.3
	Injection site haematoma	10	0.2
	Pain in extremity	8	0.2
	Injection site pain	6	0.1

MedDRA=Medical Dictionary for Regulatory Activities

- Of the 168 patients (3.8%) who experienced serious AEs (SAEs), only 9 (0.2%) experienced SAEs considered to be possibly related to treatment.
  - Two patients (a 6-year old girl [GHD] and a 4-year old boy [SGA]) experienced intracranial hypertension; rhGH treatment was temporarily interrupted/permanently discontinued, respectively, and the SAE resolved completely in both cases.
  - A 5-year old girl with GHD experienced recurrence of craniopharyngioma with mild hydrocephalus. Treatment with Omnitrope® continued and the craniopharyngioma resolved completely after treatment; the outcome of mild hydrocephalus was not reported.
  - An 8-year old boy with GHD, and a medical history that included skeletal dysplasia and syndactyly, experienced gait disturbance. Omnitrope® treatment was permanently discontinued and the SAE was completely resolved.
  - A 19-year old boy with GHD experienced progression of his underlying craniopharyngioma. Omnitrope® treatment was temporarily interrupted.
  - A 6-year old boy with SGA experienced otitis and adenoidal hypertrophy. Treatment with Omnitrope® was continued and unchanged. The adenoidal hypertrophy resolved completely after treatment.
  - An 8-year old boy with SGA experienced osteochondrosis. Omnitrope® treatment was permanently discontinued.
  - A 14-year old girl born SGA developed type 1 diabetes mellitus; rhGH treatment was permanently discontinued.
  - A 16-year old boy born SGA experienced acute cardiac injury due to progression of congenital pulmonary atresia; Omnitrope® treatment was permanently discontinued and the SAE was resolved.
- There have been no clinically relevant positive anti-hGH antibody titres (n=64) related to Omnitrope® treatment in the patients tested so far.
- To date, there have been no reports of rhGH-related malignancies or any additional safety concerns.

Efficacy

- After 3 years of treatment, Omnitrope® resulted in significant improvements in growth parameters across all indications, irrespective of gender or pre-treatment status.
- Greater height gains at 3 years were observed amongst naïve patients, with a mean HV (SD) of 6.7 (1.9) and 6.5 (1.8) cm/year in naïve patients with GHD and SGA, respectively.
- Figure 1 indicates the positive effect of Omnitrope® on mean HSDS in both naïve and pre-treated patients with GHD or born SGA.
  - The effect of Omnitrope® was more evident in naïve patients, whom at year 3 achieved HSDS values of Δ+1.29 and Δ+1.30 (patients with GHD or SGA, respectively).
- Similarly, Figure 2 shows a greater impact of Omnitrope® on mean peak-centred HVSDS in naïve patients with GHD (Δ+4.9) or SGA (Δ+4.2).

Figure 1. Height SDS for pre-treated and growth hormone-naïve GHD and SGA patients following 3 years of Omnitrope® treatment

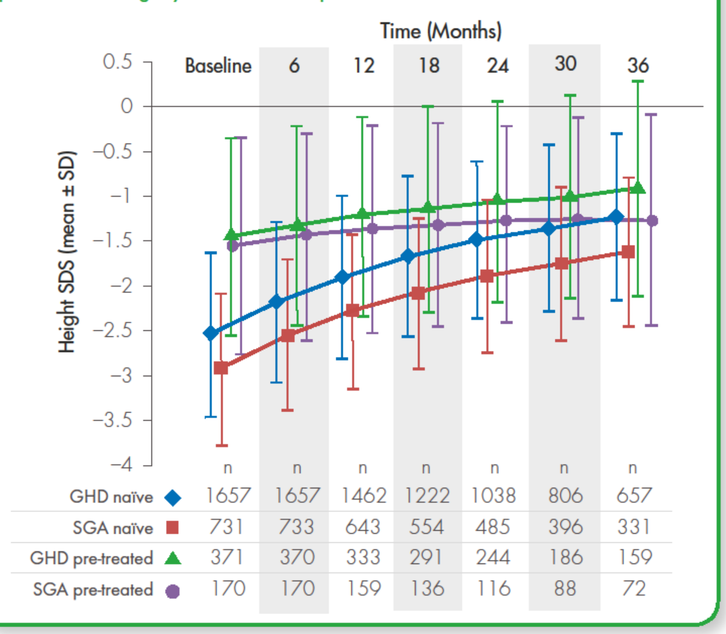
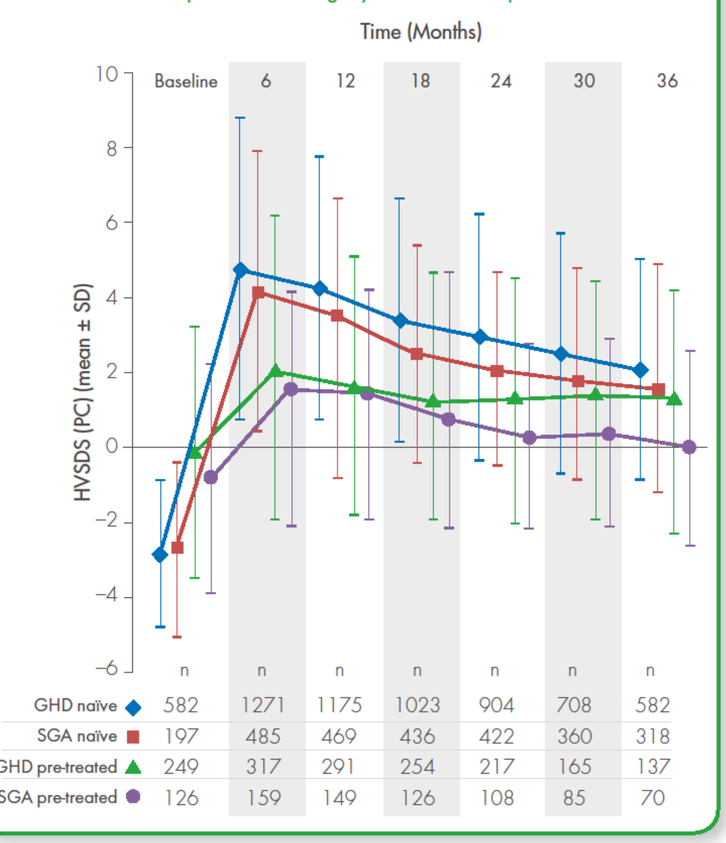


Figure 2. Peak-centred height velocity SDS for pre-treated and growth hormone-naïve GHD and SGA patients following 3 years of Omnitrope® treatment



Conclusions

- The results of this 3-year analysis demonstrate that Omnitrope® treatment remains efficacious and well tolerated in the majority of rhGH-treated children.
- Across all the indications examined, the data on evaluable patients to date show no evidence for an increased risk of developing unexpected AEs, diabetes or new malignancies during Omnitrope® treatment.
- The ongoing PATRO Children study will continue to provide valuable safety and efficacy data for long-term treatment with Omnitrope®

Table 1. Patient characteristics at baseline

Indication	Total (n)	Male/female (n)	Naïve/ pre-treated[a] (n)	Mean age, years (SD)	Mean BMI (SD)	Mean HSDS (SD)	Mean HV, cm year (SD)	Mean HVSDS (PC)
GHD	2511	1676/835	2056/434	9.9 (3.8)	17.0 (3.3)	−2.3 (1.1)	4.1 (2.2)	−2.1 (3.2)
SGA	1127	581/546	912/191	8.2 (3.4)	15.4 (2.4)	−2.7 (1.1)	4.3 (2.1)	−2.0 (2.8)
TS	199	0/199	146/48	9.4 (4.3)	18.2 (3.7)	−2.7 (1.2)	3.8 (2.2)	−1.8 (2.9)
PWS	141	67/74	112/25	4.2 (4.3)	18.1 (4.1)	−1.3 (1.5)	7.6 (4.2)	−2.0 (3.2)
CRI	32	19/13	27/3	6.9 (4.5)	16.5 (3.3)	−2.8 (1.3)	3.6 (2.6)	−5.4 (2.6)
ISS	47	34/13	24/23	10.1 (3.6)	17.4 (2.4)	−1.8 (1.1)	4.9 (3.8)	−0.8 (5.3)
Other	291	178/113	238/51	9.8 (3.7)	16.6 (3.0)	−2.6 (1.3)	4.0 (2.4)	−2.6 (3.0)
Unknown	49	31/18	8/0	9.2 (3.5)	18.1 (2.9)	−2.8 (0.4)	2.9 (0.7)	−4.3 (2.4)
Total	4397	2586/1811	3523/775	9.2 (3.9)	16.6 (3.2)	−2.4 (1.1)	4.2 (2.4)	−2.1 (3.1)

[a]Pre-treatment information was unavailable for 99 patients; BMI, body mass index; CRI, chronic renal insufficiency; GHD, growth hormone deficiency; HV, height velocity; HSDS, height standard deviation score; ISS, idiopathic short stature; PWS, Prader-Willi syndrome; SD, standard deviation; HVSDS, HV standard deviation score; SGA, born small for gestational age; TS, Turner syndrome

References

1. Bell J, Parker KL, Swinford RD, et al. Long-term safety of recombinant human growth hormone in children. *J Clin Endocrinol Metab* 2010; 95: 167–177.
2. European Medicines Agency 2008. Omnitrope® – European Public Assessment Report 2008. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR-Scientific_Discussion/human/000607/WC500043692.pdf
3. Pfäffle R, Schwab KO, Marginean O, et al. Design of, and first data from, PATRO Children, a multicentre, noninterventional study of the long-term efficacy and safety of Omnitrope® in children requiring growth hormone treatment. *Ther Adv Endocrinol Metab* 2013; 4: 3–11.

Acknowledgements and disclosures

This study was funded by Sandoz Biopharmaceuticals. Ellen Schuck and Markus Zabransky are employees of Sandoz.

Medical writing support was provided by Sarah Stuffield and Tony Reardon, Spirit Medical Communications Ltd., supported by Sandoz International GmbH.