Four-year results from PATRO Children, 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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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 biosimilar 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, Canada and Brazil 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 4 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® were enrolled. Patients previously treated with another somatropin product could 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, insulin levels, glycosylated haemoglobin 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

- As of July 2016, 5007 patients have been enrolled; all patients have been included in the safety set.
- The baseline characteristics are presented in Table 1. The mean age for the total population is 9.1 years and 61.8% are males (excluding TS patients).
- In total, 775 patients (15.5%) had been pre-treated with another rhGH before study entry and were transferred to Omnitrope®.
- The mean (SD) treatment duration of Omnitrope® was 32.4 (22.8) months. The mean (SD) daily dose of Omnitrope® at baseline was 0.033 (0.01) mg/kg/day.

Safety

- 1640 patients have discontinued treatment; most commonly due to reaching final height/bone maturation (29.8%), with very few (3.5%) discontinuing due to AEs (Table 2). The reason was unknown or not documented in 0.6% of patients.
- Overall, 1924 patients (38.4%) experienced AEs, most of which were mild to moderate. rhGH treatment was interrupted in 126 patients (2.5%) and the rhGH dose was reduced in 43 patients (0.9%) (Table 3).
- Of the 323 patients (6.5%) who experienced serious AEs (SAEs), only 30 (0.6%) experienced SAEs considered to be possibly related to treatment. Of these, 10 resulted in discontinuation or interruption of Omnitrope® treatment (Table 4).

Table 2. Reasons for treatment discontinuation

	Total (n=1640) (%)
Patient reached final height/bone age maturation	29.8
Miscellaneous reasons	16.8
Lost to follow-up	12.1
Patient does not wish to continue the injections	10.7
Switch to other growth hormone product	6.9
Patient satisfied with current height	5.2
Reached near final height	5.2
Non-responder	4.8
Adverse event	3.5
Patient non-compliant	3.1
Referral to adult endocrinologist	0.7
Unknown	0.6
Height velocity <1 cm/year	0.4
Withdrawal of informed consent	0.2

Table 3. Summary of AEs

	Total number of subjects n=5007	n	%
	Any AE	**1924**	**38.4**
Relationship to study drug	Not suspected	1836	36.7
	Suspected	284	5.7
Intensity	Mild	1481	29.6
	Moderate	861	17.2
	Severe	186	3.7
	Missing	326	6.5
Changes to Omnitrope® treatment	Not changed	1790	35.7
	Increased	66	1.3
	Reduced	43	0.9
	Interrupted	126	2.5
	Permanently discontinued	56	1.1
	Missing	93	1.9
SAEs	No	1832	36.6
	Yes	323	6.5
Treatment-related AEs (>5 patients), by MedDRA preferred term	Headache	75	1.5
	Arthralgia	19	0.4
	Injection site haematoma	19	0.4
	Injection site pain	18	0.4
	Hypothyroidism	13	0.3
	Pain in extremity	10	0.2
	Scoliosis	8	0.2
	Insulin-like growth factor increased	8	0.2
	Drug ineffective	7	0.1
	Myalgia	5	0.1
	Glucose tolerance impaired	5	0.1
	Insulin resistance	5	0.1

MedDRA=Medical Dictionary for Regulatory Activities

- In total, 126 samples from 67 patients were assessed for anti-hGH antibodies. Only one positive anti-hGH antibody titre occurred transiently in a treatment-naïve patient at baseline; all subsequent results for this patient were negative. So far, 12 patients have been tested for anti-hGH antibodies following two years of Omnitrope® treatment; no positive anti-hGH antibody titres have been reported in these patients.
- To date, there have been no reports of any additional safety concerns.

Efficacy

- After 4 years of treatment, Omnitrope® resulted in improvements in growth parameters across all indications, irrespective of gender or pre-treatment status.
- Greater height gains at 4 years were observed amongst naïve patients, with a mean HV (SD) of 6.4 (1.9) and 5.8 (1.6) cm/year in naïve patients with GHD and SGA, respectively.
- The effect of Omnitrope® was more evident in naïve patients, whom at year 4 achieved HSDS values of Δ+1.49 and Δ+1.47 (patients with GHD and SGA, respectively) (Figure 1).
- Omnitrope® had a greater impact on mean peak-centred HVSDS in naïve patients with GHD (Δ+4.6) and SGA (Δ+3.6) (Figure 2).

Table 4. Drug-related SAEs resulting in treatment disruption

Gender, Age	Indication	SAE (preferred term)	Action taken with treatment	Outcome
Male, 9	GHD	Headache	Interrupted	Resolved completely
Female, 6	GHD	Benign intracranial hypertension	Interrupted	Resolved completely
Male, 8	GHD	Gait disturbance	Interrupted	Resolved completely
Male, 19	GHD	Neoplasm progression	Interrupted	Resolved completely
Male, 4	SGA	Intracranial pressure increased	Permanently discontinued	Resolved completely
Male, 14	SGA	Heart injury	Permanently discontinued	Resolved completely
Female, 14	SGA	Type I diabetes mellitus	Permanently discontinued	Ongoing
Male, 8	SGA	Osteochondrosis	Permanently discontinued	Ongoing
Male, 10	PWS	Upper airway resistance syndrome	Interrupted	Ongoing
Male, 16	ISS	Kyphosis	Permanently discontinued	Ongoing

Figure 1. The positive effect of Omnitrope® on mean HSDS in both naïve and pre-treated patients with GHD or born SGA.

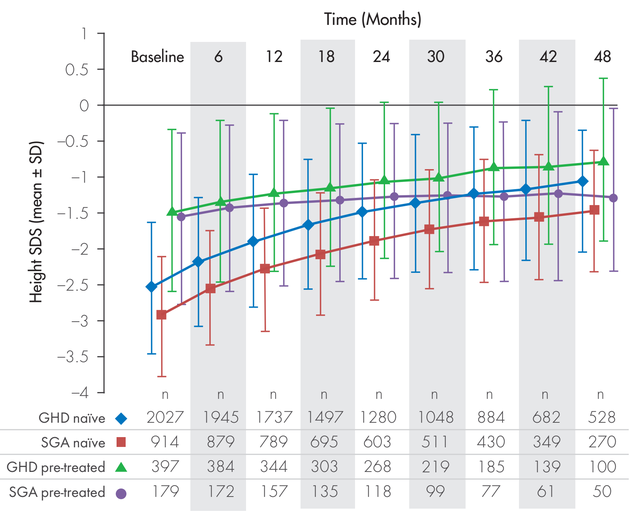
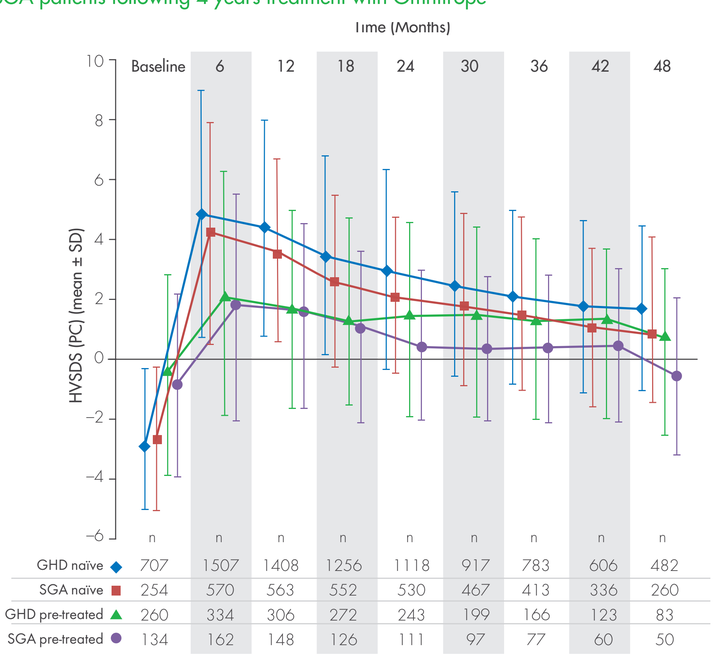


Figure 2. Height velocity SDS (peak-centred) for pre-treated and naïve GHD and SGA patients following 4 years treatment with Omnitrope®



Conclusions

- Across all the indications examined, the data on evaluable patients to date show no evidence for an increased risk of developing unexpected AEs or new malignancies during Omnitrope® treatment.
- The results of this 4-year analysis demonstrate that Omnitrope® treatment remains efficacious and well tolerated in the majority of rhGH-treated children.
- 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	Naïve/pre-treated[a]	Total (n)	Male/female (n)	Mean age, years (SD)	Mean BMI SDS (SD)	Mean HSDS (SD)	Mean HV,cm/year (SD)	Mean peak-centred HV SDS (SD)
GHD	Naïve	2421	1611/810	9.5 (3.8)	−0.2 (1.3)	−2.5 (0.9)	3.7 (2.0)	−2.9 (2.6)
	Pre-treated	433	290/143	11.4 (3.4)	−0.1 (1.3)	−1.5 (1.1)	5.2 (2.4)	−0.3 (3.3)
SGA	Naïve	1088	557/531	7.8 (3.3)	−0.8 (1.3)	−2.9 (0.8)	4.0 (2.1)	−2.7 (2.3)
	Pre-treated	192	112/80	10.1 (2.8)	−0.3 (1.3)	−1.6 (1.2)	4.9 (2.1)	−0.9 (3.0)
TS	Naïve	178	−/178	8.9 (4.5)	0.2 (1.4)	−3.1 (1.1)	3.5 (1.8)	−2.4 (1.9)
	Pre-treated	50	−/50	10.6 (3.7)	0.9 (1.0)	−1.8 (1.2)	4.2 (2.2)	−1.3 (3.1)
PWS	Naïve	130	66/64	3.0 (3.2)	0.2 (2.2)	−1.6 (1.5)	8.8 (4.7)	−3.1 (2.4)
	Pre-treated	24	12/12	8.6 (4.9)	1.6 (1.5)	−0.2 (1.3)	5.4 (2.9)	−1.0 (3.4)
CRI	Naïve	32	20/12	6.6 (4.6)	0.0 (1.8)	−2.8 (1.2)	3.6 (2.7)	−5.6 (2.4)
	Pre-treated	4	2/2	10.3 (3.0)	0.5 (2.0)	−2.4 (1.1)	6.7 (–)	0.8 (–)
ISS	Naïve	24	16/8	9.6 (3.6)	0.0 (1.4)	−2.3 (1.1)	2.0 (2.5)	−4.6 (3.4)
	Pre-treated	23	18/5	10.6 (3.6)	−0.2 (0.8)	−1.4 (0.9)	6.6 (3.2)	1.4 (4.8)
Other	Naïve	298	177/121	9.6 (3.7)	−0.4 (1.4)	−2.8 (1.2)	3.6 (2.0)	−3.0 (2.7)
	Pre-treated	49	37/12	9.8 (3.7)	−0.2 (1.1)	−1.7 (1.3)	5.1 (2.7)	−1.2 (2.9)
Unknown	Naïve	3	2/1	9.3 (6.5)	−1.5 (1.5)	−3.0 (0.5)	2.2 (–)	−6.9 (–)
Total		5007	2951/2056	9.1 (3.9)	−0.3 (1.4)	−2.5 (1.1)	4.2 (2.4)	−2.2 (3.0)

Pre-treatment information was unavailable for 58 patients (31 male, 27 female); 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; PC, peak-centred

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