Safety and effectiveness of paediatric growth hormone therapy: Results from the full cohort in KIGS

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Introduction

- Recombinant human growth hormone (rhGH) is indicated to treat children with growth disorders, including growth hormone deficiency (GHD), Prader-Willi syndrome (PWS), children born small for gestational age (SGA), Turner syndrome (TS), Noonan syndrome, idiopathic short stature (ISS), chronic renal insufficiency (CRI), and short stature homeobox-containing gene (SHOX) deficiency
- Treatment with rhGH is generally safe,[1,2] but concerns remain about potential long-term effects of rhGH on risks for stroke, cancer, and mortality[3-5]
- KIGS (Kabi/Pfizer International Growth Database; 1987-2012), first established as a survey, evolved into a large, international, observational study to evaluate long-term safety and treatment outcomes of paediatric rhGH (Genotropin® [somatropin]; Pfizer, NY) in real-world, clinical settings

Objective

- To analyse and summarise accumulated safety and efficacy data from all rhGH-treated patients until KIGS close in 2012

Methods

- Children with growth disorders treated with rhGH (Genotropin® [somatropin]; Pfizer, NY) were enroled
- Safety outcomes included all adverse events (AEs) and serious AEs (SAEs); causal relationships of AEs with rhGH treatment were assessed by the investigators
- Auxological data, including height (Ht), Ht standard deviation score (Ht-SDS), Ht velocity (HtV), HtV-SDS, difference between Ht-SDS and mid-parental Ht-SDS (Diff-SDS), weight, and body mass index, were collected for efficacy analysis
- Definitions
  - SDS for Ht: calculated according to Prader references[6]
  - Start of puberty: breast Tanner II (girls), testicular volume 4 mL (boys)[7,8]
  - Near-adult height (NAH): HtV <2 cm/yr during the last year and age >14 yr (girls) or >16 yr (boys)

Results

Patient Characteristics

Safety cohort

- A total of 83,803 patients were treated with rhGH, most frequently for idiopathic GHD (IGHD; 47%), for a median duration of 2.7 years (total 277,267 patient-years [PY]) and median follow up of 3.1 years (total 322,576 PY)
- Median age of patients at treatment start was 11 years; 58% of patients were male and most were Caucasian (70%) (**Table 1**)
- Median initial rhGH dose was 0.17 to 0.33 mg/kg/wk for different indications (**Table 1**)

Efficacy cohort

- Efficacy was evaluated in 55,284 patients who had ≥1 year of treatment and completed height assessment at year 1
- Median age at rhGH start was 9.8 years, and initial rhGH dose varied by indication (**Table 1**)

Safety

*Adverse events (**Table 2**)*

- 23,163 AEs were reported in 14.4% of patients (treatment-related in 3.1%); the overall incidence rate of all-causality AEs was 94.2 per 1000 PY
- 3981 SAEs occurred in 3.7% of patients (treatment-related in 0.7%)
- Most frequently reported AEs and SAEs are shown in **Table 2**
- 1030 (1.2%) patients discontinued rhGH due to SAEs (345 [0.4%] were treatment-related SAEs)

Table 1. Demographic characteristics of the safety and efficacy cohorts

	Safety (N=83,803)		Efficacy (N=55,284)	
Sex, n (%)				
Male	48,620 (58.0)		31,943 (57.8)	
Female	35,183 (42.0)		23,341 (42.2)	
Race/Ethnicity, n (%)				
Asian	12,082 (14.4)		8470 (15.3)	
Black	943 (1.1)		540 (1.0)	
Caucasian	59,022 (70.4)		39,741 (71.9)	
Hispanic	1989 (2.4)		937 (1.7)	
Other	2363 (2.8)		1496 (2.7)	
Unknown	7404 (8.8)		4100 (7.4)	
Age at rhGH start (yr)[a]	10.7 (4.6, 14.9)		9.8 (4.2, 14.1)	
Years of rhGH treatment[a]	2.7 (0.3, 7.2)		3.5 (1.4, 7.9)	
Years of follow up[a]	3.1 (0.5, 8.2)		4.0 (1.6, 9.0)	
Diagnosis	n (%)	Initial rhGH dose (mg/kg/wk)[a]	n (%)	Initial rhGH dose (mg/kg/wk)[a]
Idiopathic GHD	39,298 (46.9)	0.20 (0.12, 0.31)	25,810 (46.7)	0.21 (0.15, 0.31)
Neurosecretory dysfunction	2187 (2.6)	0.22 (0.14, 0.32)	1537 (2.8)	0.22 (0.16, 0.33)
Congenital GHD	3323 (4.0)	0.21 (0.12, 0.32)	2189 (4.0)	0.22 (0.15, 0.32)
Craniopharyngioma	1381 (1.6)	0.17 (0.08, 0.26)	965 (1.7)	0.17 (0.11, 0.26)
Medulloblastoma	998 (1.2)	0.20 (0.11, 0.29)	703 (1.3)	0.20 (0.14, 0.29)
Other cranial tumours	1750 (2.1)	0.18 (0.10, 0.28)	1209 (2.2)	0.18 (0.12, 0.28)
Extracranial malignancy	940 (1.1)	0.20 (0.11, 0.30)	680 (1.2)	0.21 (0.14, 0.29)
Idiopathic short stature	6867 (8.2)	0.21 (0.13, 0.35)	4336 (7.8)	0.20 (0.16, 0.34)
Turner syndrome	7714 (9.2)	0.30 (0.16, 0.38)	5580 (10.1)	0.30 (0.18, 0.38)
Prader-Willi syndrome	2338 (2.8)	0.22 (0.04, 0.30)	1501 (2.7)	0.23 (0.14, 0.31)
Other syndromes	2602 (3.1)	0.25 (0.14, 0.38)	1801 (3.3)	0.25 (0.16, 0.39)
Small for gestational age	7936 (9.5)	0.26 (0.13, 0.44)	4892 (8.8)	0.27 (0.19, 0.45)
Chronic renal insufficiency	2399 (2.9)	0.33 (0.15, 0.39)	1514 (2.7)	0.33 (0.19, 0.39)
Other causes	4070 (4.9)	0.22 (0.12, 0.34)	2567 (4.6)	0.23 (0.15, 0.35)

rhGH, recombinant human growth hormone; GHD, growth hormone deficiency. [a]Presented as median (10th percentile, 90th percentile)

Patient characteristics associated with SAEs

- SAEs were more prevalent in those who had longer treatment (duration ≥3 years vs <3 years, 4.7% vs 2.6%, *P*<0.0001)
- Frequency of SAEs was >10% among patients with diagnoses of craniopharyngioma (19.4%), CRI (13.9%), other cranial tumours (13.0%), and medulloblastoma (11.7%)

Mortality

- A total of 307 (0.4% of patients) deaths were reported; most frequently reported causes of death (in ≥5 patients; by MedDRA preferred term) included neoplasm recurrence (n=19), recurrent cancer (n=17), craniopharyngioma (n=7), brain neoplasm (n=6), ill-defined disorder (n=6), cerebral hemorrhage (n=5), convulsion (n=5), glioblastoma (n=5), and pneumonia (n=5)
- Death occurred most frequently among patients who attained age 10 to <15 years while in KIGS (31.9%), 15 to <20 years (28.3%), and 5 to <10 years (18.2%); and among those with medulloblastoma (3.7%), other cranial tumours (2.5%), and extracranial malignancy (2.2%)

Table 2. Frequency of AEs, SAEs, and treatment discontinuations (safety cohort N=83,803)

	All-causality, n (%)	Treatment-related, n (%)
Number of AEs[a]	23,163	3108
Patients with AEs	12,055 (14.4)	2638 (3.1)
AEs in ≥0.5% patients		
Headache	987 (1.2)	328 (0.4)
Scoliosis	514 (0.6)	162 (0.2)
Upper respiratory tract infection	474 (0.6)	4 (0.0)
Arthralgia	431 (0.5)	129 (0.2)
Pyrexia	425 (0.5)	13 (0.0)
Ear infection	408 (0.5)	3 (0.0)
Influenza	404 (0.5)	4 (0.0)
Nasopharyngitis	391 (0.5)	5 (0.0)
Number of SAEs[a]	3981	657
Patients with SAEs	3108 (3.7)	607 (0.7)
Patients with drug discontinuation[b] due to SAEs	1030 (1.2)	345 (0.4)
SAEs in ≥0.1% patients		
Craniopharyngioma recurrence	151 (0.2)	42 (0.1)
Neoplasm recurrence	99 (0.1)	23 (0.0)
Scoliosis	91 (0.1)	43 (0.1)
Recurrent cancer	91 (0.1)	26 (0.0)
Slipped capital femoral epiphysis	61 (0.1)	38 (0.0)
Convulsion	60 (0.1)	6 (0.0)
Death	59 (0.1)	5 (0.0)
Vomiting	47 (0.1)	3 (0.0)
Pneumonia	47 (0.1)	0 (0.0)
Headache	45 (0.1)	11 (0.0)
Epilepsy	43 (0.1)	4 (0.0)
Appendicitis	42 (0.1)	1 (0.0)

AE, adverse event; SAE, serious adverse event. [a]Summarised by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. [b]Temporary, permanent, or delayed drug discontinuation.

Efficacy

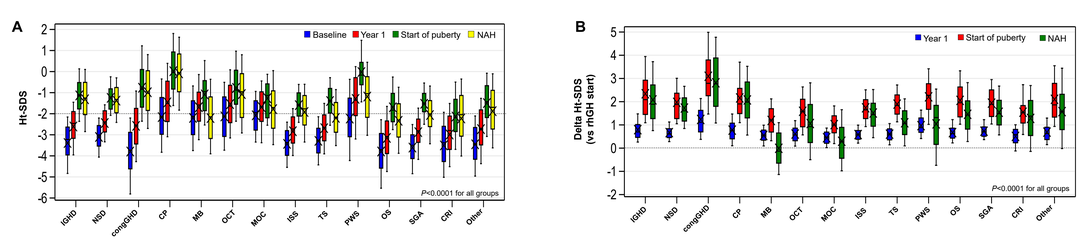
*Efficacy during the first year (**Table 3**)*

- Ht-SDS increased in all groups of the efficacy cohort after 1 year of treatment
- Among patients who remained prepubertal during the first year of rhGH exposure, median delta Ht-SDS ranged from 0.38 (extracranial malignancy) to 1.01 (congenital GHD)

Effect on NAH

- NAH was analysed in 7911 patients who had received rhGH for ≥5 years (≥2 years prepubertal treatment)
- Prepubertal Ht-SDS increased from baseline to puberty onset
- Median Ht-SDS at NAH was >-2 SD in patients with IGHD, neurosecretory dysfunction, congenital GHD, craniopharyngioma, other cranial tumours, extracranial malignancy, ISS, PWS, and other causes (**Figure 1A**)

Figure 1. Growth outcomes of (A) Ht-SDS and (B) Delta Ht-SDS in the NAH subgroup



congGHD, congenital GHD; CP, craniopharyngioma; CRI, chronic renal insufficiency; GHD, growth hormone deficiency; Ht-SDS, height SDS; IGHD, idiopathic GHD; ISS, idiopathic short stature; MB, medulloblastoma; MOC, malignancy outside the cranium; NAH, near-adult height; NSD, neurosecretory dysfunction; OCT, other cranial tumours; OS, other syndromes; PWS, Prader-Willi syndrome; SDS, standard deviation score; SGA, small for gestational age; TS, Turner syndrome.

Table 3. Growth outcomes at year 1 in the efficacy cohort

Diagnosis	Total		Prepubertal[a]		Pubertal[b]	
	n	Delta Ht-SDS	n	Delta Ht-SDS	n	Delta Ht-SDS
Idiopathic GHD	25,810	0.57 (0.11, 1.19)	13,882	0.66 (0.22, 1.40)	8365	0.48 (0.02, 0.96)
Neurosecretory dysfunction	1537	0.54 (0.09, 1.03)	800	0.63 (0.23, 1.12)	592	0.41 (-0.04, 0.89)
Congenital GHD	2189	0.89 (0.07, 2.04)	1740	1.01 (0.15, 2.22)	340	0.49 (-0.06, 1.14)
Craniopharyngioma	965	0.65 (-0.02, 1.43)	652	0.75 (0.07, 1.50)	255	0.52 (-0.12, 1.18)
Medulloblastoma	703	0.42 (-0.06, 0.88)	306	0.51 (0.07, 0.90)	334	0.32 (-0.14, 0.84)
Other cranial tumours	1209	0.49 (-0.15, 1.15)	512	0.59 (0.01, 1.25)	585	0.45 (-0.16, 1.08)
Extracranial malignancy	680	0.33 (-0.14, 0.83)	265	0.38 (-0.06, 0.86)	358	0.28 (-0.18, 0.83)
Turner syndrome	5580	0.54 (0.01, 1.05)	4067	0.58 (0.05, 1.08)	1269	0.44 (-0.08, 0.93)
Prader-Willi syndrome	1501	0.83 (-0.03, 1.70)	1198	0.94 (0.12, 1.78)	224	0.30 (-0.29, 1.14)
Other syndromes	1801	0.57 (0.07, 1.16)	1290	0.63 (0.16, 1.30)	388	0.40 (-0.08, 0.87)
Idiopathic short stature	4336	0.48 (0.04, 0.93)	2125	0.55 (0.18, 1.00)	1443	0.39 (-0.10, 0.85)
Small for gestational age	4892	0.65 (0.19, 1.16)	3487	0.71 (0.30, 1.23)	997	0.48 (-0.03, 0.99)
Chronic renal insufficiency	1514	0.54 (-0.12, 1.24)	935	0.63 (-0.06, 1.41)	408	0.41 (-0.19, 1.04)
Other causes	2567	0.48 (-0.09, 1.11)	1416	0.56 (-0.01, 1.28)	874	0.36 (-0.14, 0.94)

GHD, growth hormone deficiency; Ht-SDS, height standard deviation score (Prader reference). Data are presented as median (10th percentile, 90th percentile) unless noted otherwise. [a]Patients who remained prepubertal during year 1. [b]Patients who already reached puberty at treatment start or went into puberty during year 1.

- From treatment start to NAH, median total Ht-SDS gain was >0 SD in all diagnostic groups, except for the medulloblastoma group (-0.13), and highest in patients with congenital GHD (2.77), craniopharyngioma (1.98), and IGHD (1.89) (**Figure 1B**). Median Diff-SDS also increased for all but the medulloblastoma group

Conclusions

- Data from the full cohort of KIGS patients (median 3.1 years follow up [322,576 PY]) showed that rhGH was safe and well-tolerated in children with growth disorders as prescribed in real-world settings
- Treatment with rhGH was effective, as Ht-SDS increased from start of treatment to year 1, start of puberty, and NAH in most diagnostic groups
- Data compiled from KIGS, the largest and longest running global database of rhGH-treated children, complement results from clinical trials and other registries, and support the favorable benefit-risk profile of daily rhGH in paediatric patients

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