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Abstract

Recombinant human growth hormone for the treatment of growth disorders in children: a systematic review and economic evaluation

A Takeda, K Cooper, A Bird, L Baxter, GK Frampton, E Gospodarevskaya, K Welch and J Bryant*

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Background: Recombinant human growth hormone (rhGH) is licensed for short stature associated with growth hormone deficiency (GHD), Turner syndrome (TS), Prader–Willi syndrome (PWS), chronic renal insufficiency (CRI), short stature homeobox-containing gene deficiency (SHOX-D) and being born small for gestational age (SGA).

Objectives: To assess the clinical effectiveness and cost-effectiveness of rhGH compared with treatment strategies without rhGH for children with GHD, TS, PWS, CRI, SHOX-D and those born SGA.

Data sources: The systematic review used a priori methods. Key databases were searched (e.g. MEDLINE, EMBASE, NHS Economic Evaluation Database and eight others) for relevant studies from their inception to June 2009. A decision-analytical model was developed to determine cost-effectiveness in the UK.

Study selection: Two reviewers assessed titles and abstracts of studies identified by the search strategy, obtained the full text of relevant papers, and screened them against inclusion criteria.

Study appraisal: Data from included studies were extracted by one reviewer and checked by a second. Quality of included studies was assessed using standard criteria, applied by one reviewer and checked by a second. Clinical effectiveness studies were synthesised through a narrative review.

Results: Twenty-eight randomised controlled trials (RCTs) in 34 publications were included in the systematic review. GHD: Children in the rhGH group grew 2.7 cm/year faster than untreated children and had a statistically significantly higher height standard deviation score (HtSDS) after 1 year: –2.3 ± 0.45 versus –2.8 ± 0.45. TS: In one study, treated girls grew 9.3 cm more than untreated girls. In a study of younger children, the difference was 7.6 cm after 2 years. HtSDS values were statistically significantly higher in treated girls. PWS: Infants receiving rhGH for 1 year grew significantly taller (6.2 cm more) than those untreated. Two studies reported a statistically significant difference in HtSDS in favour of rhGH. CRI: rhGH-treated children in a 1-year study grew an average of 3.6 cm more than untreated children. HtSDS was statistically significantly higher in treated children in two studies. SGA: Criteria were amended to include children of 3+ years with no catch-up growth, with no reference to mid-parental height. Only one of the RCTs used the licensed dose; the others used higher doses. Adult height (AH) was approximately 4 cm higher in rhGH-treated patients in the one study to report this outcome, and AH-gain SDS was also statistically significantly higher in this group. Mean HtSDS was higher in treated than untreated patients in four other studies (significant in two). SHOX-D: After 2 years' treatment, children were approximately 6 cm taller than the control group and HtSDS was statistically significantly higher in treated children. The incremental cost per quality adjusted life-year (QALY) estimates of rhGH compared with no treatment were: £23,196 for GHD, £39,460 for TS, £135,311 for PWS, £39,273 for CRI, £33,079 for SGA and £40,531 for SHOX-D. The probability of treatment of each of the conditions being cost-effective at £30,000 was: 95% for GHD, 19% for TS, 1% for PWS, 16% for CRI, 38% for SGA and 15% for SHOX-D.

Limitations: Generally poorly reported studies, some of short duration.

Conclusions: Statistically significantly larger HtSDS values were reported for rhGH-treated children with GHD, TS, PWS, CRI, SGA and SHOX-D. rhGH-

treated children with PWS also showed statistically significant improvements in body composition measures. Only treatment of GHD would be considered cost-effective at a willingness-to-pay threshold of £20,000–30,000 per QALY gained. This analysis suggests future research should include studies of longer than 2 years reporting near-final height or final adult height.

Contents

List of abbreviations

AE	adverse event
AH	adult height
AUC	area under the curve
AO-GHD	adult-onset growth hormone deficiency
BA	bone age – a measure of skeletal maturity evaluated on the basis of the relative positions of the bones generally in the left hand and wrist
BMC	bone mineral content
BMI	body mass index (kg/m^2)
BNF	*British National Formulary*
BSA	body surface area
BSPED	British Society for Paediatric Endocrinology and Diabetes
CA	chronological age
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CGHAC	Canadian Growth Hormone Advisory Committee
CI	confidence interval
CKD	chronic kidney disease
CO-GHD	childhood-onset growth hormone deficiency
CRF	chronic renal failure
CRI	chronic renal insufficiency
CUA	cost–utility analysis
DARE	Database of Abstracts of Reviews of Effectiveness
DEC	Development and Evaluation Committee
DEXA	dual-energy X-ray absorptiometry
DNA	deoxyribonucleic acid
EMEA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
ERF	established renal failure
ESRF	end-stage renal failure
EUROCAT	European Surveillance of Congenital Abnormalities
FDA	Food and Drug Administration
FGR	fetal growth restriction
FH	final height
FM	fat mass
FT4	free thyroxine
GFR	glomerular filtration rate
GH	growth hormone
GHD	growth hormone deficiency
GV	growth velocity (generally cm/year)
GVSDS	growth velocity standard deviation score – growth velocity relative to distribution of growth in children of the same chronological age (or bone age if specified)
HDL-C	high-density lipoprotein cholesterol
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
HTA	Health Technology Assessment

continued

HtSDS	height standard deviation score – height relative to distribution of height in children of the same chronological age (or bone age if specified)
HV	height velocity
HVSDS	Height Velocity Standard Deviation Score
ICER	incremental cost-effectiveness ratio
IGF	insulin-like growth factor
IGFBP	insulin-like growth factor building proteins
IQR	interquartile range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISS	idiopathic short stature
ITT	intention to treat
IU	international unit (3 IU = 1 mg)
IUGR	intrauterine growth restriction/retardation
KDOQI	Kidney Disease Outcomes Quality Initiative
KIGS	Kabi International Growth Study Database (now Pfizer)
KIMS	Kabi International Metabolic Study Database (now Pfizer)
LBM	lean body mass
LDL	low-density lipoprotein
LWS	Léri–Weill syndrome
m^2	square metres (in this context referring to body surface area)
met-GH	methionyl growth hormone
mg	milligram
MPHD	multiple pituitary hormone deficiency
MS	manufacturer's submission
MTA	multiple technology appraisal
NCHS	National Centre for Health Statistics
NFH	near-final height – height measured when growth is assumed to be near completion
NHS CRD	National Health Service Centre for Reviews and Dissemination
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NKF	National Kidney Foundation
nr	not reported
ns	not statistically significant
OLS	ordinary least squares
PAH	predicted adult height – extrapolating adult height from childhood height
Pla	placebo
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PWS	Prader–Willi syndrome
QALY	quality-adjusted life-year
QoL	quality of life
QoL-AGHDA	quality of life assessment of growth hormone deficiency in adults
QoL-$AGHDA_{UTILITY}$	utility-weighted score
RCT	randomised controlled trial
rhGH	recombinant human growth hormone
SAE	serious adverse event
SAR-SR	Social Adjustment Scale-self rating
s.c.	subcutaneous
s.c.i.	subcutaneous injection

SD	standard deviation
SDS	standard deviation score
SF-36	Short Form questionnaire-36 items
SG	standard gamble
SGA	small for gestational age
SHOX	short stature homeobox-containing gene
SHOX-D	short stature homeobox-containing gene deficiency
SHTAC	Southampton Health Technology Assessments Centre
SMR	standardised mortality rate
TS	Turner syndrome
TTO	time trade-off
U	unit
WtSDS	weight standard deviation score

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Recombinant human growth hormone (rhGH) is licensed for short stature that is associated with growth hormone deficiency (GHD), Turner syndrome (TS), Prader–Willi syndrome (PWS), chronic renal insufficiency (CRI), short stature homeobox-containing gene deficiency (SHOX-D) and being born small for gestational age (SGA). The National Institute for Health and Clinical Excellence (NICE) guidance currently recommends rhGH treatment for children with GHD, TS, PWS or CRI, but does not cover SGA or SHOX-D.

Objectives

The aim of this report was to assess the clinical effectiveness and cost-effectiveness of rhGH compared with treatment strategies without rhGH for children with GHD, TS, PWS, CRI, SHOX-D and those born SGA. The report extends the previous review by actively searching for studies that report growth outcomes, body composition, biochemical markers or quality of life (QoL).

Methods

Data sources

The systematic review of clinical effectiveness used a priori methods that are described in the research protocol. We searched key databases (e.g. MEDLINE, EMBASE, NHS Economic Evaluation Database and eight others) for relevant studies from their inception to June 2009, limiting to the English language. Relevant conferences, bibliographies of included papers, our expert advisory group and manufacturers' submissions (MSs) to NICE were also consulted to identify any additional published or unpublished references. We developed an economic model using the best available evidence to determine cost-effectiveness in the UK.

Study selection

Two reviewers assessed titles and abstracts of studies identified by the search strategy, obtained the full text of relevant papers, and screened them against the inclusion criteria as defined in the research protocol. Any differences in opinion throughout the process were resolved through discussion.

Key inclusion criteria were:

- *patients* children with GHD, TS, PWS, CRI, SHOX-D or born SGA
- *treatment* rhGH
- *comparator* treatment strategies without somatropin
- *outcomes* height, height standard deviation score (HtSDS), growth velocity (GV) and SDS, body composition, biochemical markers, QoL, adverse events (AEs)
- *study type* randomised controlled trials (RCTs), systematic reviews.

Data extraction and quality assessment

Data from included studies were extracted by one reviewer and checked by a second. The quality of included studies was assessed using standard criteria. Criteria were applied by one reviewer and checked by a second, with differences in opinion resolved by discussion and involvement of a third reviewer where necessary.

Data synthesis

Clinical effectiveness studies were synthesised through a narrative review, with tabulation of results of included studies. Meta-analysis was not appropriate due to heterogeneity of study design and participants.

Economic model

A decision-analytical model was developed to estimate the cost-effectiveness of rhGH treatment compared with no treatment for a cohort of children with GHD, TS, PWS, SGA, CRI and SHOX-D. The model was based upon that developed in a previous Health Technology Assessment (HTA) report but was extended by including QoL factors. The perspective of the

analysis was that of the UK NHS and Personal Social Services (PSS). The model was informed by a systematic search of the literature to identify parameters on the natural history and epidemiology of the indicated conditions, health-related quality of life (HRQoL) and costs. The model estimated the lifetime costs and benefits of rhGH with discount rates of 3.5%. The intervention effect in terms of improvement of HtSDS was derived from the systematic review of effectiveness. The outcome of the economic evaluation is reported as cost per quality-adjusted life-year (QALY) gained and cost per centimetre gained.

Results

Number and quality of studies

Of the 674 references identified, 560 were excluded on inspection of their titles and abstracts. The full papers of 114 references were retrieved, of which 28 RCTs in 34 publications were included in the systematic review of clinical effectiveness. Overall, the studies were generally poorly reported and some were of short duration.

Summary of benefits and risks

None of the studies reported QoL measures, and reporting of AEs was limited. Only one of the included studies reported adult height (AH).

Growth hormone deficiency (one RCT)

Children in the rhGH group grew 2.7 cm/year faster than children in the untreated group and had a statistically significantly higher HtSDS after 1 year: –2.3 ± 0.45 versus –2.8 ± 0.45.

Turner syndrome (six RCTs)

Girls in one study grew an average of 9.3 cm more than untreated girls. In a study of younger children, the difference was 7.6 cm after 2 years. HtSDS values were statistically significantly higher in treated than in untreated girls.

Prader–Willi (eight RCTs)

Infants who received rhGH for 1 year grew significantly taller (6.2 cm more) than those in the untreated group in the only study to report change in height. Two studies reported a statistically significant difference in HtSDS in favour of rhGH. rhGH-treated patients had statistically significantly higher lean body mass (LBM) and lower body fat than untreated patients in three studies. Effects on body mass index (BMI) were mixed.

Chronic renal insufficiency (six RCTs)

Recombinant human growth hormone-treated children in a 1-year study grew an average of 3.6 cm more than untreated children. HtSDS was statistically significantly higher in treated than in untreated children in two studies.

Small for gestational age (six RCTs)

No RCTs met the original inclusion criteria for the review, so these were amended to include children from the age of 3 years with no catch-up growth, with no reference to mid-parental height. Only one out of the six included RCTs used the licensed dose; the others used doses two or three times higher. AH was approximately 4 cm higher in rhGH-treated people in the only study to report this outcome. AH-gain SDS was also statistically significantly higher in this study's rhGH group. Mean HtSDS was higher in treated than untreated patients in four other studies, significantly so in two of these.

SHOX deficiency (one RCT)

After 2 years of treatment, children were approximately 6 cm taller than the control group and HtSDS was statistically significantly higher in treated than in untreated patients.

Summary of cost-effectiveness

The systematic review of published economic evaluations identified two North American studies for children with TS and GHD and no studies conducted in the UK. The results of the two identified studies produced two very different estimates of cost-effectiveness, largely due to the choice of utility estimates and assumptions on effectiveness.

The systematic review of QoL identified only six studies, mostly of poor methodological quality and for small numbers of individuals. One reasonable study was found for GHD. An additional study was found, which estimated QoL utilities in the general adult population according to height, using the Health Survey for England. These studies suggested that there is likely to be a small gain in utility from rhGH.

Six of the seven manufacturers submitted evidence to be considered for this review. Five out of the six manufacturers collaborated and submitted essentially the same electronic model. The model developed was based upon the previous HTA report but was extended to consider longer-term outcomes in order to estimate cost-effectiveness in terms of QALYs. In the manufacturers' base case, the cost-effectiveness results for all conditions were less than £30,000 per QALY gained.

From the model we developed for this review, the incremental cost per QALY estimates of rhGH compared to no treatment were: £23,196 for GHD, £39,460 for TS, £135,311 for PWS, £39,273 for CRI, £33,079 for SGA and £40,531 for SHOX-D. A further analysis was run for PWS, which included a lifelong improvement in body composition of 1.8 BMI and an associated additional utility of 0.031. Under these assumptions, the cost-effectiveness of PWS reduced to £54,800 per QALY gained.

The effects of a range of parameter values for the economic model were evaluated in sensitivity analyses. The model results were found to be most sensitive to the discount rate used. All conditions, except PWS, were cost-effective for a willingness-to-pay threshold of £30,000 per QALY when the previous NICE discount rates of 6% for costs and 1.5% for benefits were used. The model results are also sensitive to treatment start age and length, compliance and utility gain. The probability sensitivity analysis (PSA) estimated the probability of each of the conditions to be cost-effective at £30,000 to be: 95% for GHD, 19% for TS, 1% for PWS, 16% for CRI, 38% for SGA and 15% for SHOX-D.

Discussion

The systematic review was restricted to RCTs because these provide the highest level of evidence for clinical effectiveness. However, very few of these reported either final height (FH) or QoL as outcome measures, most were only 1 or 2 years in length, and some had very few participants. We did not identify any RCTs that met the original inclusion criteria for children born SGA, so these had to be amended. Only one of the included trials used the licensed dose, so results from the other five could overstate the effectiveness of rhGH treatment for this patient group.

The QoL gains were highest for individuals with lower starting heights; for those with starting height of less than < –2 HtSDS the QoL gain was minimal. For example, those with PWS had a starting height of –2 HtSDS, and so for this group of patients the health gain (in terms of height) is small; therefore, rhGH treatment has high incremental cost-effectiveness ratio (ICER) values compared with no treatment. Patients with PWS may experience an improvement in body composition due to rhGH treatment, and this is often the point of treatment rather than gain in height, but this was difficult to quantify, especially in the long term.

The cost-effectiveness results in the current report varied from those in the MS and the previous HTA report. The incremental costs reported are generally consistent between the three models. In general, the results, presented in terms of centimetres gained, are more favourable in the current analyses than in those in the previous HTA report. The ICERs in the MS are considerably more favourable than the current analysis, due to higher estimates of utility gain.

The current analysis has not considered other benefits in addition to height gain within the model, apart from as a scenario analysis for PWS. The base case does not include possible benefits from changes in body composition, such as reduced risk of diabetes or cardiovascular disease, which may result in increases in life expectancy. At this stage, these health gains would be purely speculative due to lack of data, and it is not possible to quantify them. It is also possible that there may be additional psychological benefits such as improved self-esteem.

Conclusions

The included studies reported statistically significantly larger HtSDS values for rhGH-treated children than untreated children with GHD, TS, PWS, CRI, SGA and SHOX-D. rhGH-treated children with PWS also showed statistically significant improvements in body composition measures compared with controls. The cost-effectiveness estimates from our model vary between conditions. Only GHD would be considered cost-effective according to a willingness-to-pay threshold of £20,000–30,000 per QALY gained. TS, CRI, SGA and SHOX-D have ICERs between £33,000 and £40,500 per QALY gained. PWS has an ICER of between £55,000 and £135,000 per QALY gained, depending on assumptions.

Key research priorities

- Longer studies beyond 2 years, reporting near-FH or final AH.
- A standardised QoL assessment specifically designed for children and adults, to be used in future RCTs and QoL studies.
- Good-quality trials of rhGH in children born SGA, where the children included and the dose administered match the licensing criteria.
- Good-quality studies of the long-term effects of rhGH on body composition, psychological benefits, long-term morbidities (such as diabetes or cardiovascular disease) and life expectancy, particularly for individuals with PWS.

Chapter 1
Background

Description of health problem

The first part of the chapter (see sections Growth hormone deficiency to Small for gestational age) describes the health problem individually for the different conditions covered in this review, in terms of their aetiology and epidemiology. The second part of the chapter (see sections Impact of health problem to Current usage in the NHS) covers the impact of the health problems and measurement of disease for all the conditions combined.

Growth hormone deficiency

Growth hormone deficiency (GHD) occurs when the pituitary gland fails to produce sufficient levels of growth hormone (GH).

There is some debate about the diagnostic criteria for GHD: the diagnosis of GHD includes short stature, growth velocity (GV) below the 25th percentile for at least 1 year, and delayed bone age.[1] Rosenfeld[2] suggests other criteria: height > 3 standard deviations (SDs) below the mean, < –2 SD to –3 SD for age and deceleration in growth (such as GV < 25th percentile for age), GV < 5th percentile where there is no other explanation, a predisposing condition along with growth deceleration or other signs of pituitary dysfunction. Juul and colleagues[3] found 'large heterogeneity in the current practice of diagnosis and treatment of childhood GHD'. Their survey of European paediatricians found that the cut-off points of GH peak response used for diagnosis of deficiency clustered around 10 ng/ml or 20 mU/l.

The primary goals of recombinant human growth hormone (rhGH) treatment for children with GHD are to normalise height during childhood, for the treated child to reach a 'normal' adult height (AH) as defined by the parental target and for mature somatic development to be reached around age 25.[4] The British Society for Paediatric Endocrinology and Diabetes (BSPED) recommends 3- or 6-monthly growth monitoring, annual insulin-like growth factor-1 (IGF-1)/ insulin-like growth factor building protein-3 (IGFBP-3) monitoring, and compliance assessment at each appointment.[5]

Aetiology, pathology and prognosis

Growth hormone deficiency can be caused by a variety of factors, but in many cases the cause is unknown. In some children, failure or reduction in GH secretion is congenital, and may be accompanied by other pituitary hormone deficiencies. In others, GHD is acquired as a result of trauma (either at birth or later in childhood), histiocytic infiltration (build up of tissue cells), lymphoma or leukaemia, tumours involving the pituitary gland or hypothalamus or following radiotherapy.[6] Untreated patients have a final height (FH) of 134–146 cm in males and 128–134 cm in females.[1]

Incidence and prevalence

The UK Child Growth Foundation estimates that GHD of unknown origin occurs in about one in every 3800 births,[7] but reliable figures are difficult to obtain for GHD that is associated with radiotherapy and other causes. Figures from a study in Belgium[8] indicate an overall prevalence of GHD of 1 in 5600. The origin of GHD was stated to be unknown in 41% of the patients in this Belgian study, congenital in 20% and acquired in 35%.[8] While the authors of this study state that these yearly numbers have remained similar across the 16 years of the study, these were not collected as part of a formal screening study, and, as a result, the study authors believe that this figure is an underestimation.[8]

A Danish study calculated incidence rates of childhood-onset growth hormone deficiency (CO-GHD), based on 1823 patients incident during 1980–99. The average incidences per 100,000 population were calculated to be 2.58 [95% confidence interval (CI) 2.3 to 2.88] for males, and 1.70 (95% CI 1.48 to 196) for females. The differences between the sexes was statistically significant ($p < 0.001$).[9] Other sources suggest that the disorder is two to three times more common in boys than in girls.[7] A hereditary factor may be identified in some children; about 3% of children with GHD also have an affected sibling.[7]

Turner syndrome

Aetiology, pathology and prognosis

Turner syndrome (TS) is caused by the complete or partial absence of the second sex chromosome in girls, with or without cell line mosaicism (the presence of two populations of cells with different genotypes in one individual), leading to the presence of characteristic physical features including, but not limited to, short stature.[10,11] Other features of TS can include skeletal abnormalities, higher risk of scoliosis, cardiovascular abnormalities, lymphoedema, and higher rates of hearing problems and ear malformations.[11]

While short stature is the most common clinical feature of TS,[11] in the majority of girls with TS the missing or abnormal second chromosome causes ovarian failure, leading to lack of pubertal progression and sexual maturation. TS girls therefore receive estrogen replacement therapy as part of their treatment.

Untreated, the average AH deficit in women with TS is 20 cm, with the average height being 143 cm (4 ft 8 in.).[12] Cases of reduced stature are thought to be predominantly due to haploinsufficiency of the short stature homebox-containing (SHOX) gene.[13] Not all girls with TS will require rhGH treatment and the condition does not necessarily involve a deficiency in natural GH secretion, although there may be a relative lack of sensitivity to GH, and, in some cases, diminished secretion.[6,14]

Incidence and prevalence

The European Surveillance of Congenital Abnormalities (EUROCAT) reported in 2003 that TS occurred in 2.08 per 10,000 births in the UK in 2002,[15] which equates to approximately one in 2500 live-born females.[11] A Belgian study analysed age at diagnosis of 242 TS girls who were treated with rhGH between 1991 and 2002.[16] The median age at diagnosis was 6.6 (range 0–18.3) years. Although the survey found that 22% of girls were diagnosed after the age of 12 years, there was a general increase in earlier diagnosis in infancy and childhood compared with a previous survey.

A study in Denmark[17] identified a standardised mortality rate (SMR) of 2.89 in their TS population, which was increased compared with the general population. However, this significantly decreased over the 3 years of the study. It is unclear if this is due to a real decrease in mortality, better care of individuals with TS, or an increase in karyotypes with lower mortality.[17]

Prader–Willi syndrome

Prader–Willi syndrome (PWS) is a genetic disorder characterised by short stature, abnormal body composition, hypogonadism, obesity, dysmorphic features, hyperphagia (compulsive overeating), hypotonia (diminished muscle tone), and specific learning and behavioural issues.[18]

Aetiology, pathology and prognosis

The genetic basis of the syndrome is a deletion on the long arm of the paternally derived chromosome 15 (15q11-q13), which is found in approximately 70% of affected individuals.[19] Other abnormalities have been identified, including maternal uniparental disomy (two maternal copies of chromosome 15 and no paternal chromosome 15), imprinting mutations and translocations. Abnormalities to chromosome 15 lead to disruption of the hypothalamus, which controls appetite. The combination of impaired growth, abnormal body composition and hypothalamic dysfunction (hyperphagia, hypogonadism) is suggestive of GHD.

Birth length and weight are normal or just below normal in PWS, but growth is slow due to poor feeding. The child is noticeably short from around the first year of life and remains short throughout childhood [mean height standard deviation score (HtSDS) –2] despite normal growth rate.[20] Hypotonia at birth improves towards the end of the first year of life, and developmental milestones are achieved although delayed. By 2 or 3 years of age the hyperphagic phase of the condition begins, and, unless eating is controlled, the child will become obese.[18]

Behavioural features include food seeking, temper tantrums, obsessive–compulsive disorders, high pain threshold, sleep disturbances, and skin picking. Learning disabilities are always present to some degree.[20] Hypogonadism causes delayed but complete puberty in females, although menses are infrequent or absent. Males have cryptorchidism (undescended testis) at birth and usually require androgen replacement therapy from mid-puberty, even after successful orchidopexy.[18]

During adolescence, the growth rate declines as a result of the absence of pubertal growth spurt. Reported mean FHs in the UK are 155 cm (–3.2 SD) for males and 147 cm (–2.8 SD) for females.[21] Body composition shows increased fat mass (FM) and reduced fat-free mass, resulting in a high fat–lean body mass (LBM) ratio, even in children with normal weight–height ratios.

In addition, bone mineral density is reduced. The reduced bone density is multifactorial; in older patients this is due to sex steroid deficiency (hypogonadism), whereas in younger patients this is due to hypotonia, which responds to rhGH therapy.[22]

The prognosis of the condition in adulthood can be reasonable if the person can find occupation and can live in an environment where access to food can be controlled. However, many adults with the disorder develop morbid obesity, often accompanied by type 2 diabetes, resulting in premature death from cardiorespiratory failure.[18]

Incidence and prevalence

One UK study estimated a birth incidence for PWS of 1 : 20,000, with a lower bound of 1 : 29,000.[23] The study gave a population prevalence of 1 : 52,000, considered the lower bound, with county rates varying from 1 : 42,000 to 1 : 67,000.[23] The overall death rate for the PWS population aged 3.4–56 years was found to be around 3% in one UK study compared with the standard death rate of about 0.3% each year for people in England and Wales up to the age of 55 years.[23]

Chronic renal insufficiency

Chronic renal insufficiency (CRI) is defined as a persistent elevation of serum creatinine and/or urea level. It can be caused by a variety of conditions, including congenital disorders, glomerular disorders and infections. Growth failure associated with CRI can be caused by acidosis, rickets, GH resistance, inadequate nutrition and anorexia.[24] Children with CRI experience impaired growth once their glomerular filtration rate (GFR) falls to 50% of normal, with increasing problems once the GFR falls below 25%.[25] Following kidney transplantation, chronic graft rejection and treatment with steroids can restrict growth and development.[26] Patients undergoing haemodialysis or peritoneal dialysis can be considered for rhGH treatment, as well as those who have received kidney transplantations.

Aetiology, pathology and prognosis

Chronic renal insufficiency is characterised by a GFR of < 75 ml/min per 1.73 m^2 of body surface area (BSA).[27] The term *chronic kidney disease* (CKD) is also sometimes used,[27] following guidelines developed by the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI).[28]

The aetiology of growth failure in children with CRI includes abnormalities in the GH-IGF-1 axis, together with nutritional and metabolic problems.[27] Nutritional supplementation in malnourished children with CRI can improve growth.[29–31] The NKF KDOQI guidelines recommend that patients' existing nutritional deficiencies and metabolic abnormalities should be corrected before considering treatment with rhGH.[32] However, it is estimated that growth remains suboptimal, even with energy intake above 80% of the recommended daily allowance.[33]

Not all patients with CRI will be shorter than average, but figures from the UK Renal Registry indicate that 29% of transplant patients and 41% of dialysis patients are below the second percentile for height.[34] Children with congenital disorders (approximately 60% of children with CRI)[26] are usually of normal length at birth, but are below the 3rd percentile for height within their first year and remain parallel to normal percentiles throughout childhood.[26] A cohort study of CRI patients who grew up before rhGH treatment was available reported that more than two-thirds remained shorter than the average population.[35] One study reported a mean height from birth to age 10, which was –2.37 SD ± 1.6 below the mean.[26] Similarly, FH is reported to be reduced to below the 3rd percentile in patients who developed end-stage renal failure (ESRF) in childhood.[26] Adult FH was more than 2 SDs below the mean for approximately 60% of boys and 41% of girls who started renal replacement therapy before they were 15 years old.[36]

Incidence and prevalence

It is difficult to find accurate figures for CRI, and these do not appear to be available nationally. The UK Renal Registry reports an incidence of established renal failure (ERF) of 8.0 per million of the population who are under the age of 15 years.[37] However, ERF is more severe than CRI, so can really serve only as a guide to the minimum number of patients for whom rhGH might be appropriate.

The UK Renal Registry reported that in 2005 there were 748 patients under the age of 18 years who were on renal replacement therapy in the UK's 13 paediatric renal centres,[34] corresponding to a prevalence of 47.7 per million.[37] However, the number of patients with CRI will be higher than this, as not all will require renal replacement

therapy. ERF is reported to be more common in males than in females (ratio 1.54 : 1), due to the prevalence of males with renal dysplasia and obstructive uropathy causing ERF.[37]

Small for gestational age

There are various thresholds for defining a child as being born 'small for gestational age' (SGA), the most commonly used being where the birth height or weight is ≤ 2 SDs below the population average, or is below the 10th centile for birthweight.[38] However, this group is heterogeneous in composition. Between 50% and 70% of these babies are 'constitutionally small' but otherwise healthy. The other babies in the group are those who have not reached their height or weight potential, having possibly experienced fetal growth restriction (FGR).[38] For this reason, the terms intrauterine growth restriction/retardation (IUGR) and SGA are not synonymous: a child born SGA has not necessarily undergone IUGR or FGR, and a child who has IUGR or FGR may not necessarily be born SGA.

Aetiology, pathology and prognosis

There are several possible causes for children being born SGA. These include maternal factors (such as age, ethnicity, weight, height, parity, medical conditions, smoking, malnutrition and alcohol abuse), placental factors, and fetal factors (such as chromosomal abnormalities and genetic defects).[39] Children classified as SGA may have concurrent diagnoses, such as familial short stature, TS, GHD or skeletal dysplasia.[39]

More than 80% of babies born SGA will achieve catch-up growth (GV greater than the median for chronological age and gender[39]) during their first 6 months,[40] with catch-up growth completed within 2 years for most SGA infants.[41,42] However, babies born prematurely who are SGA may take around 4 years to achieve catch-up growth.[43] Around 50% of the children who do not experience catch-up growth at this stage will go on to achieve their target height. It has been estimated that approximately 10% of SGA children remain at a height below –2 SD throughout their childhood.[44,45] Children who are born SGA with low birth weight and who do not achieve catch-up growth by the age of 2 years face a relative risk of short stature (< –2 SDs) of 5.2 at the age of 18 years.

Incidence and prevalence

A study of US births estimated an annual incidence of 91,000 infants born SGA, using a definition of SGA as –2 SDs, or equivalent to the 2.3 percentile.[39] A Swedish study of full-term births in 1973–5 found that 5.4% of neonates were SGA, defined as being < –2 SD for birth length and/or height.[46] However, other studies have cited an incidence of around 3% of babies being born SGA.[47,48]

SHOX deficiency

Aetiology, pathology and prognosis

The SHOX gene is located on the distal ends of the X and Y chromosomes. This gene plays a significant role in long bone growth, and normal growth requires two functional copies.[49,50] Growth impairment can result from having a haploinsufficiency of SHOX, or from mutations.[49] Clinical features associated with short stature homeobox-containing gene deficiency (SHOX-D) include disproportionate shortening of the middle sections of the limbs (mesomelia), bowing of the forearms and lower legs, cubitus valgus (increased carrying angle of elbow) and Madelung deformity of the wrist.[49] However, not all people with SHOX-D will have these physical characteristics. Langer syndrome is a rare homozygous (or compound heterozygous) form of SHOX-D. It is characterised by extreme dwarfism, profound mesomelia and severe limb deformity.[49,51,52]

Incidence and prevalence

Short stature homeobox-containing gene deficiency could be the underlying cause of restricted height in some children whose short stature cannot be explained by an underlying pathology. Estimates of the prevalence of SHOX haploinsufficiency in children with short stature of unknown origin range from 1% to 12.5%.[13,53–59] Rappold and colleagues[56] studied 900 short children and found SHOX mutations in 2.4% of the patients with short stature of unknown origin, implying a prevalence of at least 1 in 2000 children. Binder and colleagues[57] reported a lower prevalence of SHOX haploinsufficiency, estimating it to be 1 : 4000.

Short stature homeobox-containing gene deficiency also causes short stature in people with concurrent diagnoses. Huber and colleagues[59] reported that 68% of 56 children with dyschondrosteosis (a rare form of dwarfism) had SHOX anomalies. Other screening studies have reported it as the cause of short stature in approximately 70% of patients with Léri–Weill syndrome (LWS).[60] Girls with TS have only one copy of the SHOX gene, and this haploinsufficiency causes short stature in some girls and women with the condition.[49]

A small study[61] that compared 26 SHOX-haploinsufficient people with 45 of their relatives and general population standards found that the SHOX haploinsufficient cohort was 2.14 SDs (3.8 cm) shorter at birth and 2.1 SDs shorter throughout childhood. Females were more severely affected than males, with women's FH being 2.4 SDs (14.4 cm) shorter than unaffected siblings, and men's FH being 0.8 SDs (5.3 cm) shorter. SHOX haploinsufficiency led to short stature in 54% of the cohort, short arms in 92% and Madelung deformity in 73%. It is not clear whether the SHOX haploinsufficient cohort in this study had concurrent diagnoses.[61]

Impact of health problem

Severe short stature may be physically debilitating in untreated children,[62] with children being at greater risk of bullying at school and social isolation.[63] Some children with short stature may also have difficulties with emotionally immature behaviour, anxiety and poor school performance.[64] However, not all children who are shorter than their peers will experience problems. For example, the Royal College of Obstetricians and Gynaecologists states that the majority of children born SGA do not have any appreciable morbidity or mortality.[38] However, others indicate that children born SGA who remain short may suffer from alienation, low self-esteem, impaired social dynamics, behavioural problems, lower educational achievement and professional success.[39,43]

Children with short stature can also be at increased risk of morbidity and mortality in later life. For example, the risk of cardiovascular morbidity is increased in patients with GHD,[65] TS,[66] and PWS,[67] while some patients with growth disorders may also be at increased risk of type 2 diabetes and metabolic syndrome.[67,68] Low birth weight is also associated with future increased risk of coronary heart rate and stroke.[69]

Outcome measures

The main parameter used to measure the efficacy of rhGH treatment is growth. This reflects the main goals of therapy, which are physiological catch-up growth if possible, achievement of normal height during childhood, timely and normal growth during puberty and normal height in adulthood. In children with PWS, treatment with rhGH aims to improve body composition as well as boosting growth.

Measures of growth include:

- *Final height (FH) or adult height (AH)* Measured either in centimetres or expressed as a standard deviation score (SDS), this is the best measure of how rhGH treatment affects growth. FH has been achieved when the growth rate has slowed to less than some specified amount (e.g. 1–2 cm/year), and radiographs of the wrist and hand show that the epiphyses have closed (often expressed as a bone age of more than 14–15 years).[6] Ideally, FH would be calculated in comparison with an untreated control group in a randomised controlled trial (RCT). Some non-RCT designs use historical controls, which may overestimate the effects of rhGH treatment. Similarly, database studies may not include all relevant factors or be representative samples of treated patients.[6]
- *Near-final height (NFH)* Sometimes reported where it is assumed that FH has been reached using the above criteria, but it is acknowledged that growth may not yet be quite complete.[6]
- *Height* Usually measured standing, using a wall-mounted Harpenden stadiometer or a similar device. For very young children, supine length is measured.
- *Height standard deviation score (HtSDS)* This expresses height relative to norms for children of the same age, allowing comparisons that are independent of age or gender. The normal population mean is zero and a normal SD score will lie between –2 and +2 SDs. Increase over time in SDS or upward centile crossing implies catch-up growth and a decrease implies growth failure. Calculation of SDS depends on the reference data used, i.e. normal height for children in the same country.
- *Growth velocity (GV)* Also referred to as height velocity, this is the change in height over a specified period, e.g. cm/year. Although the overall effectiveness of rhGH in treating short stature is to be found in measures of FH, velocity may be a better interim growth measure than height attained at a particular age, as it is independent of growth in previous years.
- *Growth velocity standard deviation score (GVSDS)* This is the GV relative to norms for children of the same age.
- *Bone age (BA)* A measure of skeletal maturity, usually determined by examining the relative positions of the bones in the left hand and wrist from a radiograph. The measurement of BA relative to chronological age is important in height-prediction models. In addition, BA

assessments are used to evaluate when the epiphyses have closed and growth is complete. The interim assessment of BA is important in determining whether treatment is advancing bone maturity, such that short-term GV might come at the expense of early closure of the epiphyses. Clinical trials often measure BA to monitor whether this is accelerating undesirably fast in rhGH-treated patients compared with control patients. Height for BA can also be used as an estimate of improved height potential in response to rhGH therapy, especially in short-term studies.

Measures of body composition assess obesity and the amount of fat relative to other body tissues. Body mass index (BMI) calculates the ratio of body mass to the square of body height, expressed as kg/m^2. The National Institute for Health and Clinical Excellence (NICE) recommends BMI as providing a practical estimate of overweight in children, although mentions that it needs to be interpreted with caution as it is not a direct measure of adiposity.[70] Dual-energy X-ray absorptiometry (DEXA) can be used to measure lean mass (fat-free mass) and percentage body fat, which can be used to indicate body composition.

Physiological outcomes reported in studies of rhGH may include assessments of the concentrations of hormones, glucose, cholesterol, and markers of bone and general metabolism. Such measures are important for assessing the biochemical, metabolic and adverse effects of rhGH, and can have implications for long-term health. IGF-1 is an endocrine hormone that is produced by the liver, and its production is stimulated by GH. Lower than normal levels are therefore seen in people with growth disorders. The insulin-like growth factor building proteins (IGFBPs) act as carrier proteins for IGF-1. There are six IGFBPs, with IGFBP-3 being the most abundant.[71] IGF-1 is monitored during rhGH therapy as there is a theoretical concern that persistently elevated levels may predispose the patient to other diseases later in life. Monitoring levels also helps to tailor the dose to the individual. As IGFBP-3 binds IGF-1, monitoring this gives an indication of the levels of 'free' IGF-1 in circulation. High levels of IGF-1 with low levels of IGFBP-3 may be linked with breast, colorectal and prostate cancer.[72,73]

Current service provision

Management of rhGH therapy

Children who receive rhGH therapy require regular review by consultant paediatric endocrinologists. Older children and adolescents in need of continued rhGH therapy may enter transitional care arrangements that involve consultations with both paediatric and adult growth specialists.[74] A system of shared care is sometimes used for rhGH therapy in the UK,[1] with diagnosis and assessment of growth being carried out in hospital outpatient consultations and some GPs writing prescriptions and possibly monitoring adverse events (AEs). In other areas, all care including prescriptions and monitoring of compliance and side effects takes place in secondary care.

Administration of rhGH is usually carried out at home by the patient or a family member, after training, by subcutaneous injection, using either needled or needle-free devices, usually pharmaceutical companies' devices rather than syringe and needle. Termination of rhGH therapy is indicated if there is a poor response (< 50% increment in GV within the first year) or when FH is achieved. In children with CRI, therapy with rhGH is stopped at the time of a transplant. Therapy would not resume until at least 1 year post transplant, and is dependent upon the absence of catch-up growth.[1]

Relevant guidance

Current guidance from NICE on the use of rhGH in England and Wales for children with growth failure due to GHD, TS, PWS or CRI was published in 2002.[75] This is discussed further later in the chapter (see Place of the intervention in the treatment pathway). Since 2002, a range of guidance on the use of rhGH in children with short stature has been published by various national health agencies and clinical expert groups for GHD, TS, CRI, PWS and SGA, but guidance for children with SHOX-D is lacking.

Guidelines on the use of rhGH for the treatment of girls and women with TS (published in 2007, relevant to US practice) recommended that treatment with rhGH should be considered as soon as growth failure has been identified, and its potential risks and benefits have been discussed with the family. It also provided rhGH dosing information and a comprehensive set of recommendations for the diagnosis, evaluation, monitoring and ongoing care of children with TS.[11]

Summary guidelines[76] and detailed recommendations[27] on the use of rhGH for short stature in children with CRI (published in 2005–6, relevant to US practice) recommended that therapy should not commence unless patients

exhibit clearly defined CRI and attain appropriate phosphorus and parathyroid hormone status.[76] The detailed recommendations included rhGH dosing information and a treatment algorithm outlining appropriate steps to improve growth and overall health outcomes.[27]

Consensus statements on using rhGH therapy in children and adults born SGA (published in 2003[39] and 2007,[77] relevant to European and US practice) emphasised the need for accurate diagnosis of SGA and recommended that rhGH therapy should be considered in children who are SGA and older than 2 years of age. However, this reflects differences in licensing in Europe and America. The Food and Drug Administration (FDA) authorisation is for children aged 2 years and over with no catch-up growth (no criteria specified), and no specified HtSDS at start of treatment or reference to mid-parental height.[78] By contrast, the European Medicines Agency (EMEA) authorisation is for children aged 4 years and over, with a HtSDS of –2.5 at start of treatment, with a GV < 0 SDs and HtSDS > 1 SD below mid-parental height.[79] In addition, the licensed dose is 70 µg/kg/day in the USA and 35 µg/kg/day in Europe.

For UK populations, guidelines on rhGH therapy for children with GHD, TS, CRI, PWS and SGA was published in 2006 by BSPED.[1] This guidance provided recommendations for shared care between GPs and specialists, together with dosing information and treatment entry and exit criteria.

Description of technology under assessment

Somatropin (rhGH) has been available since 1985, following the withdrawal of cadaveric human pituitary GH due to possible transmission of Creutzfeldt–Jakob disease.[6] rhGH is a synthetic form of human GH, produced by recombinant deoxyribonucleic acid (DNA) technology, having a sequence identical to that of pituitary-derived human GH. Licensed dosages vary for the different indications (*Table 1*), depending on whether the treatment is aiming to replace GH to normal levels (for children with GHD) or being used in supraphysiological doses where there is no hormone deficiency but some lack of sensitivity to the hormone. It is given as a subcutaneous injection, usually at night (to mimic the child's natural fluctuations in GH).[6]

Seven pharmaceutical companies have UK marketing authorisations for various indications, as shown in *Table 1*.

Adverse events (AEs) have been reported in patients using rhGH. For example, sleep apnoea and sudden death among patients with PWS who have one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnoea, or untreated respiratory infection.[80,81] There are potential risks of acromegaly, hyperglycaemia and glucosuria if the recommended dosage is exceeded.[81] Patients receiving rhGH should be monitored for glucose intolerance, as the drug may induce a state of insulin resistance.[81] It is also recommended that thyroid function should be monitored.[81] Possible side effects mentioned for 1–10% of patients include hypersensitivity to solvent, hypothyroidism, injection site pain (reaction) and oedema.[81] Treatment should be discontinued in the event of intracranial hypertension,[81] although it may be possible to restart treatment at a lower dose for patients who develop benign intracranial hypertension. Treatment with rhGH leads to increasing sensitivity to GH, expressed as an increase in serum IGF-1.[81]

Omnitrope, marketed by Sandoz, is a biosimilar product. This means that it is an active substance that is similar, but not identical, to the other drugs considered in this review. The issue of rhGH therapy and biosimilars in clinical practice was the subject of a recent Parliamentary Summit.[30] The current review assesses the clinical effectiveness and cost-effectiveness of rhGH, without reference to the brand product or manufacturer. Discussion of the comparative safety and efficacy of biosimilars compared with reference products is therefore beyond the scope of this review.

Place of the intervention in the treatment pathway

The place of rhGH in the treatment pathway depends on the child's particular condition or syndrome, and age at diagnosis. Appropriate timing of treatment with rhGH will depend on the underlying pathology. rhGH therapy is contraindicated in cases of progressive tumour activity and should not be used for growth promotion in children with closed epiphyses.

GHD

Treatment with rhGH is currently recommended by NICE to help increase the growth of children with GHD.[75] For children with congenital GHD, rhGH therapy is not generally started before the child is 4 years old.[6] However, if there is profound growth

TABLE I *Indications for the use of rhGH in children*

Indication	Dose[a]	Licensed drugs (manufacturers)
GHD	23–39 mcg/kg daily, or 0.7–1.0 mg/m^2 daily	Humatrope (Eli Lilly & Co. Ltd) Zomacton (Ferring Pharmaceuticals UK) NutropinAq (Ipsen Ltd) Norditropin Simple Xx (Novo Nordisk Ltd) Genotropin (Pfizer Ltd) Omnitrope (Sandoz Ltd) Saizen (Merck Serono)
TS	45–50 mcg/kg daily or 1.4 mg/m^2 daily	Humatrope (Eli Lilly & Co. Ltd) Zomacton (Ferring Pharmaceuticals UK) NutropinAq (Ipsen Ltd) Norditropin Simple Xx (Novo Nordisk Ltd) Genotropin (Pfizer Ltd) Omnitrope (Sandoz Ltd) Saizen (Merck Serono)
PWS, with GV > 1 cm/year (in combination with energy-restricted diet)	35 mcg/kg daily or 1.0 mg/m^2 daily; max. 2.7 mg daily	Genotropin (Pfizer Ltd) Omnitrope (Sandoz Ltd)
CRI in children	45–50 mcg/kg daily or 1.4 mg/m^2 daily	Humatrope (Eli Lilly & Co. Ltd) NutropinAq (Ipsen Ltd) Norditropin Simple Xx (Novo Nordisk Ltd) Genotropin (Pfizer Ltd) Omnitrope (Sandoz Ltd) Saizen (Merck Serono)
SHOX-D	45–50 mcg/kg daily	Humatrope (Eli Lilly & Co. Ltd)
Growth disturbance (current HtSDS –2.5 and parental adjusted HtSDS, –1) in short children born SGA, with a birth weight and/or length below –2 SDs, who failed to show catch-up growth (HV SDS < 0 during the last year) by 4 years of age or later	35 mcg/kg daily or 1.0 mg/m^2 daily	Humatrope (Eli Lilly & Co. Ltd) Norditropin Simple Xx (Novo Nordisk Ltd) Genotropin (Pfizer Ltd) Omnitrope (Sandoz Ltd) Saizen (Merck Serono)

a Dosing information from the Electronic Medicines Compendium (http://emc.medicines.org.uk/), accessed 30 April 2008.

failure or evidence of recurrent hypoglycaemia, which may occur in infants under the age of 1, treatment may be started earlier. For children who acquire GHD at an older age, treatment can start at a time that is appropriate to their condition and stage of growth. Treatment is discontinued after the first year if there is a poor response, i.e. < 50% increase in growth rate, or if compliance or growth rate remains poor thereafter. Otherwise treatment can continue until GV is < 2 cm/year, assessed over 6–12 months, when FH is achieved. Other clinical advice suggests that treatment is necessary for the patient to attain peak bone mass, which may not be until the age of 25 or 26 in some people. A recent survey of paediatric endocrinologists (56 responses out of 72 questionnaires) found that 56% of clinics provide transfer clinics for patients ending paediatric treatment and transferring to the care of an adult endocrinologist. Of the 56 respondents, 80% retest for GHD prior to transfer, 55% transfer all rhGH-treated patients and the remainder transfer only those who are still GH deficient on retesting.[74]

Transition phase

The transition phase in GHD is defined as the period from near FH, usually around the mid to late teens, until about 25 years of age, or when final adult height has been reached. At the stage of near FH, it is important to re-evaluate whether the patient is still GH deficient, and if they need to continue with treatment and

monitoring. Some cases, such as isolated GHD with a genetically identified mutation or multiple pituitary hormone deficiency (MPHD), severe GHD due to genetic causes, pituitary abnormalities, congenital hypopituitarism or acquired GHD from tumours or cranial irradiation, are likely to require a continuation of therapy. However, cases of unknown origin and isolated cases of GHD carry a lower likelihood of requiring continuing treatment.[4] The BSPED consensus document suggests testing IGF-1 levels: if these are lower than –2 SD then these patients require GH stimulation retests. A peak GHD level of < 5μg/l during the transition phase is indicative of severe GHD.[5]

During the transition phase the authors of the consensus paper recommend that monitoring of patients should include weight and BMI at least 6-monthly, IGF-1, quality of life (QoL), waist circumference and fasting glucose annually, and body composition and total and low-density lipoprotein (LDL) cholesterol every 2–5 years.[5]

Turner syndrome

Current NICE guidance recommends that rhGH treatment for girls with TS should begin at the earliest age possible, to boost growth.[75] Some patients with profound growth retardation and failure to thrive may commence treatment earlier than those who are diagnosed later. A Belgian study[16] found that median age at diagnosis of 242 girls was 6.6 (range 0–18.3) years, although the survey found that 22% of girls were diagnosed after the age of 12 years. Some clinical expert advice suggests that the mean age for starting treatment is 8–9 years of age as many girls are not diagnosed until later in childhood, although there has been a recent trend towards earlier diagnosis.

Prader–Willi syndrome

NICE guidance currently recommends the use of rhGH for children with PWS to improve height, body composition and bone mineral density. For children with PWS, treatment with rhGH is intended to improve body composition and metabolism as well as increase FH. Its place in the treatment pathway depends on age at diagnosis. Children with PWS are assessed for obesity, potential for obstructive sleep apnoea and ongoing respiratory illness before treatment is considered. Low muscle tone and its impact on the child's development are also considered.

Chronic renal insufficiency

Treatment with rhGH is currently recommended by NICE to help increase the growth of prepubertal children with CRI.[75] The guidance recommends that treatment should be stopped after a renal transplantation, and re-established after only 1 year if it has been ascertained that catch-up growth has not occurred.[75] The place of rhGH in the treatment pathway for children with CRI depends on age at diagnosis, and on clinical factors related to management of the child's condition. rhGH treatment can take place either before or after renal transplant, although allograft rejection can be a concern if rhGH treatment is given post transplant.

Small for gestational age

Previous NICE guidelines did not consider children born SGA, as rhGH was not licensed for this indication at the time.[82] Children born SGA but with no comorbidities may not be diagnosed until they fail to achieve catch-up height by the age of 2–4 years,[39] or when they start school. The International SGA Advisory Board indicated that SGA children aged 2–4 years who show no evidence of catch-up with a height of –2.5 SD should be eligible for rhGH treatment. They also recommended that treatment should be considered in children older than four years who show no catch up at a height –2 SD or less.[39] The European licence for rhGH is for children aged 4 years and over.

SHOX deficiency

Currently, there is no NICE guidance available for the use of rhGH in children with SHOX-D. Initiation of rhGH treatment for children with SHOX-D depends on age at diagnosis. Clinical evaluation is used to assess growth failure, but GH provocation tests are not required once SHOX-D has been established via a positive SHOX DNA blood test.

Current usage in the NHS

According to a survey of endocrine clinics published in 2006 by BSPED,[74] 4758 patients have been receiving rhGH in the UK, of which 4168 were in England and Wales. Responses to the survey gave a breakdown of rhGH use by diagnosis for 3951 of the 4758 patients, indicating

that 57.4% of the patients on rhGH were treated for GHD, 18.7% for TS, 4.6% for PWS, 5.2% for SGA, 2.5% for CRI, and 11.6% for other diagnoses. If we assume that these 3951 patients are a representative sample of the total population of rhGH-treated patients in the UK, the total numbers of rhGH-treated patients with each diagnosis would be around 2731 with GHD, 890 with TS, 219 with PWS, 247 with SGA, 119 with CRI, and 552 with other diagnoses. It is possible that the number of children with CRI who received rhGH in this survey was underestimated, as some patients with CRI are managed in nephrology clinics, rather than paediatric endocrine clinics.[74] The number of patients treated with rhGH for SHOX-D was not reported in the survey and published figures are not available. Expert advice indicates that very few SHOX-deficient patients are currently receiving rhGH, for example only two of between 350 and 400 patients in one unit receiving rhGH are being treated for this. The level of service provision for SHOX-deficient patients would be similar to that required for a patient with TS.

Anticipated costs associated with intervention

The costs associated with rhGH therapy interventions comprise:

- the drug (dose adjusted for body weight)
- self-therapy training of the patients and their parents (involving home visits by specialist and community nurses)
- monitoring of treatment effectiveness (involving paediatric endocrinology outpatient visits for blood tests, a test of pituitary function, and an assessment of BA by hand radiograph).

The costs of training patients and their parents are limited to the first year of treatment. During each year of treatment, until they stop growing, patients would typically attend two outpatient consultations. Estimates of the current costs of these components of the rhGH interventions for patients with GHD, TS, PWS, CRI and SGA are provided in Chapter 4 (see Estimation of costs).

Chapter 2

Definition of the decision problem

Decision problem

Recombinant human growth hormone is currently recommended by NICE[75] for children with a proven clinical diagnosis of GHD, TS or PWS, and for prepubertal children with CRI. Since the last review, rhGH has received marketing authorisation for the treatment of children born SGA and for children with growth failure associated with SHOX-D. The scope of the current project is broader than that for the previous systematic review[6] in that it covers body composition as an outcome measure for all disease areas, and also includes biochemical and metabolic markers. In addition, evidence for the use of rhGH for children born SGA, or with SHOX-D (conditions not considered in the original review) are included in this report. For these reasons, the current systematic review was undertaken as a complete review not an update. The aim of this health technology assessment (HTA) is to assess the clinical effectiveness and cost-effectiveness of rhGH for children with GHD, TS, PWS, CRI, SHOX-D and those born SGA.

Interventions

The intervention is rhGH, also known as somatropin. It is marketed as the following products: Humatrope (Eli Lilly & Co.); Zomacton (Ferring Pharmaceuticals); NutropinAq (Ipsen); Norditropin SimpleXx (Novo Nordisk); Genotropin (Pfizer); Omnitrope (Sandoz) and Saizen (Merck Serono).

Population, including subgroups

The population consists of children with one of the following conditions: GHD, TS, PWS, CRI, SHOX-D, being born SGA. No age-specific definition of a child was given during the scoping process for this review. Possible subgroups could be children with different causes of GHD, and children with CRI who are either pretransplant or post transplant. However, analysis of the effectiveness of rhGH treatment for any of these subgroups of patients is limited by the available data and the statistical power of the identified trials.

Transition of care from paediatric to adult endocrine services of young people requires patients to have repeat testing of their GH axis to be sure that they need to continue treatment. This transition period is only considered within this review where evidence from the identified studies allows for patients whose linear growth is not complete.

Relevant comparators

The standard comparator for this review is management strategies without rhGH. This includes placebo injections and no treatment.

Outcomes

Clinical outcomes of interest include: FH gained, HtSDS, GV, GVSDS, body composition, biochemical/metabolic markers, AEs of treatment; health-related quality of life (HRQoL). Direct costs include estimates of all health-care resources consumed in the provision of the intervention, including diagnostic tests, administration and monitoring costs – as well as consequences of those interventions, such as treatment of adverse effects.

Overall aims and objectives of assessment

The aim of this report is to assess the clinical effectiveness and cost-effectiveness of rhGH treatment for children with GHD, TS, PWS, CRI, SHOX-D and those born SGA.

The objectives are to:

- summarise the evidence of clinical effectiveness and cost-effectiveness of rhGH when compared with management strategies without rhGH
- develop, where appropriate, an economic model adapting an existing cost-effectiveness model[6] or constructing a new model using best available evidence to determine cost-effectiveness in the UK
- identify priorities for future research.

Chapter 3
Assessment of clinical effectiveness

Methodology

The methods for the systematic review of clinical effectiveness were described a priori in the research protocol (Appendix 1), which was sent to experts for comment. We received helpful comments relating to the general content of the research protocol, but there was none that identified specific problems with the methods of the review. The methods are summarised below.

Search strategy

An experienced information specialist developed and tested search strategies for this review. Separate searches were carried out to identify studies reporting clinical effectiveness, cost-effectiveness, HRQoL, resource use and costs, and epidemiology/natural history of the conditions. The search strategy for MEDLINE, shown in Appendix 2, was adapted as appropriate for a number of other electronic databases. We searched: The Cochrane Database of Systematic Reviews (CDSR); The Cochrane Central Register of Controlled Trials; NHS Centre for Reviews and Dissemination (NHS CRD, University of York) Database of Abstracts of Reviews of Effectiveness (DARE) and the NHS Economic Evaluation Database (NHS EED); MEDLINE (OVID); EMBASE (OVID); National Research Register (NRR); Current Controlled Trials; ISI Proceedings; Web of Science; and BIOSIS. For all disease areas we searched the databases from their inception to June 2009. This meant there was some duplication of earlier work for the previous review, but this was necessary as the present review required searches for additional outcomes, such as biochemical and metabolic markers. Searches were limited to the English language.

Relevant conferences (European Society for Paediatric Endocrinology, The Endocrine Society, American Association of Endocrinologists, Paediatric Academic Societies) were searched for recent abstracts (up to June 2009) to assess against the inclusion criteria. Bibliographies of related papers were screened for relevant studies, and we contacted experts to identify any additional published or unpublished references. We also assessed the MSs to NICE for any additional studies that met the inclusion criteria.

Inclusion and data extraction process

Titles and abstracts of studies identified by the search strategy were assessed for potential eligibility by two reviewers. The full text of relevant papers was then obtained, and inclusion criteria were applied by two independent reviewers. At both stages of the screening process, any differences in opinion on inclusion of a particular study were resolved through discussion. Data from included studies were extracted by one reviewer using a standard data extraction form and checked by a second reviewer. Any discrepancies were identified and resolved through discussion.

Quality assessment

The quality of included studies was assessed using NHS CRD (University of York) criteria.[83] Quality criteria were applied by one reviewer and checked by a second reviewer, with differences in opinion resolved by discussion. The criteria used are shown in Appendix 3. Publication bias was not assessed.

Inclusion criteria

Patients

The inclusion criteria required the patient group to be children with growth disturbance due to one of the following licensed conditions:

- insufficient secretion of GH (GHD)
- Turner syndrome, confirmed by chromosome analysis
- Prader–Willi syndrome, confirmed by genetic testing
- chronic renal insufficiency (prepubertal children only)
- short stature homeobox-containing gene deficiency, confirmed by DNA analysis
- small for gestational age (see below).

The licensed indication[81] for SGA is for growth disturbance (current HtSDS –2.5 and parental adjusted HtSDS –1) in short children born SGA,

with a birth weight and/or length below –2 SD, who failed to show catch-up growth [height velocity (HV) SDS < 0 during the last year] by 4 years of age or later. However, the review group could not find any RCTs whose inclusion criteria matched these criteria exactly. Following discussions with NICE, the team amended the criteria to be: 'growth disturbance (current HtSDS < –2.5, *but with no reference to parental height*) in short children born SGA with a birth weight and/or length below –2 SD, who failed to show catch-up growth (*with no particular criteria specified*) by *3* years of age or later.'

Studies that included adolescents and young adults who have completed linear growth were excluded from the systematic review of effectiveness.

Interventions

Recombinant human growth hormone (somatropin).

Comparators

Management strategies without somatropin.

Outcomes

The following outcomes were included in the review, where data were available:

- final height gained
- height standard deviation score (height relative to the distribution of height in children of the same chronological age)
- growth velocity
- growth velocity standard deviation score (GV relative to the distribution of growth in children of the same chronological age or bone age)
- body composition
- biochemical and metabolic markers
- adverse effects of treatment
- HRQoL.

Types of studies

- Fully published RCTs were included in the review, and systematic reviews of RCTs were included as sources of information. Indicators of a systematic review include: explicit search strategy, inclusion criteria, data extraction and assessment of quality. While important information on FH and long-term AEs will only be available in longer, observational studies, there was a practical limit on the number of studies that could be included for this review. A pragmatic decision was therefore taken to limit study type to RCTs, in an attempt to capture the most methodologically robust data for all six of the disease areas included in this review.
- Studies published only as abstracts or conference presentations were included in the primary analysis of clinical effectiveness and cost-effectiveness if sufficient details were presented to allow an appraisal of the methodology and assessment of results.
- Non-English language studies were excluded.
- In an effort to capture all randomised evidence, all identified RCTs were included with no restriction on length of treatment, size of study population, or design (parallel group or crossover design). Crossover studies could potentially be problematic as children's growth continues without treatment, making comparisons between the different arms less straightforward than in a parallel-group trial. However, we have attempted to include discussion of this in the quality assessment of studies.

Data synthesis

- Clinical effectiveness studies were synthesised through a narrative review with tabulation of results of included studies. Key outcome measures are reported in tables in the text, and other outcomes are shown in the full data extraction forms in Appendix 4. For conciseness, where a study reported outcome measures after 1 and 2 years, only the final year's outcomes are included in the table, as these show the longest duration of treatment effect.
- Where data were of sufficient quality and homogeneity, a meta-analysis of the clinical effectiveness studies was considered using REVIEW MANAGER 5.0 software.
- Quality-of-life studies were synthesised using the same methods as above, i.e. narrative review and meta-analysis only if feasible.

Results

A brief overview of the results of the searches is presented below. Owing to the extensive nature of this multiple technology appraisal (MTA), the clinical effectiveness results for the six different disease areas are presented separately (see sections Growth hormone deficiency to SHOX-D). For all disease areas throughout the screening and data extraction process, differences in opinion were generally minor and easily resolved without the involvement of a third reviewer.

Quantity and quality of research available

The number of references considered at each stage of the review is shown in *Figure 1*. Of the 674 references identified, 560 were excluded on inspection of their titles and abstracts. The full papers of 114 references were retrieved and assessed against the inclusion criteria. A total of 77 of the retrieved full papers were rejected at this stage, mostly due to the patient group not meeting the inclusion criteria ($n = 40$) or due to a non-RCT study design ($n = 27$). A list of papers excluded at this stage is included in Appendix 5, together with reasons for exclusion. A total of 28 RCTs in 34 publications were included in the systematic review of clinical effectiveness. Appendix 6 lists conference abstracts that were identified as being of interest, but which contained insufficient information to be included in the review of clinical effectiveness.

An overview of the included studies is given in *Table 2*. Only one SGA paper and one TS paper reported FH; none of the other conditions' studies reported FH as an outcome measure. None of the papers reported specific QoL measures. All disease areas included at least one paper which reported outcomes on height gained, body composition, biochemical markers and AE. The characteristics and quality assessment of the included studies are discussed in each of the relevant disease-specific results chapters.

Comparison with previous review

The previous review by Bryant and colleagues[6] included a number of studies that were excluded from the present review. As described above (see Inclusion and data extraction process) and in the research protocol, the present review included only RCTs as these form the highest level of evidence in the hierarchy of clinical trial designs.[83] The previous review included two non-RCT studies for GHD,[115,116] four for TS,[117–120] two for CRI[121,122] and one for PWS.[123] In addition, the previous review included two RCTs for TS, which have been excluded from the present review. The first of these, by Rosenfeld and colleagues,[124,125] was excluded from the present review as it used methionyl growth hormone (met-GH) rather than rhGH. The second TS RCT was by Ross and colleagues,[126] which reported cognitive function. This was not one of the outcome measures listed in the inclusion criteria for the present review,

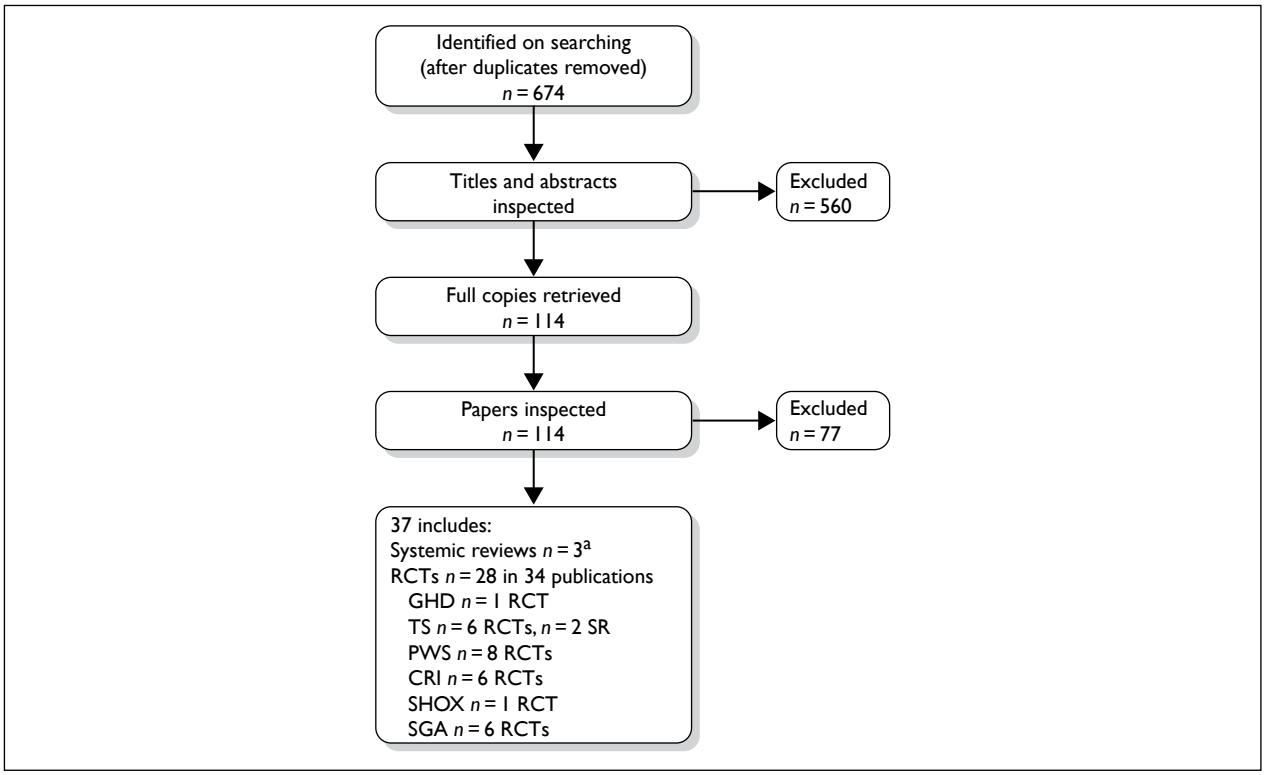

FIGURE 1 *Flow chart of identification of published studies for inclusion in the systematic review of clinical effectiveness. [a]One of the systematic reviews was the previous Health Technology Assessment report written for the National Institute for Health and Clinical Excellence, so this was not data extracted. It is discussed briefly (in Summary of previous systematic reviews).*

TABLE 2 *Included RCTs*

Author and date	Total (*n*)	Outcomes included in the systematic review						
		FH	Height gained/ HtSDS	GV/ growth SDS	Body composition	Biochemical/ metabolic markers	QoL	AE
GHD								
Soliman[84]	19		✓	✓		✓		
TS								
Davenport 2007[85]	89		✓	✓	✓	✓		✓
Stephure 2005[86] and Rovet 1993[87]	154	✓	✓	✓				✓
Quigley 2002[12]	232			✓				✓
Gravholt 2002[88]	12				✓	✓		
Gravholt 2005[89]	9				✓	✓		
Johnston 2001[90]	58		✓					
PWS								
Festen 2007[91]	20		✓		✓	✓		
Festen 2007[92]	29		✓		✓	✓		✓
de Lind van Wijngaarden 2009[93] and Festen 2008[94]	42 infants, 49 children		✓		✓	✓		
Carrel 1999[95] and Myers[96]	54		✓	✓	✓	✓		✓
Carrel 2004[22] and Myers[97] and Whitman[98]	32		✓	✓	✓	✓		✓
Hauffa 1997[99]	19		✓	✓		✓		✓
Lindgren[100,101]	29		✓	✓	✓	✓		✓
Haqq 2003[102]	14		✓	✓	✓	✓		✓
CRI								
Sanchez 2002[103]	23		✓	✓	✓			✓
Hokken-Koelega 1991[104]	20			✓		✓		✓
Hokken-Koelega 1996[105]	11			✓		✓		✓
Powell 1997[106]	69		✓		✓	✓		
The Pharmacia and Upjohn Study Group 1996[107]	203		✓	✓				
Fine 1994[108]	125		✓	✓	✓	✓		✓
SHOX-D								
Blum 2007[49]	52		✓	✓		✓		✓
SGA								
De Schepper 2007[109]	40		✓		✓			✓
Lagrou 2008[110]	40		✓		✓			✓
Carel 2003[111]	168	✓	✓					✓
de Zegher 1996[112]	54		✓	✓	✓	✓		✓
de Zegher 2002[113]	13		✓	✓	✓			
Philip 2009[114]	151		✓			✓		

so this RCT was excluded. The previous review also included a PWS RCT by Whitman and colleagues,[127] which was considered for the current review. However, the study reported psychological outcomes rather than a measure of HRQoL, so this study did not meet our inclusion criteria.

Growth hormone deficiency

Quantity and quality of research available

One study met the inclusion criteria for this review, and the key characteristics are presented in *Table 3*. The full data extraction form in Appendix 4 has further details.

Soliman and Abdul Khadir[84] recruited two groups of GH-deficient children and one group of children who were not GH deficient. These groups were then subdivided into treatment groups: group 1a received 30 units (U)/m^2/week of rhGH and group 1b received 15 U/m^2/week. Group 2a received 15 U/m^2/week and group 2b received no treatment. Group 3 (non-GHD short children) was subdivided in the same way as group 2. Group 2 was the only group in this study with GHD and with children randomised to either rhGH or no treatment, and, as such, is the only group considered in this report. The treatment groups' baseline characteristics were similar. The study used a dose of 15 U/m^2/week, and it is not clear how this corresponds to the licensed dose as neither milligrams (mg) nor international units (IUs) are used.

Overall the quality of the reporting of the included study was mixed (*Table 4*). No details were given on randomisation or allocation to treatment groups. For example, Soliman and Abdul Khadir[84] recruited children into specified groups according to peak GH response to provocation, and these groups were then divided at random into two subgroups. No further details were given. The low patient numbers will affect interpretation of results from this trial.

The comparator group did not receive placebo: this could mean that both care providers and patients would have been aware of whether they were receiving treatment, which, in turn, can affect reporting of some outcomes. Soliman and Abdul Khadir[84] appear to have carried out an intention-

TABLE 3 *Characteristics of GHD study*

Reference	Intervention	Control group	Total randomised and withdrawals	Duration of randomised treatment
Soliman *et al.* 1996[84]	GH 15 U/m^2/week *n* = 9 Overall mean age ± SD: 6.8 ± 2.1	No treatment *n* = 10 Overall mean age ± SD: 6.8 ± 2.1	Total *n* = 19 No withdrawals reported	1 year

TABLE 4 *Quality assessment of included GHD study*

	Soliman[84]
1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Inadequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Inadequate
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Adequate
10. Were withdrawals and dropouts completely described?	Adequate

to-treat analysis (ITT), which can protect against attrition bias.

Growth outcomes

The Soliman[84] study reported GV and HtSDS, and these are presented in *Table 5*. The data extraction forms in Appendix 4 list further outcome measures, such as BA.

Children in the treated group in the Soliman study grew an average of 2.7 cm/year faster than those receiving no treatment in the 12 months of the study, and the difference between groups was statistically significant ($p < 0.05$). Similarly, children in the treated group had a statistically significantly higher HtSDS: –2.3 ± 0.45 versus –2.8 ± 0.45 in the untreated group ($p < 0.05$).

Body composition outcomes

Soliman and Abdul Khadir[84] did not report body composition outcomes.

Biochemical markers

The results reported for IGF-1 levels in the Soliman study[84] are shown in *Table 6*. Further biochemical markers, such as insulin, are included in the data extraction tables in Appendix 4.

The IGF-1 levels at 12 months are statistically significantly higher in the treated than in the untreated group: 91.2 ± 30.4 versus 49.4 ± 19.

Quality of life

Soliman and Abdul Khadir[84] did not report QoL results.

Adverse events

Adverse events were not reported by Soliman and Abdul Khadir.[84]

Summary

One trial examining the effectiveness of rhGH for GHD met the inclusion criteria for the review.

- The quality of the included study was mixed. It was an unblinded study, which can have an impact on outcome reporting but did report an ITT analysis.
- Children in the rhGH group grew 2.7 cm/year faster than children in the untreated group during the 1-year study, and had a statistically significantly higher HtSDS: –2.3 ± 0.45 versus –2.8 ± 0.45.
- The IGF-1 levels were statistically significantly higher in the treated group than in the untreated group.
- The included study did not report QoL or AE.

Turner syndrome

Quantity and quality of research available

Six studies assessing the effectiveness of GH for growth restriction in TS met the inclusion criteria for the review.[12,85,86,88–90] The key characteristics of these studies are presented in *Tables 7–12*. Appendix 4 has further details.

Two of the included studies were of a crossover design,[88,89] and these compared doses of 0.1 IU/kg/day[88] and a mean of 1.3 ± 0.3 mg/day (alone or in combination with oestradiol)[89] with placebo. The group receiving oestradiol is not discussed further here. Of the remaining studies,

TABLE 5 *Growth outcomes for GHD*

Study	Mean (SD)	GH	No treatment	*p*-value
Soliman[84]	HtSDS	–2.3 ± 0.45	–2.8 ± 0.45	< 0.05
GH 15 U/m²/week (*n* = 9) vs no treatment (*n* = 10); 12 months	8.4 ± 1.4	5.7 ± 1.8	< 0.05	

TABLE 6 *Biochemical markers in GHD studies*

Study	Outcomes	GH	Control	*p*-value
Soliman[84]	IGF-1 (ng/ml)	91.2 ± 30.4	49.4 ± 19	< 0.05
GH 15 U/m²/week (*n* = 9) vs no treatment (*n* = 10); 12 months				

TABLE 7 *Characteristics of TS studies*

Reference	Intervention	Control group	Total randomised and withdrawals	Duration of randomised treatment
Stephure and CGHAC 2005[86] and Rovet *et al.*, 1993 [87]	rhGH 0.30 mg/kg/week (*n* = 76) Mean age (± SD): 10.3 ± 1.8	No rhGH treatment (*n* = 78) Mean age (± SD): 10.9 ± 1.7	Total *n* = 154 Sample attrition: rhGH, *n* = 15; control, *n* = 35	Until HV < 2 cm/year and BA ≥ 14 year
Davenport *et al.* 2007[85]	rhGH 50 μg/kg/day (*n* = 45) Mean age (± SD): 1.98 ± 1.01	No treatment (*n* = 44) Mean age (± SD): 1.97 ± 1.01	Total n = 89 Sample attrition: rhGH, *n* = 4; control, *n* = 6	2 years
Gravholt *et al.* 2002[88]	rhGH 0.1 IU/kg/day Overall age range: 9.5–14.8 years (median 12.9)	Placebo Overall age range: 9.5–14.8 years (median 12.9)	Total *n* = 12 Withdrawals not reported	Crossover RCT, 2 months in each arm
Gravholt *et al.* 2005[89]	rhGH (1.3 ± 0.3) mg/day Overall mean age (± SD): 15.9 ± 1.8	Placebo Overall mean age (± SD): 15.9 ± 1.8	Total *n* = 9 Sample attrition: *n* = 1	Crossover RCT, 2 months in each arm
Johnston *et al.* 2001[90]	rhGH 28–30 IU/m^2/week (*n* = 22) Mean age (range): 9.0 (5.2–15.4)	Ethinyloestradiol[a] 50–75 ng/kg/day (*n* = 13) Mean age (range): 9.1 (6.0–13.7)	Total *n* = 58[b] Sample attrition: *n* = 12	1 year
Quigley *et al.* 2002[12]	rhGH 0.27 mg/kg/week (*n* = 45) Mean age (± SD): 9.7 ± 2.7 rhGH 0.36 mg/kg/week (*n* = 49) Mean age (± SD): 9.8 ± 2.9	Placebo (*n* = 41) Mean age (± SD): 9.4 ± 2.7	Total *n* = 232[b] Sample attrition: *n* = 8	18 months

CGHAC, Canadian Growth Hormone Advisory Committee.
a Low-dose estrogen.
b Including additional study arm(s) not relevant here.

TABLE 8 *Quality assessment of included TS studies*

	Stephure and CGHAC[86]	Davenport *et al.*[85]	Gravholt *et al.* 2002[88]	Gravholt *et al.* 2005[89]	Johnston *et al.*[90]	Quigley *et al.*[12]
1. Was the assignment to the treatment groups really random?	Un	Ad	Un	Un	In	Un
2. Was the treatment allocation concealed?	Un	Ad	Un	Un	Un	Un
3. Were the groups similar at baseline in terms of prognostic factors?	Rep	Rep	Not rep	Not rep	Rep	Rep
4. Were the eligibility criteria specified?	Ad	Ad	In	In	In	Ad
5. Were outcome assessors blinded to the treatment allocation?	Un	Un	Un	Un	Un	Un
6. Was the care provider blinded?	In	In	Un	Un	Un	Un
7. Was the patient blinded?	In	In	Un	Ad	Un	Par
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Ad	Ad	Ad	Ad	Ad	In
9. Did the analyses include an ITT analysis?	In	In	In	In	In	In
10. Were withdrawals and dropouts completely described?	Ad	Ad	In	Ad	Ad	Ad

Ad, adequate; In, inadequate; Not rep, not reported; Par, partial; Rep, reported; Un, unknown.

two compared rhGH with no treatment,[85,86] one with low-dose estrogen,[90] and one with placebo.[12] Stephure and colleagues[86] administered a rhGH dose of 0.30 mg/kg/week, with a maximum weekly dose of 15 mg. The dose of 50 μg in the Davenport study[85] is comparable with that of Stephure and colleagues. Those in the Quigley study[12] were slightly different: group 1 received 0.27 mg/kg/week and group 2 received 0.36 mg/kg/week. Johnston and colleagues[90] gave a dose of 28–30 IU/m^2/week. All studies included at least one treatment arm with a dose that was broadly comparable with the licensed dose of 45–50 µg/kg/day or 1.4 mg/m^2/day.

Four of the six included studies reported growth outcomes, including height gain and change in HtSDS.[12,85,86,90] The remaining two studies reported body composition and biochemical marker outcomes.[88,89]

The trials varied considerably in size. The two crossover trials were small, with 12[88] and nine[89] participants. The Stephure[86] and Quigley[12] studies were larger, with 154 and 232 participants, respectively. Johnston and colleagues[90] recruited 58 patients, and Davenport and colleagues recruited 89.[85] The included trials also ranged in length. The groups in Quigley and colleagues[12] remained randomised for 18 months, the Davenport study[85] for 2 years and the Johnston study lasted for 1 year.[90] Protocol completion in the Stephure[86] study was defined as annualised GV less than 2 cm/year and BA of 14 years or greater, which we have interpreted to mean FH. In contrast, the two Gravholt studies[88,89] were short crossover trials, with rhGH treatment for 2 months.

Five[12,86,88–90] of the six trials recruited broadly similar age groups, whilst the sixth by Davenport and colleagues[85] specifically targeted very young girls with TS. As a result their girls have much younger mean ages of 1.98 ± 1.01 and 1.97 ± 1.01 for treatment and control groups, respectively.

Four of the included studies reported baseline characteristics that were similar between groups.[12,85,86,90] However, none reported *p*-values for between-group differences, so there may have been small differences at baseline. For example, in the study by Stephure and the Canadian Growth Hormone Advisory Committee (CGHAC) 2005,[86] girls in the rhGH group were on average 3 cm shorter than those in the control group. The SD values indicate overlapping CI, suggesting there is no statistically significant difference between the two groups. However, the 3-cm difference could have an impact on end of study height. The other two studies, reported by Gravholt and colleagues, were of crossover design. One reported baseline characteristics for the whole study group[89] and the other did not appear to report any baseline conditions.[88]

The six included trials were generally of poor methodological quality, and poorly reported (*Table 8*). Only one reported adequate methods of randomisation to treatment groups.[85] Davenport and colleagues[85] stratified their participants by age and then randomised them using a blinded phone-in process. Four of the six trials did not describe randomisation techniques.[12,86,88,89] Johnston and colleagues[90] reported that five participants were reallocated from the oestrogen group to receive rhGH: it is unclear when this occurred and therefore method of randomisation was judged inadequate.

Concealment of treatment allocation was also judged to be adequate in the Davenport trial, and 'unknown' in the remaining five. In the Gravholt[89] study it is unclear how allocation to treatment groups had taken place. The study had only nine participants, and these were simply reported to have been given the treatment regimen sequentially and in random order.

Blinding of participants, those who provide care and those who assess outcomes can protect against the reporting of some outcomes being affected by the knowledge of which treatment is being received. Blinding of outcome assessors, care providers and patients was judged 'unknown', 'inadequate' or 'partial' in five out of the six trials; Gravholt and colleagues[89] adequately blinded their patients by administering placebo in place of both rhGH and the oestradiol.

None of the six studies included here used an ITT analysis. This kind of analysis can protect the study from attrition bias, where, for example, participants withdrawing from the treatment arm could represent AE or treatment failure.

Growth outcomes

Four out of the six included studies reported growth outcomes, and key measures are shown in *Table 9*. Please see Appendix 4 for additional outcomes. Neither of the studies by Gravholt and colleagues[88,89] reported growth outcomes.

TABLE 9 *Growth outcomes for TS studies*

Study	Outcomes (mean ± SD)	GH	Control	*p*-value
Stephure and CGHAC[86] Protocol completion, rhGH 0.30 mg/kg/week (*n* = 61) vs no treatment (*n* = 43)	Height (cm)	147.5 ± 6.1	141.0 ± 5.4	< 0.001
	Change in height (cm)	28.3 ± 8.9	19.0 ± 6.1	< 0.001
	HtSDS (age-specific turner)	1.4 ± 1.0	0.2 ± 0.9	< 0.001
	HtSDS (adult Turner)	0.7 ± 0.9	–0.3 ± 0.8	< 0.001
	Change in HtSDS (age-specific Turner)	1.6 ± 0.6	0.3 ± 0.4	< 0.001
Stephure and CGHAC[86] Addendum follow-up, rhGH 0.30 mg/kg/week (*n* = 40) vs no treatment (*n* = 19)	Height (cm)	149.0 ± 6.4	142.2 ± 6.6	< 0.001
	Change in height (cm)	30.3 ± 8.3	21.6 ± 6.2	< 0.001
	HtSDS (age-specific Turner)	0.9 ± 0.9	–0.1 ± 1.0	< 0.001
	HtSDS (adult Turner)	0.9 ± 0.9	–0.1 ± 1.0	< 0.001
	Change in HtSDS (age-specific Turner)	1.1 ± 0.5	0.0 ± 0.5	< 0.001
Davenport *et al.*[85] GH (*n* = 41) vs no treatment (*n* = 37); 2 years	Height (cm)	99.5 ± 7.6	91.9 ± 7.2	< 0.0001
	HtSDS	–0.34 ± 1.10	–2.16 ± 1.22	< 0.0001
	GV (cm/year)	8.4 ± 1.6	5.5 ± 1.8	< 0.0001
	GV SDS	0.70 ± 1.11	–1.63 ± 1.29	< 0.001
Johnston *et al.*[90] rhGH 28–30 IU/m^2/week (*n* = ?)[a] vs estrogen (*n* = ?);[a] 1 year	Change in HSDS in first year	+0.7 (0.7)	+0.4 (0.9)	< 0.05
Quigley *et al.*[12] GH 1, rhGH 0.27 (*n* = 45); GH 2, rhGH 0.36 (*n* = 49) vs placebo (*n* = 41); 1 year	GV 0–18 months (cm/year)	1: 6.6 ± 1.12 2: 6.8 ± 1.1	4.2 ± 1.1	< 0.001

a '*n*' unclear for this outcome.

Two studies reported height at the end of the study: both found a statistically significant difference between the treated and untreated groups ($p < 0.0001$).[85,86]

Children in the treated group in the Stephure study[86] were 6.5 cm taller on average than the untreated group at protocol completion. However, there was a 3-cm difference between the groups' mean heights at baseline. Mean change from baseline was therefore 9.3 cm more in the rhGH than in the untreated group at the end of protocol completion (28.3 ± 8.9 vs 19.0 ± 6.1).

The Stephure study[86] also reported an addendum follow-up (approximately 10 years since randomisation), which included 66% of rhGH patients and 44% of the control group. The treated group's mean FH was 149.0 ± 6.4 cm compared with 142.2 ± 6.6 cm in the untreated group ($p < 0.001$), i.e. a difference of 6.8 cm. Mean change from baseline to FH was 8.7 cm more in the rhGH than in the untreated group.

In the Davenport study[85] the mean difference was 7.6 cm (height at study end was 99.5 ± 7.6 cm in the treated group vs 91.9 ± 7.2 cm in the untreated group, $p < 0.0001$).

Height standard deviation score is also reported by Davenport and colleagues[85] and Stephure and CGHAC.[86] Both authors report statistically significant differences between groups for this outcome, with the treated groups both achieving higher HtSDS. In the Stephure study[86] the HtSDS is reported for the age-specific Turner population and for the adult Turner population.

The difference in change in height was statistically significant between groups in the two studies that reported it. Stephure and colleagues[86] report a change in height at protocol completion of 28.3 ± 8.9 cm versus 19 ± 6.1 in the untreated group, $p < 0.001$. Davenport and colleagues[85] reported a 2-year height gain of 20.4 ± 3.3 cm (treated group) versus 13.6 ± 3.5 cm (untreated group), $p < 0.001$ (not shown in table). Change in HtSDS in both the

Stephure[86] and Johnston[90] studies was higher in the treated than untreated group: 1.6 ± 0.6 (treated) versus 0.3 ± 0.4 (untreated), $p < 0.001$, at protocol completion in the Stephure study; 0.7 (0.7) versus 0.4 (0.9), $p < 0.05$, in the Johnston study[90] after 1 year.

Growth velocity was statistically significantly greater in the treated groups in the Stephure,[86] Davenport[85] and Quigley[12] studies. Davenport and colleagues[85] reported GV at the end of the first and second year. Although this was greater in the treated groups at both times, GV fell in the second year in both groups: 8.4 ± 1.6 cm/year (treated group) versus 5.5 ± 1.8 (untreated). Additionally, Davenport and colleagues[85] measured GV SDS at the end of the first and second years. Again, this was greater in the treated group at the end of the first year: 1.75 ± 1.25 versus 0.8 ± 0.95, $p < 0.001$, but was reduced by the end of the second year in both groups: 0.70 ± 1.11 (treated) versus –1.63 ± 1.29 (untreated), $p < 0.001$. Quigley and colleagues reported GV after 18 months. This was broadly similar in both the lower- and higher-rhGH-dose groups: both were significantly higher than that in the placebo (Pla) group: 6.6 ± 1.1 (GH 0.27/Pla group) versus 6.8 ± 1.1 (GH 0.36/Pla group) versus 4.2 ± 1.1 (Pla/Pla group), $p < 0.001$ compared with placebo.

Bone age differences for the younger participants in the Davenport study were statistically significant:[85] the GH-treated group at 2 years had a mean BA of 4.24 ± 1.35 versus 3.38 ± 1.11 in the untreated group, $p = 0.0033$. Davenport and colleagues[85] also reported BA/chronological age; this is lower in the treated group, and the difference was statistically significant: 0.64 ± 0.80 versus 0.21 ± 0.96, $p < 0.001$.

Body composition outcomes

Three of the TS studies reported body composition outcomes, and these are presented in *Table 10*. One of the studies reported weight, weight standard deviation score (WtSDS) and BMI,[85] whereas the remaining two reported FM, bone mineral content (BMC) and LBM for arms, legs, trunk and head, and as a total.[88,89] Please see Appendix 4 for BMC results.

Weight and WtSDS were significantly greater in the group receiving rhGH than in the untreated group in the Davenport study,[85] reported as 16.62 kg ± 2.86 versus 13.81 kg ± 2.50, and 0.20 ± 1.06 versus –1.37 ± 1.36, respectively ($p < 0.0001$ for both comparisons).

Two studies considered FM, BMC and LBM.[88,89] In both studies the total FM was greater in the untreated group than in the treated group, and LBM was slightly higher in treated than in untreated patients (*Table 10*). The differences between groups were of borderline statistical significance in one study[88] but no *p*-values were presented in the other study.[89]

Biochemical markers

Three of the studies[85,88,89] reported biochemical outcomes. Key results are shown in *Table 11* – other outcomes are in Appendix 4.

Two studies reported mean levels of IGF-1 at end of treatment. In both studies IGF-1 levels were statistically significantly higher in the group receiving rhGH. One study[88] reported values of 380.5 ± 116.3 versus 179.8 ± 79.4 in the treated and untreated groups, respectively ($p < 0.0005$). The other[89] reported 661 ± 192 versus 288 ± 69 (*p*-value not reported) for treated and untreated patients, respectively.

Davenport and colleagues[85] reported that IGF-1 SDS was significantly greater in the treated group (1.26 ± 0.72 vs –0.69 ± 0.84, $p < 0.0001$). Change in IGF-1 SDS from baseline to year 2 was 1.53 ± 0.93 versus –0.09 ± 0.87 in the treated and untreated groups, respectively.

One Gravholt study[88] reported that IGFBP-3 levels were statistically significantly higher in the treated group than in the untreated group (5982 ± 1557 vs 4344 ± 787, respectively, $p = 0.002$). The other study by Gravholt and colleagues[89] reported higher IGFBP-3 SDS values in treated patients, but no clear *p*-value was reported.[89] Davenport and colleagues[85] found that IGFBP-3 SDS was higher in their treated group (0.97 ± 0.94 vs –1.12 ± 1.13, $p < 0.0001$).

Fasting glucose and fasting insulin were reported in the two studies by Gravholt and colleagues,[88,89] both of which were raised in the groups receiving GH in each study. Mean glucose (nmol/l) was 4.28 ± 0.59[88] and 4.46 ± 0.40[89] in the treated groups, versus 4.02 ± 0.44[88] and 4.04 ± 0.47[89] in the untreated groups. This difference reached statistical significance in the first study,[88] $p = 0.046$. Mean fasting insulin levels in the first Gravholt study[88] were 17.17 ± 8.30 versus 8.58 ± 4.27, $p = 0.007$.

TABLE 10 *Body composition outcomes for TS studies*

Study	Outcomes (mean ± SD)	GH	Control	*p*-value
Davenport *et al.*[85]	Weight (kg)	16.62 ± 2.86	13.81 ± 2.50	< 0.0001
GH (*n* = 41) vs no treatment (*n* = 37); 2 years	WtSDS	0.20 ± 1.06	–1.37 ± 1.36	< 0.0001
	BMI (kg/m^2)	16.72 ± 1.70	16.24 ± 1.29	0.1724
Gravholt *et al.*[88]	FM total (g/kg)	231.0 ± 49.5	247.8 ± 58.1	0.04
GH 0.1 IU/kg/day vs placebo; 2 months[a]	LBM total (g/kg)	725.4 ± 44.8	710.5 ± 54.6	0.05
Gravholt *et al.*[89]	FM total (g/kg)	274.5 ± 55.5	312.9 ± 74.7	nr
GH 1.3 mg/day vs placebo; 2 months[b]	LBM total (g/kg)	692.8 ± 55.5	655.2 ± 73.7	nr

nr, not reported.
a Crossover study, total *n* = 12.
b Crossover study, total *n* = 9.

TABLE 11 *Biochemical markers in TS studies*

Study	Outcomes (mean ± SD)	GH	Control	*p*-value
[a]**Davenport *et al.*[85]**	IGF-1 SDS	1.26 ± 0.72	–0.69 ± 0.84	< 0.0001
GH (*n* = 41) vs no treatment (*n* = 37); 2 years	IGFBP-3 SDS	0.97 ± 0.94	–1.12 ± 1.13	< 0.0001
	ΔIGF-1 SDS	1.53 ± 0.93	–0.09 ± 0.87	nr
Gravholt *et al.*[88]	IGF-1 (μg/l)	380.5 ± 116.3	179.8 ± 79.4	< 0.0005
GH 0.1 IU/kg/day vs placebo; 2 months[a]	IGFBP-3 (μg/l)	5982 ± 1557	4344 ± 787	0.002
Gravholt *et al.*[89]	IGF-1 (μg/l)	661 ± 192	288 ± 69	nr
GH 1.3 mg/day vs placebo; 2 months	IGFBP-3 (μg/l)	5157 ± 741	4146 ± 573	Unclear

a Baseline data missing for eight control subjects and three GH treated subjects; end point data missing for four control subjects and seven rhGH subjects.

Quality of life

None of the TS studies reported QoL as an outcome.

Adverse events

Adverse events were reported by only four of the studies.[12,85,86,90] Details presented by three of the studies are shown in *Table 12* (the fourth study did not present figures[90]).

The group receiving GH in the Stephure study[86] experienced a statistically significantly greater level of all AEs (where statistical significance was reported), with the exception of goitre, and one instance of death from ruptured aortic aneurysm, which occurred in the untreated group. The one case of elevated transamine levels in the treated group led to withdrawal from the study.

Davenport and colleagues[85] report the same level of serious adverse events (SAEs) for both the treated and untreated groups. For treatment-emergent AEs, defined as 'events or conditions that began or worsened after study entry', the results were similar. There were 42 (93%) in the treated group and 43 (98%) in the untreated group. Most treatment-emergent AEs were ear disorders.

Quigley and colleagues[12] found a significant difference in levels of occurrence or worsening of otitis media between the treated group (29%) and the control group (13%), $p = 0.037$. Ear pain and ear disorder were reported as not differing between groups. Three girls discontinued rhGH due to hypertension, ulcerative colitis and brain tumour. The authors stated that these were not directly related to GH. Overall, AEs were not presented separately for the groups; however,

TABLE 12 *Adverse events for TS studies*

Study	AE (*n*)	GH	Control	*p*-value
Stephure and CGHAC[86]	Surgical procedures	37	17	0.005
GH (*n* = 74) vs no treatment (*n* = 64)	Otitis media	35	17	0.014
	Ear disorder	15	4	0.024
	Joint disorder	10	2	0.036
	Respiratory disorder	8	1	0.037
	Sinusitis	14	4	0.041
	Goitre	0	4	0.004
	Death (ruptured aortic aneurysm)	0	1	nr
	Elevated transamine levels	1	0	nr
	Intracranial hypertension	1	0	nr
Davenport *et al.*[85]	Serious AEs, *n* (%)	4 (9)	4 (9)	nr
GH (*n* = 45) vs no treatment (*n* = 44), 2 years	Treatment-emergent AEs, *n* (%)	42 (93)	43 (98)	nr
Quigley *et al.*[12]	Otitis media (occurrence/worsening), *n* (%)	54/186 (29%)	6/46 (13%)	0.037

nr, not reported.

five were reported to have accidentally overdosed on the study drug. Five further events described as possibly related to the study drug were hypertension (two), surgical procedures (two) and scoliosis (one).

Five participants were reallocated from the group receiving estrogen to rhGH after concerns over early breast development in the study by Johnston and colleagues.[90] Seven patients developed 'coincidental disorders' not severe enough to warrant treatment discontinuation. The authors reported that compliance problems led to the withdrawal of four patients, but no details were given. It is unclear which treatment groups these latter events occurred in.

Summary

Six trials examining the effectiveness of GH for growth disturbance in patients with TS met the inclusion criteria for the review.

The reporting and methodological quality of the studies was poor. Of the six included studies, one reported adequate randomisation to treatment groups,[85] one study described adequate concealment of treatment allocation[85] and one adequately blinded the patient to treatment by administering placebo.[89] None of the included trials used an ITT analysis.

Children in the rhGH group in the Stephure[86] study grew an average of 9.3 cm more from baseline than those in the untreated group. In a study of younger children[85] the difference was 7.6 cm. Both of these were statistically significant results. In the same two studies[85,86] the groups receiving rhGH achieved a significantly higher HtSDS.

Change in height and change in HtSDS were statistically significantly greater in the groups treated with rhGH.[85,86,90]

Growth velocity was greater in the treated groups in three studies that reported this outcome,[12,85,86] although this was greater in the first year and fell in the second year in both treatment groups where this was reported separately.[85]

One study[86] found a significant difference in BA between groups, being higher in the treated patients.

Fat mass and LBM were reported in two studies.[88,89] In both, the total FM was at a lower level in the treated groups, compared with those untreated, and LBM was higher in the treated groups compared with untreated. There was no statistically significant difference in BMI between treated and untreated girls in one study.[85]

The IGF-1 levels were substantially higher in the treated groups in the studies reporting this

outcome.[88,89] IGF-1 SDS was also significantly higher in the group receiving GH.[85] Levels of IGFBP-3 and IGFBP-3 SDS were also found to be higher in children treated with GH.[85,88,89]

Levels of fasting glucose and fasting insulin were both raised in the treated groups in two studies.[88,89]

There were variable levels of detail in the reporting of AEs across the six studies. Two studies did not discuss these.[88,89] In those studies that did, no clear picture emerges. One found greater levels of AEs in the treated group,[86] one found similar levels across groups,[85] one found significantly higher levels of or worsening of otitis media, and one reported seven patients with 'coincidental disorders' and four withdrawals due to compliance problems, but gave no further details.

Prader–Willi syndrome

Quantity and quality of research available

Eight RCTs in 13 publications of the clinical effectiveness of rhGH in patients with PWS met the inclusion criteria for this review.[22,91–102] Their key characteristics are shown in *Table 13* – see Appendix 4 for further details.

It was not possible to perform any meta-analysis of outcomes from the PWS studies due to variation in the trials' participants' ages, dosing calculations, and methods of presenting results. The included studies had well-matched patient groups, whose baseline characteristics were generally similar in the treated and untreated groups. Median baseline HtSDS was lower in the rhGH group than in the untreated group in the study reported by both Festen and colleagues[94] and by de Lind van Wijngaarden and colleagues,[93] although the interquartile ranges (IQRs) were similar [–2.0 (–3.1 to –1.7) versus –2.5 (–3.3 to –1.9), respectively]. Other exceptions were the crossover study by Haqq and colleagues,[102] which presented baseline characteristics for the study population as a whole, and the study by Lindgren and colleagues,[100,101] which reported slightly lower baseline GV SDS in the rhGH group [–1.9 ± 2.0, range –6.4 to –0.9, vs –0.1 (SD not reported) range –1.7 to –2.71].

Five of the studies were RCTs, which compared 1 mg/m^2/day rhGH with no treatment for 1[22,92–98] or 2[91,93,94] years. The study by Haqq and colleagues[102] was a crossover RCT, which compared 0.043 mg/kg/day of rhGH with placebo injections, with patients spending 6 months in each treatment arm. There does not appear to have been a washout phase between the two treatment phases, which could affect the generalisability of results.

The doses used in the included studies reflect the various marketing authorisations for this drug (0.035 mg/kg body weight or 1.0 mg/m^2 BSA), with 1 IU of rhGH being equivalent to approximately 0.33 mg/kg. The study reported by both de Lind van Wijngaarden and colleagues[93] and Festen and colleagues[94] reported results separately for infants and children. Two RCTs reported results for infants and toddlers aged between 1 and 2.5 years.[22,92,97,98] The five remaining trials were in children aged between approximately 6 and 10 years old. The studies were generally small, randomising between 14[102] and 54[95,96] children. The study reported by both de Lind van Wijngaarden and colleagues[93] and Festen and colleagues[94] had a total of 91 participants, but as children and infants were randomised separately, the randomised comparisons were of rhGH versus no treatment within two smaller groups (42 infants and 49 children). This was the only study to report a sample size/power calculation,[93,94] and it is not clear whether the other studies were adequately powered to detect a difference between treatment groups.

With the exception of the two RCTs by Festen and colleagues,[91,92] the studies did not clearly state which of their reported outcomes were primary or secondary measures of effect. Seven of the eight trials reported measures of body composition. The two RCTs by Festen and colleagues[91,92] focused on body composition and biochemical markers, and did not report any measure of change in height. The other six studies all reported GV SDS or an indicator of linear GV.[102] IGF-1 and other biochemical markers were reported by five RCTs.[22,92–99]

One RCT was reported in three papers, by Carrel and colleagues,[22] Myers and colleagues[97] and Whitman and colleagues.[98] The most complete data were reported by Carrel and colleagues,[22] and these data are included in the tables in this section.

The included studies were generally poorly reported (*Table 14*) and lacked information on method of randomisation or concealment of allocation. It is possible that selection bias could have affected the trials if they were not properly randomised, but there is insufficient information provided on which to make such a judgement. The trial by Haqq and colleagues[102] was a crossover

TABLE 13 *Characteristics of included PWS studies*

Reference	Intervention	Control group	Total randomised and withdrawals	Duration of randomised treatment
Carrel *et al.* 2004,[22] Myers *et al.* 2007,[97] and Whitman *et al.* 2004[98]	rhGH 1 mg/m^2/day *n* = 15 Mean age ± SD (months): 13 ± 8	No treatment *n* = 14 Mean age ± SD (months):15 ± 0	*n* = 32 Sample attrition: *n* = 3[a]	1 year
Carrel *et al.* 1999[95] and Myers *et al.* 1999[96]	GH 1 mg/m^2/day *n* = 35 Mean age (years): 9.8	No treatment *n* = 19 Mean age (y): 10.0	*n* = 54 No withdrawals	1 year
de Lind van Wijngaarden *et al.* 2009[93] and Festen *et al.* 2008[94]	1 mg/m^2/day Infants (< 3.5 years): *n* = 19 Children (> 3.5 years): *n* = 23 Median (IQR) age: infants 2.0 (1.6–3.1), children 6.8 (5.4–8.8)	No treatment Infants (< 3.5 years): *n* = 19 Children (> 3.5 years): *n* = 21 Median (IQR) age: infants 1.3 (1.0–2.8); children 5.9 (4.7–7.4)	*n* = 104 enrolled Sample attrition: 4 infants and 5 children	1 year for infants, 2 years for children
Festen *et al.* 2007[91]	GH 1 mg/m^2/day *n* = 10 Median age (IQR) (years): 6.2 (5.1–71)	No treatment *n* = 10 Median age (IQR) (years): 5.8 (4.9–7.8)	*n* = 20 Withdrawals: none	2 years
Festen *et al.* 2007[92]	GH 1 mg/m^2/day *n* = 15 Median (IQR) age, yr: 2.3 (1.7–3.0)	No treatment *n* = 14 Median (IQR) age, year: 1.5 (1.2–2.7)	*n* = 43 Sample attrition: *n* = 14	12 months
Haqq *et al.* 2003[102]	GH 0.043 mg/kg/day *n* = 6 Overall mean age ± SD (years): 9.7 ± 3.3	Placebo *n* = 6 Overall mean age ± SD (years): 9.7 ± 3.3	14 randomised Sample attrition: *n* = 2	Crossover RCT, 6 months in each arm
Hauffa 1997[99]	GH: 0.15 IU/kg/day *n* = 8 Mean age ± SD (years): 8.25 ± 2.4	No treatment *n* = 9 Mean age ± SD (years): 7.56 ± 2.0	*N* = 19 Sample attrition: *n* = 3	1 year
Lindgren *et al.* 1998[101] and 1997[100]	GH 0.1 IU/kg/day *n* = 15 Mean age (range) (years): 6.8 (3.6–11.9)	No treatment *n* = 14 Mean age (range) (years): 6.4 (3.3–11.7)	Total *n* = 29 Sample attrition: *n* = 2	1 year

a Difference between patient numbers in Whitman[97] and Carrel[22] = 3.

study, and did not report baseline characteristics separately for the two groups. The other studies reported baseline characteristics, which indicated that patients in the two treatment groups were comparable at the start of the study. With the exception of the crossover trial by Haqq and colleagues,[102] which had a placebo-injection group, the studies were open label, with the comparator groups receiving no treatment. Although this could have allowed a degree of bias in reporting and assessing results, measurement of objective outcomes, such as height gained, is less likely to be open to bias. Only two of the studies reported results on an ITT basis,[91,96] so attrition bias could have affected the remaining studies.

The outcome measures for the included studies are shown in *Tables 15–17*. The *p*-values in the tables refer to between-group differences, as this is the comparison of interest for this report. Some

TABLE 14 *Quality assessment of included PWS studies*

	Carrel *et al.*,[22] Myers *et al.*,[97] Whitman *et al.*[98]	Carrel *et al.*,[95] Myers *et al.*[96]	de Lind van Wijngaarden *et al.*,[93] Festen *et al.*[94]	Festen *et al.*[91]	Festen *et al.*[92]	Haqq *et al.*[102]	Hauffa *et al.*[99]	Lindgren *et al.*,[101] Lindgren *et al.*[100]
1. Was the assignment to the treatment groups really random?	Un	Un	Un	Un	Un	Un	Un	Un
2. Was the treatment allocation concealed?	Un	Un	Un	Un	Un	Un	Un	Un
3. Were the groups similar at baseline in terms of prognostic factors?	Rep	Rep	Rep	Rep	Rep	Not rep	Rep	Rep
4. Were the eligibility criteria specified?	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad
5. Were outcome assessors blinded to the treatment allocation?	Un	Un	Un	Un	Un	Un	Un	Un
6. Was the care provider blinded?	In	In	In	In	In	Un	In	In
7. Was the patient blinded?	In	In	In	In	In	Ad	In	In
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Ad	Ad	Ad	Ad	Ad	Ad	In	Ad
9. Did the analyses include an ITT analysis?	In	Ad	In	Ad	In	In	In	In
10. Were withdrawals and dropouts completely described?	In	Ad	Ad	Ad	In	In	In	Ad

Ad, adequate; In, inadequate; Not rep, not reported; Rep, reported; Un, unknown.

of the studies reported statistical significance in change from baseline for each of the treatment groups individually, but not for between-group comparisons. To avoid confusion with the between-group comparison *p*-values, such results have not been included in the tables below and are not discussed in the text. The full data extraction tables in Appendix 4 include any statistical significance for change from baseline for individual treatment groups without between-group comparisons.

Growth outcomes

Changes in height and other growth outcome measures are shown in *Table 15*. The infants in the study by Carrel and colleagues[22] who received rhGH for a year grew an average of 6.2 cm more than those in the untreated group ($p < 0.001$). None of the other studies reported change in height as an outcome measure.

Two studies reported a statistically significant difference in HtSDS at end of treatment between treated and untreated patients.[93–96] Treated patients in the study reported by both Carrel and colleagues[95] and Myers and colleagues[96] had a mean HtSDS of -0.6 ± 1.2 compared with -1.6 ± 1.2 in the untreated group ($p < 0.01$). The studies reported by de Lind van Wijngaarden and colleagues[93] and by Festen and colleagues[94] also reported statistically significant improvements in height for rhGH-treated infants and children compared with unmatched controls. The rhGH-treated infants in their study had a median HtSDS of –0.9 compared with –1.8 in the untreated patients ($p = 0.003$). This reflected a change from baseline HtSDS of +1.2 for treated infants and –0.2 for untreated infants ($p < 0.0001$). After 2 years of treatment with rhGH, children had a median HtSDS of –0.5 compared with –2.6 in untreated children ($p < 0.001$).[93]

TABLE 15 *Growth outcomes for PWS studies*

Study	Outcomes (mean ± SD)	GH	Control	*p*-value
Carrel *et al.*[22] rhGH 1 mg/m²/day (*n* = 15) vs. no treatment (*n* = 14); 1 year	Change in height (cm)	15.4 ± 2.3	9.2 ± 3.2	< 0.001
	Height SDS	–0.2 ± 1.5	–1.5 ± 0.7	nr
	GV SDS	5.0 ± 1.8	1.2 ± 1.4	nr
Carrel *et al.*[95] and Myers *et al.*[96] GH 1 mg/m²/day (*n* = 35), vs. no treatment (*n* = 19); 1 year	Height SDS	–0.6 ± 1.2	–1.6 ± 1.2	< 0.01
	Mean GV (cm/year)	10.1 ± 2.5	5.0 ± 1.8	< 0.01
	Mean GV SDS	4.6 ± 2.9	–0.7 ± 1.9	< 0.01
de Lind van Wijngaarden *et al.*,[93] Festen *et al.*[94] (infants) rhGH 1 mg/m² (*n* = 19) vs. no treatment (*n* = 19); 1 year	HtSDS median (IQR)	–0.9 (–1.6 to –0.1)	–1.8 (–3.5 to –1.4)	0.003
	ΔHtSDS median (IQR)	1.2 (1.0 to 1.6)	–0.2 (–0.6 to 0.3)	< 0.0001
de Lind van Wijngaarden *et al.*,[93] Festen *et al.*[94] (children) rhGH 1 mg/m² (*n* = 23) vs. no treatment (*n* = 21); 2 years	HtSDS median (IQR)	–0.5 (–0.8 to 0.0)	–2.6 (–3.4 to –2.3)	< 0.0001
	ΔHtSDS median (IQR)	1.4 (1.3 to 1.8)	–0.1 (–0.4 to 0.1)	< 0.0001
Festen *et al.*[91] rhGH 1 mg/m²/day (*n* = 10) vs. no treatment (*n* = 10); 2 years	Height SDS median (IQR)	–0.6 (–0.9 to –0.3)	–3.0 (–3.5 to –1.8)	nr
Festen *et al.*[92] rhGH 1 mg/m²/day (*n* = 15) vs. no treatment (*n* = 14); 1 year	Height SDS median (IQR)	–1.6 (–2.1 to –0.8)	–2.3 (–3.9 to –1.5)	nr
Haqq *et al.*[102] rhGH 0.043 mg/kg/day (*n* = 12) vs. placebo (*n* = 12); 6 months	HtSDS	–1.2 ± 1.1	–1.3 ± 1.3	nr
	GV (cm/year)	7.5 ± 3.5	4.5 ± 2.7	< 0.05
Hauffa[99] rhGH 0.15 IU/kg/day (*n* = 7) vs. no treatment (*n* = 9); 1 year	Height SDS	1.07	–0.25	nr
	HV SDS	5.5	–2.3	0.0012
Lindgren *et al.*[101] and Lindgren *et al.*[100] rhGH 0.1 IU/kg/day (*n* = 15) vs. no treatment (*n* = 12); 1 year	HtSDS mean (range)	–0.4 (–2.7 –1.9)	–1.8 (–5.1 –0.2)	nr
	GV (SDS) mean ± SD (range)	6.0 ± 3.2 (1.4–11.9)	–1.4 (–3.2 –0.3)	nr

Festen and colleagues[91] reported that the difference between the two groups was statistically significant at year 1 (year 1 HtSDS –1.3 vs –2.8, $p < 0.01$). At year 2, the difference between the two groups was even greater (–0.6 compared with –3.0 in the treated and untreated groups, respectively), but no *p*-value was reported.[91] The other five studies all reported that HtSDS values were higher in treated than in untreated children, but did not report whether or not differences between groups were statistically significant.

The five studies that used GV as an outcome measure all reported faster growth in the treated group than in the untreated group, although statistical significance for differences between groups was only reported for three of these. The mean GV in the studies reported by Carrel and colleagues[95] and by Myers and colleagues[96] was twice as fast in the treated children as in the untreated children (10.1 vs 5.0, $p < 0.01$). The corresponding mean GV SDS values were 4.6 in the treated children and –0.7 in the untreated children ($p < 0.01$), indicating faster than average growth in the treated group and slower than average growth in the untreated patients. Similarly, Hauffa and colleagues[99] reported a positive GV SDS for treated children and a negative one for untreated children (5.5 vs –2.3, $p = 0.0012$). Haqq and colleagues[102] calculated GV that was 3 cm/year faster in patients receiving rhGH than in patients in the placebo arm (7.5 vs 4.5, $p < 0.05$).

Two of the included studies reported BA as an outcome measure. There was no statistically significant difference in BA at follow-up between

patients in the treated and untreated groups in the study reported by both Carrel and colleagues[95] and by Myers and colleagues.[96] Lindgren and colleagues[100,101] reported similar change from baseline in both groups (1.4 in the treated group, 1.5 in the untreated group), but did not report whether or not there was any statistical significance to their results.

Body composition

Seven of the trials reported changes in body composition, as shown in *Table 16*.[22,91–94,100–102] The trial by Hauffa and colleagues[99] did not report any results but stated that there were no significant within- or between-group changes for BMI, skinfold thickness, waist or hip circumference.

TABLE 16 *Body composition outcomes for PWS studies*

Study	Outcomes (mean ± SD)	GH	Control	*p*-value
Carrel *et al.*[22]	Mean % body fat	23.2 ± 8.9	32.7 ± 8.8	0.03
rhGH 1 mg/m²/day (*n* = 15) vs no treatment (*n* = 14); 1 year	Change in body fat (%)	–4.8 ± 5.7	+4.1 ± 4.6	0.001
	Change in LBM (kg)	3.6 ± 0.5	1.8 ± 0.7	< 0.001
Carrel *et al.*,[95] Myers *et al.*[96]	Body fat (%)	38.4 ± 10.7	45.8 ± 8.8	< 0.01
GH 1 mg/m²/day (*n* = 35), vs no treatment (*n* = 19); 1 year	Lean mass (kg)	25.6 ± 4.3	21.7 ± 5.0	< 0.01
	BMI (kg/m²)	23.7 ± 6.3	25.2 ± 8.9	n/s
de Lind van Wijngaarden *et al.*,[93] Festen *et al.*[94] (infants)	BMI (kg/m²)	16.3 (15.7 to 18.2)	16.4 (15.4 to 19.8)	nr
rhGH 1 mg/m² (*n* = 19) vs no treatment (*n* = 19); 1 year median (IQR)	BMI (SDS)	0.3 (–0.1 to 1.6)	0.3 (–0.6 to 1.6)	0.72
de Lind van Wijngaarden *et al.*,[93] Festen *et al.*[94] (children)[a]	BMI (kg/m²)	17.5 (16.1 to 21.1)	19.1 (17.8 to 20.8)	
rhGH 1 mg/m² vs no treatment; 2 years median (IQR)	BMI (SDS)	1.1 (–0.2 to 1.7)	1.4 (1.1 to 1.6)	0.19
	Fat % (SDS)	1.9 (0.7 to 2.3)	2.4 (2.1 to 2.7)	< 0.001
	Fat (SDS)	1.1 (0.6 to 2.0)	4.5 (0.9 to 2.0)	< 0.01
	LBM_{age} (SDS)	–0.1 (–1.3 to 0.6)	–2.5 (–3.8 to –1.4)	< 0.001
	LBM_{HtSDS}	–1.9 (–2.4 to –1.4)	–2.3 (–2.7 to –1.3)	< 0.05
Festen *et al.*[91]	BMI (kg/m²)	16.3 (15.8 to 19.0)	18.5 (17.5 to 20.6)	< 0.05
rhGH 1 mg/m²/day (*n* = 10) vs no treatment (*n* = 10); 2 years median (IQR)	BMI SDS	0.4 (–0.3 to 1.1)	1.2 (0.9 to 1.5)	< 0.05
	LBM SDS	–1.2 (–1.7 to –1.1)	–2.8 (–3. to 1.9)	nr
	Fat % SDS	1.7 (0.9 to 1.9)	2.1 (1.9 to 2.4)	nr
Festen *et al.*[92]	BMI (kg/m²)	16.4 (15.2 to 18.5)	15.5 (14.9 to 17.6)	nr
rhGH 1 mg/m²/day (*n* = 15) vs no treatment (*n* = 14); 1 year median (IQR)	BMI SDS	0.3 (–0.9 to 1.8)	–0.4 (–0.8 to 1.3)	nr
	Body fat (%)	22.5 (11.3 to 33.2)	22.8 (19.5 to 32.9)	nr
	LBM (%)	74.8 (63.7 to 82.3)	73.6 (61.6 to 75.9)	nr
Haqq *et al.*[102]	BMI (kg/m²)	31.2 ± 8.9	32.8 ± 9.7	< 0.05
rhGH 0.043 mg/kg/day (*n* = 12) vs placebo (*n* = 12); 6 months	BMI (SDS)	2.4 ± 0.5	2.5 ± 0.6	nr
	Body fat (%)	49.7 ± 5.8	54.1 ± 5.6	< 0.05
	FM (kg)	26.1 ± 12.8	29.1 ± 14.1	< 0.05
	Lean mass (kg)	24.1 ± 8.8	22.4 ± 8.5	< 0.05
Lindgren *et al.*,[101] Lindgren *et al.*[100]	BMI (SDS)	2.0 (–2.4 to 6.7)	2.5 (0.1 to 6.1)	nr
rhGH 0.1 IU/kg/day (*n* = 15) vs. no treatment (*n* = 12)	Body fat (%)	30.9 ± 11.4	38.2 ± 9.1	nr

n/s, not significant.
a '*n*' is unclear for many of these outcomes.

Four of the trials reported a statistically significantly lower percentage of body fat in patients treated with rhGH than in those with no treatment or placebo. In the trial reported by Carrel and colleagues[22] mean percentage body fat was 10% lower for treated patients than for untreated patients ($p = 0.03$). On average, treated patients in this trial experienced an approximately 5% reduction in body fat, compared with an average 4% increase in the untreated patients' body fat ($p = 0.001$). The other two trials that found a statistically significant difference reported that treated patients had approximately 4% (Haqq and colleagues[102]) or 7% (Carrel[95] and Myers[96]) less body fat than those in the comparator group. De Lind van Wijngaarden and colleagues[93] did not report percentage body fat for infants, but did report this outcome for the children in their study who were over 4 years of age (n = unclear). Children who received rhGH for 1 year had a median percentage body fat SDS of 1.5, compared with 2.3 in the control group ($p < 0.001$). After 2 years of treatment, the SDS values were 1.9 versus 2.4 for the treated and untreated groups. respectively ($p < 0.001$).

Four trials reported that patients treated with rhGH had statistically significantly higher LBM[93,95,96,102] or a larger improvement in LBM than untreated patients.[22] In the trial reported by Carrel and colleagues,[22] treated patients' LBM increased by 1.8 kg more than the improvement seen in the untreated group (3.6 vs 1.8 kg, $p < 0.001$). Treated patients in the other two studies had approximately 2 kg[102] or 4 kg[95,96] more LBM than their untreated counterparts ($p < 0.05$ and $p < 0.01$, respectively). De Lind van Wijngaarden and colleagues[93] reported that change in trunk LBM was statistically significantly better for treated than for untreated infants (1.7 vs 0.7, respectively). For children, they reported SDS for LBM adjusted for age and height, as well as change in trunk LBM. All of these outcomes were statistically significantly better for treated children than for untreated children after both 1 and 2 years of treatment.

Six of the studies reported BMI, with mixed results. Festen and colleagues[91] reported a BMI of 16.1 at year 1 for treated patients and 18.5 for untreated patients ($p < 0.05$), with similar results at year 2. Haqq and colleagues[102] also reported a statistically significant difference of 1.6 in BMI (31.2 vs 32.8 for treatment phase vs placebo phase in a small crossover RCT, $p < 0.05$). By contrast, the RCTs reported by Carrel[95] and Myers[96] and by de Lind van Wijngaarden[93] found no statistically significant difference between treated and untreated patients. Neither of the other RCTs that reported BMI gave a value for between-group statistical significance, and both treated and untreated patients had similar values.[92,100,101]

There was no statistically significant difference in bone mineral density between treated and untreated patients in the study reported by Carrel and colleagues.[22] No statistically significant differences in progression of scoliosis or onset of scoliosis in either infants or children were reported by de Lind van Wijngaarden.[93]

Biochemical and metabolic markers

The included studies reported a range of biochemical and metabolic markers, and key results are included in *Table 17* – see Appendix 4 for further outcomes. For conciseness, only the key outcomes of IGF-1, IGFBP-3, insulin and glucose are discussed in the narrative summary below.

All of the RCTs reported IGF-1 values or IGF-1 SDS as an outcome measure, and found that levels were higher in rhGH-treated patients than in untreated children. Three studies reported that IGF-1 values were statistically significantly higher in rhGH-treated patients than in untreated patients.[22,95,96,102] Three studies reported that IGF-1 SDS values were statistically significantly higher in treated than in untreated patients.[91–94]

The included studies had well-matched patient groups, whose baseline characteristics were similar in the treated and untreated groups. The only exception was the crossover study by Haqq and colleagues,[102] which presented baseline characteristics for the study population as a whole, and the study by Lindgren and colleagues,[100,101] which reported slightly lower baseline GV SDS in the rhGH group [–1.9 ± 2.0, range –6.4 to –0.9, vs –0.1 (SD not reported) range –1.7 to –2.71].

Three of the RCTs reported IGFBP-3 values,[93,95,96] and these were higher in treated patients than in untreated patients. In the trial reported by Carrel[95] and Myers,[96] patients treated with rhGH had a mean level of 3.5 mg/ml compared with 2.07 in the untreated patients ($p < 0.01$). Haqq and colleagues reported mean values of 6029 ng/ml in the treated patients and 4247 ng/ml in the untreated patients ($p < 0.01$).[102] Treated children and infants in the study reported by de Lind van Wijngaarden and colleagues[93] had higher IGFBP-33 values than

TABLE 17 *Biochemical and metabolic markers for PWS studies*

Study	Outcomes (mean ± SD)	GH	Control	*p*-value
Carrel *et al.*[22] rhGH 1 mg/m²/day (*n* = 15) vs no treatment (*n* = 14); 1 year	IGF-1 (ng/ml)	231 ± 98	51 ± 28	< 0.001
Carrel *et al.*[95] and Myers *et al.*[96] GH 1 mg/m²/day (*n* = 35), vs no treatment (*n* = 19); 1 year	IGF-1 (ng/ml)	522 ± 127	121 ± 52	< 0.01
	IGFBP-3 (mg/l)	3.5 ± 0.73	2.07 ± 0.45	< 0.01
de Lind van Wijngaarden *et al.*[93] and Festen *et al.*[94] (infants) rhGH 1 mg/m² (*n* = 19) vs no treatment (*n* = 19); 1-year median (IQR)	IGF-1 (ng/ml)	179.0 (119.5 to 241.0) (*n* = 12)	33.0 (22.5 to 47.8) (*n* = 15)	nr
	IGF-1 SDS	2.5 (1.4 to 2.9)	–2.6 (–4.1 to –0.7)	< 0.0001
	IGFBP-3 (ng/ml)	2.2 (1.6 to 2.4) (*n* = 12)	0.9 (0.7 to 1.3) (*n* = 12)	nr
	IGFBP-3 SDS	0.5 (0.0 to 1.2) (*n* = 12)	–2.4 (–3.5 to –1.2) (*n* = 12)	nr
de Lind van Wijngaarden *et al.*[93] and Festen *et al.*[94] (children)[a] rhGH 1 mg/m² vs no treatment; 2-year median (IQR)	IGF-1 (ng/ml)	424.0 (313.0 to 570.0) (*n* = 20)	92.0 (61.8 to 130.0) (*n* = 16)	nr
	IGF-1 SDS	2.4 (2.1 to 2.8)	–1.6 (–2.5 to –1.0)	< 0.0001
	IGFBP-3 (ng/ml)	2.8 (2.6 to 3.2) (*n* = 20)	1.5 (1.2 to 1.8) (*n* = 16)	nr
	IGFBP-3 SDS	0.6 (0.3 to 1.1) (*n* = 20)	–1.7 (–2.3 to –1.2) (*n* = 16)	< 0.001
Festen *et al.*[91] rhGH 1 mg/m²/day (*n* = 10) vs no treatment (*n* = 10); 2-year median (IQR)	IGF-1 SDS year 2	2.3 (2.1 to 2.9)	–2.0 (–2.7 to 1.0)	< 0.001
	IGFBP-3 SDS year 2	0.6 (0.4 to 1.1)	–1.8 (–2.7 to –1.5)	< 0.001
Festen *et al.*[92] rhGH 1 mg/m²/day (*n* = 15) vs no treatment (*n* = 14); 1-year median (IQR)	IGF-1 SDS	1.7 (0.1 to 2.5)	–2.6 (–4.1 to –0.4)	< 0.001
	IGFBP-3 SDS	0.4 (–0.3 to 1.1)	–3.1 (–4.0 to –2.2)	< 0.05
Haqq *et al.*[102] rhGH 0.043 mg/kg/day (*n* = 12) vs placebo (*n* = 12); 6 months	IGF-1 (ng/ml)	720 ± 379	232 ± 182	< 0.001
	IGFBP-3 (ng/ml)	6029 ± 1311	4247 ± 1209	< 0.01
Lindgren *et al.*[101] and Lindgren *et al.*[100] rhGH 0.1 IU/kg/day (*n* = 15) vs no treatment (*n* = 12); 1 year	IGF-1 SDS	1.8 (–0.1 to 4.1)	–1.4 (–2.9 to –0.3)	nr

a *n* = unclear for IGF-1 SDS.

untreated children, although no *p*-values were reported for between-group comparisons.

The three studies that reported IGFBP-3 SDS found positive values in the treated children, with SDS of 0.4[92,93] and 0.5 (year 1) or 0.6 (year 2).[91,93] In comparison, untreated patients' median scores were between –2.4[91,93] and –3.1[92] in year 1 and between –1.7[93] to –1.8[91] in year 2. Differences between treated and untreated patients were statistically significant in all three studies ($p < 0.05$,[92] $p < 0.001$,[93] $p < 0.001$[91]).

The RCT reported by Carrel and colleagues[22] reported that there was no statistically significant difference in fasting insulin levels between the treated and untreated infants in their study (5.6 vs 5.7 μIU/ml, respectively). Two other studies[91,95,96] reported slightly higher insulin levels in treated patients, but did not report *p*-values. The study by Haqq and colleagues[102] reported very similar levels in both treated and untreated patients. Glucose levels appeared to be similar in both treated and untreated patients in the two studies that presented this as an outcome, but neither study reported any *p*-values.[91,102]

Quality of life

None of the included studies reported a measure of HRQoL.

Adverse events

None of the studies reported AEs in any detail. Neither of the studies reported by de Lind van Wijngaarden and colleagues[93] and by Festen and colleagues[94] nor the one reported by Festen and colleagues[91] reported on AEs at all. In the other study by Festen and colleagues,[92] the paper stated that rhGH treatment did not induce disadvantageous effects on carbohydrate metabolism, sleep-related breathing disorders or thyroid hormone levels. Hauffa and colleagues[99] reported that one patient in the rhGH group developed pseudotumour cerebri after increasing the starting dose to the final dose, but their symptoms resolved on discontinuation. No abnormalities of glucose regulation were observed in either group. None of the patients in the study reported by Carrel and others[95,96] experienced pseudotumour cerebri. Two of their patients who received rhGH experienced headaches within the first 3 weeks, but these resolved with temporary stoppage and gradual reinstitution of treatment.

Carrel and colleagues[22] commented that there was no evidence of changes in the prevalence of scoliosis with rhGH treatment, although another paper reporting the same study reported that there was progression of scoliosis in one patient.[97] Lindgren and colleagues[100,101] and Haqq and colleagues[102] reported that there was no severe progression of scoliosis (angle ≥ 20°) during their RCTs.

Lindgren and colleagues[100,101] noted that one child in their study developed low levels of thyroxine without any change in TSH levels. He received substitution with L-thyroxine during the rhGH treatment. Carrel and colleagues[22] commented that no child in their RCT required thyroid hormone therapy. Haqq and colleagues[102] reported that only one patient required thyroid hormone replacement while receiving rhGH treatment.

Summary

The evidence for the clinical effectiveness of HGH as a treatment for PWS comes from eight small RCTs (one crossover trial and seven parallel group trials), reported in 13 publications. The included studies were generally poorly reported and only two[91,96] presented results on an ITT basis.

Only one of the studies reported changes in height. Infants who received rhGH for 1 year grew an average of 6.2 cm more than those in the untreated group ($p < 0.001$).[22] Two studies reported a statistically significant difference in HtSDS between treated and untreated patients. The difference was 1 SDS (favouring rhGH treatment) in one study,[95,96] and > 2 (year 2) in the other.[93]

Treated patients grew 3 cm/year faster than untreated patients in one RCT[102] and 5 cm/year faster in another.[95,96] Another study reported a positive GV SDS for treated patients and a negative one for untreated children (5.5 vs –2.3).[99] The differences between groups were statistically significant in all three studies.

Two of the included studies reported BA as an outcome measure, and this was similar in both treatment groups.[95,96,100,101]

Four trials reported a statistically significantly lower percentage of body fat (between 1%[93] and 10%[22] lower) in patients treated with rhGH than in those with no treatment or who were given placebo.

Three trials reported that patients treated with rhGH had statistically significantly higher LBM,[95,96,102] or a larger improvement in LBM, than untreated patients.[22] One study reported that LBM SDS was significantly better in treated than in untreated children.[93]

Two studies found that BMI was statistically significantly lower in treated patients than in untreated patients.[91,102] However, another RCT[95,96] found no statistically significant difference between the two groups, and three more studies did not report a *p*-value for between-group statistical significance.[92,93,100,101]

Insulin-like growth factor-1 values were statistically significantly higher in patients treated with rhGH than in untreated patients in three studies.

Two RCTs reported IGFBP-3 values that were statistically significantly higher in treated patients than in untreated patients.[95,96,102] Three studies[91–93] reported positive IGFBP-3 SDS values in treated patients and negative values in untreated children; differences between the groups were statistically significant.

Four of the studies reported insulin levels, with varying results. One study[22] reported that there was no statistically significant difference between treated and untreated infants. Insulin levels in another study[95,96] appeared to be considerably higher in treated patients than in untreated patients. Another study[91] reported higher insulin levels in treated patients at year 1 but lower levels than in untreated patients at year 2. Similar values in both groups were also reported.[102]

None of the included studies reported a measure of HRQoL.

None of the studies reported AEs in any detail.

Chronic renal insufficiency

Quantity and quality of research available

Six RCTs of patients with CRI met the inclusion criteria for this review,[103–108] and their key characteristics are shown in *Table 18* – further details are shown in Appendix 4. The inclusion criteria for this systematic review specified that children should be prepubertal. Five of the studies stated in their inclusion criteria that patients should be prepubertal/Tanner stage 1, but one study included both prepubertal and pubertal patients.[107] However, we have included outcome measures from this study where data were presented separately for prepubertal children and pubertal children.

The included RCTs were of different designs (two crossover and four parallel group). Three of the parallel-group RCTs were open label, with the comparator groups receiving no treatment,[103,106,107] and one was placebo controlled.[108] The two crossover studies[104,105] had placebo and treatment phases. There does not appear to have been a washout phase in either of the crossover trials, so a carry-over effect could have affected results. The doses all appeared to correspond to those specified in the marketing authorisation, but dosages were reported differently, with some using IUs and others using mgs, and some using doses based on weight, whereas others used surface area. Randomised treatment duration was 6 months in the two crossover trials,[104,105] 2 years in one study[108] and 12 months in the other studies.

Three of the studies investigated rhGH treatment in children who had received a kidney transplant at least 1 year before starting the study[103,105,107] and the other three studied children who had CRI.[104,106,108]

There was considerable variation in the age of children in the included studies, ranging from 5.6[106] to 12.6[107] years old. Two of the studies were relatively large ($n = 203$[107] and $n = 125$[108]), one was of medium size ($n = 69$[106]), and the remaining three were rather small ($n = 23$,[103] $n = 20$[104] and $n = 11$[105]).

Only one study[107] specified a primary outcome. The Pharmacia and Upjohn Study Group[107] designed their study to test GFR, with GV and HtSDS being used as secondary outcomes. The other studies reported various outcomes relating to growth, body composition and biochemical/metabolic markers, but did not specify which were primary outcomes. Only Sanchez and colleagues[103] mentioned a power calculation, and this appears to have been based on bone formation rates in a previous study, so it is not clear what the primary outcome was for the included study. The lack of clarity around primary outcomes and power calculations, together with the small size of three of the studies,[103–105] suggests that the trials may have been underpowered to detect differences in outcomes relating to growth and body composition.

The included studies had well-matched patient groups, whose baseline characteristics were similar in the treated and untreated groups.

None of the included RCTs provided clear information on method of randomisation or concealment of allocation (*Table 19*), so it is not possible to say whether or not selection bias may have affected these studies. The studies all reported eligibility criteria, and presented baseline characteristics that indicated that groups (within trials) were similar at the start of the studies.

The studies gave little information on whether or not outcome assessors were blinded to patients' treatment groups, although Sanchez and colleagues[103] did comment that skeletal radiographs were reviewed by a single observer who had no information about patients' clinical condition or treatment status. In addition, three of the trials gave patients in the comparator group no treatment, so it would have been clear to patients and their care providers whether or not they were receiving rhGH. In three trials, patients in the comparator group had placebo injections. It is not clear whether or not their care providers were also blinded to treatment group. Lack of blinding could have led to performance bias in measuring treatment effect, but the objective nature of outcomes such as height change and GV would have protected against bias to a certain degree.

TABLE 18 *Characteristics of CRI studies*

Reference	Intervention	Control group	Total randomised and withdrawals	Duration of randomised treatment
The Pharmacia and Upjohn Study Group 1996[107]	rhGH 1 IU/kg/week *n* = 106 Mean ± SD age (years): 12.6 ± 3.4	No treatment *n* = 97 Mean ± SD age (years): 12.1 ± 3.1	Total *n* = 203 Sample attrition: *n* = 49	1 year
Fine *et al.* 2004[108]	rhGH 0.05 mg/kg/day *n* = 82 Mean ± SD age (years): 6.0 ± 3.9	Placebo *n* = 43 Mean ± SD age (years): 5.7 ± 3.6	Total *n* = 125 Sample attrition: rhGH 26, placebo 15	2 years
Hokken-Koelega *et al.* 1991[104]	rhGH 4 IU/m^2/day then placebo *n* = 8 Median (range) age (years): 8.7 (4.4 to 11.3)	Placebo, then 4 IU/m^2/day rhGH *n* = 8 Median (range) age (years): 8.6 (4.4 to 16.0)	Total *n* = 20 Sample attrition: *n* = 4	6 months in each arm
Hokken-Koelega *et al.* 1996[105]	rhGH/placebo 4 IU/m^2 daily s.c.i. *n* = 6 Median (range) age (years): 12.1 (9.1 to 18.7)	Placebo/4 IU/m^2 rhGH daily s.c.i. *n* = 5 Median (range) age (years): 11.1 (8.3 to 14.9)	Total *n* = 11 No withdrawals	6 months in each arm
Powell *et al.* 1997[106]	rhGH 0.05 mg/kg/day *n* = 30 Mean age (years) ± SD: 5.6 ± 2.0	No treatment *n* = 14 Mean age (years) ± SD: 5.7 ± 2.6	Total: *n* = 69 Sample attrition: 20 withdrew; 4 rhGH patients and 1 control patient excluded from analyses	1 year
Sanchez *et al.* 2002[103]	rhGH 0.05 mg/kg/day *n* = 12 Mean age (± SD) 9.7 ± 4.5	No treatment *n* = 11 Mean age (± SD) 11 ± 1.8	Total: *n* = 23 Sample attrition: rhGH, *n* = 1; control, *n* = 1	12 months

s.c.i., subcutaneous injection.

TABLE 19 *Quality assessment of CRI studies*

	The Pharmacia and Upjohn Study Group[107]	Fine *et al.*[108]	Hokken-Koelega *et al.*[104]	Hokken-Koelega *et al.*[105]	Powell *et al.*[106]	Sanchez *et al.*[103]
1. Was the assignment to the treatment groups really random?	Un	Un	Un	Un	Un	Un
2. Was the treatment allocation concealed?	Un	Un	Un	Un	Un	Un
3. Were the groups similar at baseline in terms of prognostic factors?	Rep	Rep	Rep	Rep	Rep	Rep
4. Were the eligibility criteria specified?	Ad	Ad	Ad	Ad	Ad	Ad
5. Were outcome assessors blinded to the treatment allocation?	Un	Un	Un	Un	Un	Par
6. Was the care provider blinded?	In	Un	Un	Un	In	In
7. Was the patient blinded?	In	Ad	Ad	Ad	In	In
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Ad	Ad	Ad	Ad	Ad	Ad
9. Did the analyses include an ITT analysis?	In	In	In	Ad	In	In
10. Were withdrawals and dropouts completely described?	Ad	Ad	Ad	Ad	Ad	Ad

Ad, adequate; In, inadequate; Not rep, not reported; Par, partial; Rep, reported; Un, unknown.

All the studies presented results as mean values with SDs or standard errors to give a measure of variability. The studies all provided adequate details of any patients who withdrew from the study, but only one study[105] presented results on an ITT basis (no patients withdrew from this study). Attrition bias could therefore have affected the results of the non-ITT studies, i.e. if there had been unbalanced and selective withdrawal from different treatment groups within a study, or if particular patients were more likely to withdraw or be excluded from the analysis.

There was a statistically significant difference between treated and untreated children's birth length SDS in one study,[111] but baseline height was the same in both groups. The very small study by de Zegher and colleagues[113] reported slightly lower baseline GV in treated compared with untreated children [5.1 (range 4.0–6.8) vs 6.4 (range 5.3–7.5) cm/year, respectively]. Otherwise, the studies' treatment groups were generally comparable at baseline, with no discernible differences between treated and untreated patients.

The outcome measures for the included studies are shown in *Tables 20–22* below. The *p*-values in the tables refer to between-group differences.

Growth outcomes

Key growth outcome measures are shown in *Table 20* – see Appendix 4 for other outcome measures. Only one of the included studies reported height gain. Powell and colleagues[106] found that treated children grew an average of 3.6 cm more than their untreated counterparts after 1 year of treatment (9.1 cm vs 5.5 cm, $p < 0.0001$). All children in the study by The Pharmacia and Upjohn Study Group[107] experienced an improvement in HtSDS, but this was statistically significantly higher in the children treated with rhGH than in the untreated children (0.6 vs 0.1, $p < 0.0001$). RhGH-treated children in the study by Powell and colleagues[106] had a statistically significantly higher HtSDS at end of 12 months than untreated children (0.8 vs 0.0, $p < 0.0001$).

One of the six studies reported change in GV, and this was statistically significantly faster in treated than in untreated children.[107] Four studies reported GV at end of treatment, all reporting statistically significantly faster growth in children who received rhGH treatment than in untreated children.[103–105,107,108] The 2-year study by Fine and colleagues[108] reported that rhGH-treated patients' GV in the first year was 4.2 cm/year faster than the untreated patients' ($p < 0.00005$). The difference between the two groups was less in the second year (2.3 cm/year faster in rhGH-treated children) but the difference between groups was still statistically significant ($p < 0.00005$) when comparing the difference in change from baseline in those patients who completed 2 years of the study. A statistically significant difference in GV between groups of just over 3 cm/year was reported by both The Pharmacia and Upjohn Study Group[107] (3.4 cm/year difference, $p < 0.0001$) and by Sanchez and colleagues[103] (3.2 cm/year difference, $p < 0.01$).

The two crossover studies by Hokken-Koelega and colleagues[104,105] also reported statistically significantly faster growth velocities in patients during the rhGH phase compared with the placebo phase, with an average of 2.9 cm/6 months difference in velocity. In the study of children with CRI, patients who received rhGH followed by placebo grew at an average velocity of 5.2 cm/6 months during treatment compared with 1.5 cm/6 months in the placebo phase. Patients who received placebo followed by rhGH grew 2.4 cm/6 months during the placebo phase compared with 4.4 cm/6 months in the treatment phase. The overall mean effect of rhGH was statistically significant ($p < 0.0001$). Statistical tests showed that there was no significant carry-over effect (–0.04 cm/6 months, $p = 0.94$). The crossover study in children who had received a renal transplant had similar results. Patients grew, on average, 3.8 cm/6 months faster during the active treatment phase in the group who received rhGH followed by placebo, and 2 cm/6 months faster in the active treatment phase for patients who received placebo followed by rhGH ($p < 0.0001$ for overall effect of rhGH vs placebo).[105] Hokken-Koelega and colleagues reported that there was no significant carry-over effect (0.5 cm/6 months, $p = 0.30$).[104,105]

The two crossover trials,[104,105] but none of the parallel-group RCTs, reported GVSDS. Both trials reported positive SDS values during the active treatment phases and negative scores during the placebo phases. The reported difference in scores between active treatment and placebo phases in the trial of children with chronic renal failure (CRF) was 7.7 ($p < 0.0001$),[104] and in the trial of children who had received a renal transplant the difference was 8.0 ($p < 0.0001$).[105]

Bone age was reported by five of the six studies. The studies by Powell and colleagues[106] and Sanchez and colleagues[103] reported that there was no statistically significant difference in BA

TABLE 20 *Growth outcomes for CRI studies*

Study	Outcomes (mean ± SD)	rhGH (SD)	Control (SD)	*p*-value
The Pharmacia and Upjohn Study Group[107]	Change in HtSDS	+0.6 0.3	+0.1 ± 0.3	< 0.0001
rhGH 1 IU/kg/week (*n* = 30) vs no treatment (*n* = 28); 1 year	Change in GV (cm/year)	3.7 ± 1.6	0.3 ± 1.6	< 0.0001
Fine *et al.*[108]	HtSDS	–1.6	–2.9	nr
rhGH 0.05 mg/kg/day (*n* = 82) vs placebo (*n* = 43); 2 years	GV (cm/year)	7.8 ± 2.1 (*n* = 55)	5.5 ± 1.9 (*n* = 27)	< 0.00005
Powell *et al.*[106]	Height gain (cm)	9.1 ± 2.8	5.5 ± 1.9	< 0.0001
rhGH 0.05 mg/kg/day (*n* = 30) vs no treatment (*n* = 14); 1 year	HtSDS change from baseline	0.8 ± 0.5	0.0 ± 0.3	< 0.0001
Sanchez *et al.*[103]	HtSDS	–1.1 ± 1.0	nr	nr
rhGH 0.05 mg/kg (*n* = 12) vs no treatment (*n* = 11); 1 year	Annual GV (cm/year)	8.0 ± 2.1	4.8 ± 1.7	< 0.01
Hokken-Koelega *et al.*[104]	GV (cm/6 months)	1: 5.2 (1.2)	1: 1.5 (0.4)	< 0.0001
1: 4 IU/m^2 rhGH then placebo (*n* = 8)		2: 4.4 (1.6)	2: 2.4 (1.0)	
2: Placebo then 4 IU/m^2 rhGH (*n* = 8); 6 months each arm	HV SDS	1: 6.9 (2.4)	1: –3.0 (1.6)	< 0.0001
		2: 5.0 (4.5)	2: –0.5 (3.2)	
Hokken-Koelega *et al.*[105]	GV (cm/6 months)	1: 5.3 (1.0)	1: 1.5 (0.9)	< 0.0001
1: 4 IU/m^2 rhGH then placebo (*n* = 6)		2: 3.9 (1.3)	2: 1.9 (0.7)	
2: Placebo then 4 IU/m^2 rhGH (*n* = 5); 6 months each arm	HV SDS	1: 9.1 (2.9)	1: –1.3 (2.9)	< 0.0001
		2: 5.3 (4.0)	2: –0.4 (1.7)	

between the treated and untreated patients. The two crossover studies by Hokken-Koelega and colleagues reported small differences with slightly lower mean ages for rhGH overall compared with placebo (mean differences –0.01 years[104] and –0.5 years[105]) but did not present any *p*-values for these comparisons. Fine and colleagues[108] reported that the change in BA between baseline and 2 years was greater in patients treated with rhGH than in untreated patients for those who completed both years of the study (2.3 vs 1.6 years, $p = 0.0001$).

Body composition

Measures of body composition were reported by three of the studies, and selected outcomes are shown in *Table 21*.[103,106,108] Other outcomes are tabulated in the data extraction forms in Appendix 4. Children treated with rhGH gained statistically significantly more weight than those in the control groups in the studies reported by Fine and colleagues[108] (2.1 kg more in 2 years, $p = 0.0004$) and by Powell and colleagues[106] (1.3 kg more in 1 year, $p = 0.007$). However, there was no statistically significant difference between groups in change in weight for HtSDS. Sanchez and colleagues[103] did not report actual weight gain, but reported a statistically significant difference in change in SDS for weight that favoured treatment with rhGH (0.2 vs –0.3, $p < 0.01$). Although Powell and colleagues[106] reported a statistically significantly greater weight gain in treated patients, the weight for HtSDS was the same for both groups (0.4, $p = 0.8703$).

Biochemical markers

The included studies reported a range of biochemical and metabolic markers, and these are included in *Table 22*. For conciseness, only the key outcomes of IGF-1, IGFBP-3, insulin and glucose are discussed in the narrative summary below. In addition, the studies reported a range of markers related to liver function. These are not reported in *Table 22* or discussed in the narrative summary below, but are included in the data extraction forms in Appendix 4. No data from Sanchez and colleagues are included in *Table 22* as their results focussed on liver function and did not report IGF, insulin or glucose.

TABLE 21 *Body composition outcomes for CRI studies*

Study	Outcomes (mean ± SD)	GH	Control	*p*-value
Fine *et al.* [108] rhGH 0.05 mg/kg/day (*n* = 82) vs placebo (*n* = 43)	Weight gain after 2 years (kg)	6.7 ± 2.2	4.6 ± 2.7	0.0004
Powell *et al.* [106]	Weight gain (kg)	3.5 ± 1.5	2.2 ± 1.0	0.007
rhGH 0.05 mg/kg/day (*n* = 30) vs no treatment (*n* = 14)	Change in weight for HtSDS	0.4 ± 0.7	0.4 ± 0.5	0.8703
Sanchez *et al.* [103] rhGH 0.05 mg/kg (*n* = 12) vs no treatment (*n* = 11)	Change in SDS for weight	0.2 ± 0.3	–0.3 ± 0.3	< 0.01

TABLE 22 *Biochemical and metabolic markers from CRI studies*

Study	Outcomes (mean ± SD)	GH	Control	*p*-value
Fine *et al.* [108] rhGH 0.05 mg/kg/day (*n* = 82) vs placebo (*n* = 43)	IGF-1 (μg/l)	244 ± 128 (*n* = 47)	135 ± 80 (*n* = 20)	0.0001
Powell *et al.* [106] rhGH 0.05 mg/kg/day (*n* = 30) vs no treatment (*n* = 14)	IGF-1 SDS change from baseline	0.2 ± 1.0	nr	0.006
	IGFBP-3 SDS change from baseline	4.0 ± 3.2	nr	0.011
Hokken-Koelega *et al.* [104] 1: 41IU/m^2 rhGH then placebo (*n* = 8) 2: Placebo then 41IU/m^2 rhGH (*n* = 8)	IGF-1 ng/ml	1: 264 ± 168	1: 160 (104)	nr
		2: 268 ± 120	2: 160 (95)	
	IGF-1 SDS for BA	1: 2.6 ± 2.0	1: –0.2 ± 1.5	< 0.0001
		2: 2.9 ± 2.0	2: 0.3 ± 1.6	
	IGFBP-3 ng/ml	1: 7708 ± 2323	1: 6102 ± 1892	nr
		2: 8706 ± 2275	2: 6501 ± 1988	
	IGFBP-3 SDS for BA	1: 5.0 ± 1.3	1: 3.7 ± 1.3	< 0.0001
		2: 5.2 ± 1.4	2: 3.9 ± 1.4	
Hokken-Koelega *et al.* [105] 1: 41IU/m^2 rhGH then placebo (*n* = 6) 2: Placebo then 41IU/m^2 rhGH (*n* = 5)	IGF-1 ng/ml	1: 594 ± 180	1: 240 ± 143	nr
		2: 488 ± 237	2: 321 ± 94	
	IGF-1 SDS for BA	1: 5.4 ± 2.8	1: 1.0 ± 2.5	< 0.0001
		2: 3.4 ± 0.5	2: 6.4 ± 1.9	
	IGFBP-3 ng/ml	1: 7457 ± 2088	1: 5681 ± 1588	nr
		2: 8495 ± 2921	2: 6228 ± 2193	
	IGFBP-3 SDS for BA	1: 4.5 ± 1.5	1: 3.7 ± 2.9	nr
		2: 3.9 ± 1.5	2: 5.3 ± 1.5	

Four studies reported IGF-1 as an outcome measure,[104–106,108] and levels were higher in treated patients than in untreated patients. IGF-1 values were statistically significantly higher in treated patients at both years 1 and 2 in the study by Fine and colleagues[108] ($p = 0.0004$ and $p = 0.0001$, respectively), but only approximately one-half of the randomised patients were included in this analysis. Powell and colleagues[106] also reported that IGF-1 and IGF-1 SDS values were statistically significantly higher for treated patients than untreated patients ($p < 0.006$).[106] The two crossover studies by Hokken-Koelega and colleagues[104,105] reported that IGF-1 SDS for BA was statistically

significantly higher for treated than for untreated patients (2.7 higher in treated children with CRF[104] and 3.7 higher in treated children who were post transplant,[105] $p < 0.0001$ for both).

Three studies reported IGFBP values,[104–106] and in all three the IGFBP-3 values were higher in the treated patients. Powell and colleagues[106] reported that IGFBP-3 and corresponding SDS values were statistically significantly higher in treated patients than in untreated patients ($p < 0.011$). Hokken-Koelega and colleagues[104] reported that the IGFBP-3 SDS for bone age was statistically significantly higher for treated patients ($p < 0.0001$).

Fine and colleagues[108] reported that fasting insulin levels were statistically significantly higher in rhGH patients than in untreated patients after 2 years ($p = 0.03$). Similarly, Hokken-Koelega and colleagues[105] reported slightly higher insulin values in treated children, but did not present *p*-values.

Quality of life

Five of the included studies did not report QoL as an outcome measure. One study[107] reported QoL but did not present data for prepubertal patients (the licensed patients) separately from pubertal patients, so it is not discussed here.

Adverse events

Hokken-Koelega and colleagues[105] reported that no patients in their study had an acute rejection episode, and that there were no SAEs. Sanchez and colleagues[103] reported that two patients with normal rates of bone formation experienced acute rejection episodes after 3 and 12 months of rhGH therapy. One of these episodes was associated with non-compliance to immunosuppressive medications and both reversed after treatment with methylprednisolone. There were no rejection episodes in untreated patients.

Fine and colleagues[108] reported that there were no differences between groups in year 1. In the second year, eight of 55 rhGH patients experienced asthma or wheezing, but all episodes were preceded by upper respiratory tract infections. Fine and colleagues[108] reported that there were no clinically significant side effects associated with rhGH treatment. Hokken-Koelega and colleagues[104] reported that serum alkaline phosphate was significantly increased during rhGH treatment, but returned to pretreatment levels when rhGH therapy was replaced by placebo ($p < 0.0001$). There was no significant change in parathyroid hormone concentration during either treatment schedule, and thyroid function was reported to have been normal. The Pharmacia and Upjohn Study Group[107] did not present AEs separately for prepubertal and pubertal children, so no data are reported here. Powell and colleagues[106] did not report AEs from their study.[106]

Summary

The evidence for the clinical effectiveness of rhGH as a treatment for short stature owing to CRI comes from six RCTs, two of which were crossover trials. The trials were generally poorly reported, and only one[105] presented ITT results. Three of the studies had fewer than 25 participants, which suggests that the trials may have been underpowered to detect differences in outcomes relating to growth and body composition.

One study reported that rhGH-treated patients grew an average of 3.6 cm more than their untreated counterparts after 1 year of treatment. Two studies reported that HtSDS was statistically significantly better in treated children than in untreated children.

Five studies reported that change in GV or GV SDS was statistically significantly faster for children who received rhGH treatment than for untreated children, with between-group differences in velocity ranging from 3.2 cm/year[103] to 4.2 cm/year[108] in the parallel-group trials.

Two studies reported that there was no statistically different difference in BA between the treated and untreated patients. Two reported small differences with slightly lower mean ages for rhGH overall compared with placebo, but did not present any *p*-values for these comparisons. One study reported that the change in BA between baseline and 2 years was greater in patients treated with rhGH than in untreated patients for those who completed both years of the study.

IGF-1 levels were statistically significantly higher in treated patients than in untreated patients in two of the four studies that reported this outcome.

Three studies reported that IGFBP-3 values were higher in the treated patients. Only one of these reported that differences between groups were statistically significant.

Insulin levels were statistically significantly higher in children receiving rhGH than in those receiving placebo injections or no treatment.

Four studies presented data on AEs. Two rhGH-treated patients in one study experienced acute rejection episodes (one associated with non-compliance to immunosuppressive medications) but both reversed after treatment with methylprednisolone. There were no SAEs reported.

Children born SGA

Quantity and quality of research available

In the UK, rhGH is licensed for use in children born SGA who are over 4 years of age, have a current HtSDS of < 2.5, with a parental adjusted HtSDS of –1, had a birth weight and/or length SDS of < –2, and have failed to show catch-up growth during the previous year (HV SDS < 0). No RCTs meeting these criteria were identified. Following discussion with NICE, the criteria were amended in order to include evidence from RCTs on rhGH. As discussed above (see Inclusion criteria), the following amended criteria were agreed: growth disturbance (current height < –2.5, no reference to parental height), birth weight and/or length < –2 SD and failure to show catch-up growth (no stated criteria) by the age of 3 years.

Six studies[109–114] met the amended inclusion criteria for this review, and their key characteristics are shown in *Table 23* – see Appendix 4 for further details. In the UK, the licensed dose of rhGH for

TABLE 23 *Characteristics of SGA studies*

Reference	Intervention	Control group	Total randomised and withdrawals	Duration of randomised treatment
Phillip *et al.* 2009[114]	1: rhGH 0.033 mg/kg/day (*n* = 51), mean age (± SD): 5.5 ± 1.5 2: rhGH 0.1 mg/kg/day (*n* = 51), mean age (± SD): 5.5 ± 1.4	No treatment, (*n* = 47) Mean age (± SD): 5.6 ± 1.4	Total *n* = 151 *Sample attrition*: 2	1 year
Carel *et al.* 2003[111]	rhGH: 0.2 IU/kg/day, *n* = 112 Mean age (± SD):12.7 ± 1.4	No treatment, *n* = 56 Mean age (± SD): 12.8 ± 1.6	Total n = 168 *Sample attrition*: For treatment: rhGH, *n* = 21; control, *n* = 23 For analysis: rhGH, *n* = 10; control, *n* = 9	Until AH reached (mean = 2.7 ± 0.6 years)
De Schepper *et al.* 2007 [109]	High-dose rhGH: 66 ± 3 μg/kg/day, *n* = 11 Mean age (± SD): 5.1 ± 1.6	No treatment, *n* = 14 Mean age (± SD): 5.1 ± 1.4	Total n = 40 *Sample attrition*: *n* = 15	2 years
de Zegher *et al.* 1996[112]	1: rhGH 0.2 IU/kg/day, *n* = 20 2: rhGH 0.3 IU/kg/day, *n* = 21 Mean age (± SD): 1: 5.4 ± 0.5 2: 5.1 ± 0.4	No treatment, *n* = 13 Mean age (± SD): 4.9 ± 0.5	Total: n = 54 *Sample attrition*: rhGH 1: *n* = 2 rhGH 2: *n* = 1 Control: *n* = 1	2 years
de Zegher *et al.* 2002[113]	High-dose rhGH 100 μg/kg/day, *n* = 9 Mean age (range): 6.3 (4.0–8.0)	No treatment, *n* = 4 Mean age (range): 4.7 (2.3–6.3)	Total *n* = 13 *Sample attrition*: not reported	2 years
Lagrou *et al.* 2008[110]	rhGH 0.066 mg/kg/day, *n* = 20 Mean age (± SD): 5.5 ± 1.6	No treatment, *n* = 20 Mean age (± SD): 5.1 ± 1.3	Total n = 40 *Sample attrition*: 1	2 years

Licensed dose = 35 μg/kg/day = 0.035 mg/kg/day = 0.105 IU/kg/day.

SGA children is 0.035 mg/kg/day, which equates to 0.105 IU/kg/day. Only the study by Phillip and colleagues[114] included a treatment arm with the licensed dose; the other studies all used approximately two or three times the UK licensed dose.

Treatment duration was comparable across five of the six included studies. Four of the trials stated a treatment duration of 2 years.[109,110,112,113] Carel and colleagues[111] administered GH for an average of 2.7 ± 0.6 years, until the participants reached AH. The children in the study by Phillip and colleagues[114] received treatment for 2 years, but only the first year allowed a randomised comparison between GH and no treatment.

The mean age of participants was similar both across groups within studies and across five of the six trials included.[109,110,112–114] The mean ages of groups in these trials ranged from 4.7 (2.3–6.3)[113] to 6.3 (4.0–8.0) years. The Carel study[111] included older children with mean ages of 12.7 ± 1.4 in the rhGH group and 12.8 ± 1.6 in the control group.

The six included trials were generally of poor methodological quality (*Table 24*).

Phillip and colleagues[114] reported that a centralised computer-controlled system was used to randomly assign children to groups. In the other five trials it was unclear whether the assignment to treatment groups was really random. This was reflected in the assessment of whether treatment allocation was concealed, with one exception being the study by Carel and colleagues,[111] which reported that group assignment was not masked and this was therefore judged to be inadequate.

The blinding of outcome assessors can defend against bias affecting the measurement of some outcomes. In two trials[112,114] outcome assessors for BA were blinded to chronological age and treatment allocation. It was not stated whether this extended to assessors of other outcomes. In the remaining four trials it was not stated whether the outcome assessors were blinded.

Performance bias, where knowledge of treatment can potentially lead to differences in care provided can be protected against by blinding care givers and patients. The care provider was not blinded to treatment in the studies by Carel and colleagues[111] or Phillip and colleagues,[114] and in the four remaining trials this was unknown. In each of the

TABLE 24 *Quality assessment of included SGA studies*

	Carel *et al.*[111]	De Schepper *et al.*[109]	de Zegher *et al.*[112]	de Zegher *et al.*[113]	Lagrou *et al.*[110]	Phillip *et al.*[114]
1. Was the assignment to the treatment groups really random?	Un	Un	Un	Un	Un	Ad
2. Was the treatment allocation concealed?	In	Un	Un	Un	Un	Un
3. Were the groups similar at baseline in terms of prognostic factors?	Rep	Rep	Rep	Rep	Rep	Rep
4. Were the eligibility criteria specified?	Ad	Ad	Ad	Ad	Ad	Ad
5. Were outcome assessors blinded to the treatment allocation?	Un	Un	Par	Un	Un	Par
6. Was the care provider blinded?	In	Un	Un	Un	Un	In
7. Was the patient blinded?	In	In	In	In	In	In
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Ad	Ad	Ad	Ad	Ad	Ad
9. Did the analyses include an ITT analysis?	In	In	In	Ad	In	In
10. Were withdrawals and dropouts completely described?	Ad	Ad	Ad	Ad	In	In

Ad, adequate; In, inadequate; Not rep, not reported; Par, partial; Rep, reported; Un, unknown.

six trials blinding of the patient was inadequate as no placebo was used. Only one of the trials conducted an ITT analysis.[113] This guards against bias arising where for example only the results of patients who did not experience AE or compliance issues are included in the analysis.

Growth outcomes

All six studies[109–114] reported growth outcomes, and these are presented in *Table 25*.

Carel and colleagues[111] reported AH for the 70% of control patients and 89% of treated patients for whom these data were available. They reported a mean gain in AH of 26 ± 7 cm in the treated group compared with 22 ± 6 cm in their untreated group ($p = 0.005$). They also reported AH SDS, which was statistically significantly higher in the rhGH treated group (–2.1 ± 1.0) compared with the untreated group (–2.7 ± 1.0), $p = 0.005$. Similarly, the SDS for AH total gain was statistically significantly higher in treated patients than with untreated patients (1.1 ± 0.9 vs 0.5 ± 0.8, $p = 0.002$). Carel and colleagues[111] also reported the difference from target HtSDS. This was statistically significantly lower in the group receiving GH, compared with the control group (–0.9 ± 1.2 vs –1.7 ± 1.2, $p = 0.005$).

Children who received the licensed dose of 0.033 mg/kg/day for 1 year in the study by Phillips and colleagues[114] gained an average of 3.3 ± 0.2 cm in height compared with children in the untreated control group. Those receiving the higher dose of 0.1 mg/kg/day rhGH gained an average of 6.5 ± 0.2 cm compared with untreated children. No *p*-values were presented for between-group comparisons, although the CIs suggest a statistically significant difference.

de Zegher and colleagues[112] found that gain in HtSDS at the end of the study was higher in the group receiving a higher dose [2.1 ± 0.1 (0.2 IU/kg/day) vs 2.5 ± 0.1 1 (0.3 IU/kg/day) vs 0.2 ± 0.1 (untreated), $p < 0.001$ treated vs untreated groups]. The other study by de Zegher and colleagues[113] reported higher HtSDS in treated patients, but did not present *p*-values. However, there were only four patients in the no-treatment group, so between-group comparisons are difficult.

Phillips and colleagues[114] found that HtSDS was higher in the two rhGH-treated groups than in the untreated groups (–2.3 ± 0.6, –1.8 ± 0.8 and –3.0 ± 0.6 for the 0.033 mg/kg/day (licensed dose), 0.1 mg/kg/day and untreated groups, respectively). These scores reflected changes of 0.8 and 1.4 in SDS for the licensed- and high-dose groups, respectively, compared with a change of only 0.1 in the untreated patients' mean SDS value.

Three[109,110,113] of the included studies that used higher doses of rhGH reported that HtSDS was higher in the treated groups than in the untreated groups. De Schepper and colleagues[109] and de Zegher and colleagues[113] reported HtSDS at the end of the first and second years of treatment. In each of these studies, at both time points, the SDS was higher in the treated group, and this difference between groups increased in the second year. In De Schepper and colleagues'[109] study at the end of year 1, HtSDS in the treated group was –2.1 ± 0.7 versus –3.1 ± 1 in the untreated group ($p < 0.0001$). In year 2, HtSDS in the treated group was –1.7 ± 0.7 compared with 3.1 ± 1 in the untreated group ($p < 0.0001$). At the end of 2 years' treatment, the treated group in the Lagrou[110] study had a statistically significantly higher mean HtSDS (–1.9 ± 0.7) than the untreated group (–3.1 ± 0.9), $p < 0.001$.

Two studies[109,110] were suitable for meta-analysis of the HtSDS outcome because they were sufficiently homogeneous in terms of dose, duration of treatment, and the children's mean age at start of treatment. However, both trials were small (≤ 20 girls in each treatment group), which affects the validity of tests for heterogeneity, and both used twice the licensed dose, so a meta-analysis of these was considered unlikely to add to the evidence base.

Growth velocity (cm/year) was greater at the end of year 2 in the groups receiving rhGH in the two studies that presented results for this outcome.[112,113] de Zegher and colleagues 1996[112] found an increased GV in their group receiving a higher dose of GH, and a greater GV for their treated participants overall: 10.2 ± 0.2 (0.2 IU/kg/day) versus 11.0 ± 0.4 (0.3 IU/kg/day) versus 5.7 ± 0.3 (untreated), $p < 0.001$ untreated versus treated. The de Zegher 1996 study[112] also found that GV SDS was statistically significantly higher at the end of treatment in the treated groups [4.3 ± 0.3 (0.2 IU/kg/day) and. 5.2 ± 0.4 (0.3 IU/kg/day)] compared with –0.9 ± 0.3 in the untreated group ($p < 0.001$ for untreated vs treated groups).

TABLE 25 *Growth outcomes for SGA studies*

Study	Outcomes (mean ± SD)	rhGH	Control	*p*-value
Phillip *et al.* [114]	HtSDS	1: –2.3 ± 0.6	–3.0 ± 0.6	nr
1: rhGH 0.033 mg/kg/day (*n* = 51)		2. –1.8 ± 0.8		
2: rhGH 0.1 mg/kg/day (*n* = 51) vs untreated (*n* = 47); 1 year	Change in HtSDS	1: 0.8 ± 0.3	0.1 ± 0.3	nr
		2: 1.4 ± 0.4		
	Additional height gained (cm)[a]	1: 3.3 ± 0.2, 95% CI 2.9 to 3.7	n/a	nr
		2: 6.5 ± 0.2, 95% CI 6.0 to 6.9		
Carel *et al.* [111]	AH total height gain (cm)	26 ± 7	22 ± 6	0.005
0.2 IU/kg/day (*n* = 91) vs untreated (*n* = 33)	End of treatment: HtSDS	–2.1 ± 1.0	nr	nr
	AH HtSDS	–2.1 ± 1.0	–2.7 ± 1.0	0.005
	AH total height gain SDS	1.1 ± 0.9	0.5 ± 0.8	nr
	AH difference from target HtSDS	–0.9 ± 1.2	–1.7 ± 1.2	0.005
De Schepper *et al.* [109]	HtSDS year 2	–1.7 ± 0.7	–3 ± 1	< 0.0001
High-dose rhGH (*n* = 11) vs untreated (*n* = 14); 2 years				
de Zegher *et al.* [112]	Gain in HtSDS	1: 2.1 ± 0.1	0.2 ± 0.1	< 0.001[b]
1: rhGH 0.2 IU/kg/day (*n* = 20)		2: 2.5 ± 0.1		
2: rhGH 0.3 IU/kg/day (*n* = 19) vs untreated (*n* = 13); 2 years	Gain in HtSDS for BA	1: 1.0 ± 0.2	0.0 ± 0.3	< 0.05[b]
		2: 1.2 ± 0.4		
	GV (cm/year)	1: 10.2 ± 0.2	5.7 ± 0.3	< 0.001
		2: 11.0 ± 0.4		
	GV SDS	1: 4.3 ± 0.3	–0.9 ± 0.3	< 0.001[b]
		2: 5.2 ± 0.4		
de Zegher *et al.* [113]	HtSDS	–1.8 (–3.9 to –0.5)	–3.0 (–3.3 to –2.5)	nr
High-dose rhGH (100 µg/kg/day) (*n* = 9) vs no treatment (*n* = 4); 2 years	GV (cm/year)	8.5 (6.3 to 10.2)	5.6 (4.4 to 6.8)	nr
Lagrou *et al.* [110]	HtSDS	–1.9 ± 0.7	–3.1 ± 0.9	< 0.001
rhGH 0.066 mg/kg/day (*n* = 20) vs untreated (*n* = 19)				

a Compared with untreated controls.
b Untreated vs treated.

de Zegher and colleagues 1996[112] reported BA. The gain in BA (years) was statistically significantly greater in the groups receiving GH than in those who were untreated. The 0.2 IU/kg/day rhGH group had a mean gain of 1.35 ± 0.16, compared with 1.33 ± 0.24 in the 0.3 IU/kg/day rhGH group and 0.84 ± 0.07 in the untreated group ($p < 0.001$ treated vs untreated groups). This is reflected in the gain in HtSDS for BA: 1.0 ± 0.2 (0.2 IU/kg/day) versus 1.2 ± 0.4 (0.3 IU/kg/day) versus 0.0 ± 0.3, $p < 0.05$, treated versus untreated groups.

Body composition outcomes

Four of the included studies reported body composition outcomes.[109,110,112,113] These results are shown in *Table 26*. It should be noted that all of these studies used higher doses of rhGH than the UK licensed dose.

De Schepper and colleagues reported a WtSDS for treated patients that was almost half that for untreated patients (–1.8 vs –3.4; $p < 0.0001$). Lagrou and colleagues[110] found that WtSDS at

TABLE 26 *Body composition outcomes for SGA studies*

Study	Outcomes (mean ± SD)	rhGH	Control	*p*-value
De Schepper *et al.*[109]	WtSDS	–1.8 ± 1	–3.4 ± 1.6	< 0.0001
High-dose rhGH (*n* = 11)[a] vs untreated (*n* = 14); 2 years	Lean mass (kg)	15.5 ± 3.4	12.2 ± 2.5	< 0.0001
	FM (kg)	2.9 ± 1	3.1 ± 1.1	n/s
	Lean mass (%)	82 ± 3	77 ± 5	< 0.05
	FM (%)	15 ± 2	20 ± 5	< 0.05
de Zegher *et al.*[112]	Weight gain (kg)	1: 6.9 ± 0.6 2: 7.8 ± 0.5	3.6 ± 0.4	< 0.001[a]
1: rhGH 0.2 IU/kg/day (*n* = 20) 2: rhGH 0.3 IU/kg/day (*n* = 19) vs untreated (*n* = 13); 2 years	Gain in WtSDS	1: 1.3 ± 0.1 2: 1.8 ± 0.1	0.4 ± 0.1	< 0.001[a]
de Zegher *et al.*[113]	WtSDS (mean and range)	–2.1 (–3.6 to –0.9)	–3.8 (–4.8 to –3.2)	nr
High-dose rhGH (100 μg/kg/day) (*n* = 9) vs no treatment (*n* = 4); 2 years	BMI SDS(mean and range)	–1.2 (–3.4 to –0.4)	–2.1 (–2.9 to –1.4)	nr
Lagrou *et al.*[110]	WtSDS	–2.3 ± 1.2	–3.7 ± 1.5	< 0.01
rhGH 0.066 mg/kg/day (*n* = 20) vs untreated (*n* = 19)	BMI (SDS)	–1.5 ± 1.1	–2.0 ± 1.5	ns

ns, not significant.
a Untreated vs treated.

the end of year 2 was statistically significantly higher in their treated group (–2.3 ± 1.2) than in their untreated group (–3.7 ± 1.5; $p < 0.01$). Similar values were reported by de Zegher and colleagues,[113] although no *p*-values were given.

de Zegher and colleagues 1996[112] also reported gain in WtSDS and weight gain (kg). For both of these outcomes the difference was statistically significant and higher in the groups treated with GH. Mean weight gain (kg) was 6.9 ± 0.6 (0.2 IU/kg/day) versus 7.8 ± 0.5 (0.3 IU/kg/day) versus 3.6 ± 0.4 in the untreated group ($p < 0.001$ treated vs untreated groups). This pattern was reflected in the gain in WtSDS, which was 1.3 ± 0.1 in the 0.2 IU/kg/day group, 1.8 ± 0.1 in the 0.3 IU/kg/day group and 0.4 ± 0.1 in the untreated group ($p < 0.001$ untreated vs treated groups).

Lean mass and FM were reported in kilograms and as a percentage by De Schepper and colleagues.[109] Lean mass (kg) increased from year 1 to year 2 in both groups, and was greater in the group receiving GH at both times (13.2 ± 3.4 vs 10.9 ± 2.4 and 15.5 ± 3.4 vs 12.2 ± 2.5 for years 1 and 2, respectively). The *p*-value was reported as $p < 0.0001$, but it is unclear at which time point this *p*-value refers to. Lean mass (%) remained virtually unchanged from year 1 to year 2, but was higher in the rhGH group (82 ± 3 vs 77 ± 5 at year 2). The difference between treated and untreated groups was statistically significant ($p < 0.05$), but it is unclear whether this refers to the year 1 or year 2 data.

The difference in FM (%) between the two groups was statistically significant: 15 ± 2 versus 20 ± 5, $p < 0.05$.

Two studies reported BMI SDS.[110,113] One of these reported that there was no statistically significant difference between treated and untreated children,[110] and the other reported similar values but gave no *p*-value.[113]

Biochemical markers

Two of the included studies, both of which used higher doses than the UK licensed dose, reported biochemical markers.[112,114] These results are shown in *Table 27*.

Serum IGF-1 levels were statistically significantly higher in rhGH treated groups at the end of treatment. In one study,[112] children receiving 0.2 IU/kg/day rhGH had values of 332 ± 29, compared with 655 ± 69 in the 0.3 IU/kg/day group and 168 ± 46 in the untreated group ($p < 0.01$, 0.2 IU/kg/day vs untreated group) after 2 years' treatment. Phillip and colleagues[114] reported

TABLE 27 *Biochemical markers in SGA studies*

Study	Outcomes (mean ± SD)	rhGH	Control	*p*-value
de Zegher *et al.* [112]	Serum IGF-1 (μg/l)	1: 332 ± 29	168 ± 46	< 0.01 untreated vs group 1
1: rhGH 0.2 IU/kg/day (*n* = 20)		2: 655 ± 69		
2: rhGH 0.3 IU/kg/day (*n* = 19) vs untreated (*n* = 13)	Serum IGFBP-3 (mg/l)	1: 6.10 ± 0.35	4.00 ± 0.58	< 0.001 untreated vs group 1
2 years		2: 6.50 ± 0.52		
Phillip *et al.* [114]	IGF-1 (ng/ml)	1: 345.6 ± 177	176 ± 107	nr
1: rhGH 0.033 mg/kg/day (*n* = 51)		2. 594.3 ± 221		
2: rhGH 0.1 mg/kg/day (*n* = 51) vs untreated (*n* = 47)	IGF-1 SDS	1: 0.9 ± 1.9	–0.9 ± 1.2	nr
1 year		2. 3.3 ± 2.1		
	IGFBP-3 (μg/l)	1: 4.8 ± 1.1	3.9 ± 1.1	nr
		2: 6.1 ± 1.4		

similar IGF-1 values as de Zegher and colleagues[112] after 1 year's treatment, and, in addition, reported that IGF-1 SDS was higher in rhGH treated patients than in untreated patients. Values were 0.9 ± 1.9 and 3.3 ± 2.1 in the low- and high-dose groups, respectively, and 0.9 ± 1.2 in the untreated group.

Serum IGFBP-3 levels were also greater in the groups receiving rhGH. In the 1-year study,[114] values were lowest in untreated patients (3.9 ± 1.1 μg/l) and higher in the two rhGH groups (4.8 ± 1.1 and 6.1 ± 1.4 for the low- and high-dose groups, respectively). No *p*-values were reported. At the end of year 2 in the second study, mean values were 6.10 ± 0.35 in the 0.2 IU/kg/day rhGH group, 6.50 ± 0.52 in the 0.3 IU/kg/day rhGH group and 4.00 ± 0.58 in the untreated group ($p < 0.001$, untreated vs 0.2 IU/kg/day rhGH group).[112]

Quality of life

None of the included studies reported QoL outcomes.

Adverse events

Four of the included studies discussed AEs in varying detail.[109,111,112,114]

Carel and colleagues[111] found that 44% of patients reported AE, with 10% of these reporting four or more. It was not stated whether these patients were from the treated or untreated group. The authors described two AEs that they believed to be causally related to treatment; one slipped capital epiphysis after 1.5 years of treatment and one simple seizure episode 10 minutes after first injection. The authors do not state if these led to withdrawal. Sixteen severe AEs in 14 patients were reported. These were not thought by the authors to be related to treatment, and included trauma, psychiatric symptoms, abdominal symptoms, otitis, asthma, variocele, striae and migraine. De Schepper and colleagues[109] stated only that no participants 'had a noteworthy adverse event during the two years of study'. No further details were given.

de Zegher and colleagues 1996[112] reported four SAEs. The authors suggested that these might not be linked to GH, but gave no further details. The authors described two treated children versus one untreated child hospitalised as a result of viral disease (group/dose not reported). There was one case of aggravated cutaneous eczema reported in group 1 (0.2 IU/kg/day). Three treated children (group/dose not given) reported possible increase in size or number of pigmented naevi. Treatment was not interrupted in any of these cases.

Phillip and colleagues[114] reported AEs only for the 2-year study overall, so it was not possible to compare the treated and untreated children. The majority (349/358) of AEs in the study were of mild to moderate severity, the most common events (57%) being childhood infections. Of 16 SAEs reported, three were described as likely to be related to rhGH. Two of these (convulsions and papilloedema) resolved on discontinuation of treatment, and the third (epilepsy) stabilised when treatment was withdrawn.

Summary

Six[109–113] trials examining the effectiveness of GH in children born SGA met the inclusion criteria for the review. The quality of the included studies was generally poor, and only one undertook an ITT analysis.[113] All but one[114] of the trials used higher than licensed doses of rhGH.

One trial reported total gain in AH, and found this was approximately 4 cm higher in people who had received rhGH. The difference between groups was statistically significant ($p < 0.005$).[111] AH gain SDS was also statistically significantly higher in people who had received rhGH.[111] However, the study used a dose which was approximately twice the licensed dose, and it was carried out in children with a mean age of 12.7 years at start of treatment. This may limit the generalisability of the trial.

One study[114] reported that patients who received 0.033 mg/kg/day of rhGH (the licensed dose) gained an additional 3.3 cm height compared with untreated children, and those who received 0.1 mg/kg/day gained 6.5 cm of additional height after 1 year's treatment.

Height SDS was found to be statistically significantly higher in children treated with GH in two studies,[109,110] and higher, but with no reported *p*-value, in two others.[113,114]

Growth velocity (cm/year) was greater in the treated groups at the end of year 2 in the two studies that reported this outcome,[112,113] but the difference was reported to be statistically significant in only one.[112]

Weight standard deviation score was statistically significantly higher in children treated with rhGH in one[110] of the three studies reporting this outcome.

Lean mass was reported in one study,[109] and was statistically significantly greater in the treated group. Two studies reported BMI SDS.[110,113] One of these reported that there was no statistically significant difference between treated and untreated children,[110] and the other reported similar values but gave no *p*-value.[113]

One study[112] reported that serum IGF-1 and IGFBP-3 levels were statistically significantly higher in patients treated with rhGH, and another[114] reported similar results but did not present *p*-values.

Reporting of AEs was limited in detail, and only reported by four of the trials.[109,111,112] One trial[111] reported two events in treated children that may have been linked to GH. They did not discuss if these led to discontinuation of the drug. A second trial[109] reported only that there were 'no noteworthy' AEs recorded. A third trial[112] reported four SAEs, which were not linked to the study drug. Three of 16 SAE in another trial[114] were linked with rhGH, and these resolved/stabilised once treatment was discontinued.

SHOX deficiency

Quantity and quality of research available

Only one study of patients with SHOX met the inclusion criteria for this review,[49] and its key characteristics are shown in *Table 28*. The 2-year multicentre RCT by Blum and colleagues[49] compared a daily injection of 50 µg of rhGH with no treatment in 52 prepubertal children with confirmed SHOX-D. The manufacturer's recommended dose is 45–50 µg/kg body weight,[81] but as the study did not report mean baseline weight of participants it is not possible to comment on whether or not the study reflects the licensed dose. The study also included a non-randomised rhGH-treated group of patients with TS, but this group will not be discussed further in this report.

The included study was generally poorly reported (*Table 29*), with little information on method of randomisation or concealment of allocation.

TABLE 28 *Characteristics of SHOX-D study*

Reference	Intervention	Control group	Total randomised and withdrawals	Duration of randomised treatment
Blum *et al.* 2007[49]	rhGH 50 µg/day, *n* = 27 Mean age ± SD (years): 7.5 ± 2.7	No treatment, *n* = 25 Mean age ± SD (years): 7.3 ± 2.1	Total *n* = 52 Sample attrition: 1	2 years

TABLE 29 *Quality assessment of SHOX-D study*

1. Was the assignment to the treatment groups really random?	Un
2. Was the treatment allocation concealed?	Un
3. Were the groups similar at baseline in terms of prognostic factors?	Rep
4. Were the eligibility criteria specified?	Ad
5. Were outcome assessors blinded to the treatment allocation?	Par[a]
6. Was the care provider blinded?	In
7. Was the patient blinded?	In
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Ad
9. Did the analyses include an ITT analysis?	In
10. Were withdrawals and dropouts completely described?	In

Ad, adequate; In, inadequate; Par, partial; Rep, reported; Un, unknown.
a Blood analyses were carried out at a central facility.

Patients in the comparator arm received no treatment, so the patients themselves and their care providers would have been aware of whether or not they were receiving the study drug. The patients in the two groups had similar baseline characteristics, although target HtSDS was statistically significantly lower for the rhGH group (–1.3 ± 1.0 vs –1.5 ± 0.9, $p = 0.013$). Baseline IGFBP-3 SDS was slightly higher for the rhGH group (0.6 ± 1.3 vs 0.1 ± 1.1), although the difference was not statistically significant. The analysis was not reported on an ITT basis as one discontinuing patient was excluded from the analysis. The study did not include discussion of sample size or a power calculation, so it is not possible to determine whether or not it was adequately powered to detect a difference in the primary outcome (first-year GV).

Growth outcomes

Table 30 shows growth outcomes at the end of 2 years' treatment. Children treated with rhGH gained approximately 6 cm more height than those in the control group ($p < 0.001$). Although all children remained below average height, the HtSDS was statistically significantly lower in the untreated group (–3.0 ± 0.2 vs –2.1 ± 0.2, $p < 0.001$). Blum and colleagues[49] also commented that 41% of rhGH-treated patients reached a height within the normal range for age and gender (> –2.0 SDS), compared with only one patient in the untreated group. There was no statistically significant difference between the groups in catch-up of BA.

The difference in GV (1.9 cm/year) between the two groups during the second year of the study was statistically significant ($p < 0.001$). Children in the rhGH group had a positive HV SDS, i.e. their GV was above average for their age group. By comparison, those in the untreated group had a negative score, indicating slower growth than normal for their age group. Again, the difference between the groups was statistically significant ($p < 0.001$).

Body composition

The included study did not report body composition as an outcome measure.

Biochemical markers

Blum and colleagues[49] did not report biochemical outcomes in any detail. However, they did state that IGF-1 SDS values were in the low-normal range for both groups at baseline, but increased to the upper-normal range in the rhGH-treated group. In 10 (37%) of the rhGH-treated children, IGF-1 concentrations exceeded +2 SDS at least once during treatment, whereas none of the untreated patients experienced this. Similarly, IGFBP-3 SDS values were close to the normal mean in both groups at baseline, but increased to the upper-normal range in the treated group.

Quality of life

The included study did not report QoL as an outcome measure.

Adverse events

The rate of treatment-emergent AE was higher in the rhGH group than in the no-treatment arm

TABLE 30 *Growth outcomes for SHOX-D study*

Study	Outcomes (mean ± SD)	rhGH	Control	*p*-value
Blum *et al.*[49] rhGH 50 μg (*n* = 27) vs no treatment (*n* = 24); 2 years	Height gain (cm)	16.4 ± 0.4	10.5 ± 0.4	< 0.001
	Ht SDS	–2.1 ± 0.2	–3.0 ± 0.2	< 0.001
	HV (cm/year)	7.3 ± 0.2	5.4 ± 0.2	< 0.001
	HV SDS	2.3 ± 0.3	–0.4 ± 0.1 (*n* = 22)	< 0.001

(*Table 31*), but these were reported to have mostly been common childhood illnesses.

There were no significant changes in thyroid function reported during the study, and no SAEs occurred in the patients with SHOX-D.

Summary

The evidence for the clinical effectiveness of rhGH as a treatment for short stature owing to SHOX-D comes from the single RCT that met the inclusion criteria for this review. The study was unblinded and did not report an ITT analysis.

By the end of the second year, children treated with rhGH had gained statistically significantly more height than those in the control group (approximately 6 cm more), with no statistically significant difference in catch-up of BA. HtSDS was statistically significantly higher in treated than in untreated patients.

Treatment with rhGH led to a statistically significantly greater GV in both years 1 and 2 (3.5 cm/year greater than untreated patients in year 1, and 1.9 cm/year greater in year 2). The HV SDS was positive, i.e. above the average for chronological age, during both years of rhGH treatment whereas untreated children had negative HV SDS.

Treatment with rhGH raised IGF-1 and IGFBP-3 levels to the upper normal range.

Treatment of the children with SHOX-D in this RCT was not associated with any SAE.

Transition phase in GHD

The scope for this review requested that, if evidence allows, the assessment report should consider the transition of care from paediatric to adult endocrine services of young people whose linear growth is not complete. Although a number of 'transition phase' studies were assessed for inclusion in the review of clinical effectiveness, these included patients who had completed linear growth. Therefore, they did not meet the inclusion criteria for this review.

Once a patient's linear growth has ceased, he or she may still not have reached peak bone mass, which would increase the risk of osteoporosis later in life. Continued rhGH treatment in these patients beyond completion of linear growth can be beneficial for improving bone mass. For example, Conway and colleagues[128] randomised 160 18- to 25-year-olds with severe GHD who had received rhGH during childhood to continued treatment ($n = 109$) or no treatment ($n = 51$). They reported that 2 years of continued treatment was associated

TABLE 31 *Adverse events for SHOX-D study*

Study	Outcomes (mean ± SD)	rhGH	Control	*p*-value
Blum *et al.*[49] rhGH 50 μg (*n* = 27) vs no treatment (*n* = 24); 2 years	At least 1 treatment-emergent AE (%)	85	68	nr
	Arthralgia	3	2	nr
	Increased number of cutaneous naevi	2	0	nr
	Recurrent otitis media	1	1	nr
	Scoliosis	1	0	nr

with approximately 3.5% greater increase in bone mineral density of the lumbar spine than in those who had discontinued treatment.[128]

Continued rhGH treatment can also improve body composition in young adults whose linear growth is complete. Five papers[129–133] were identified that reported changes in body composition, biochemical markers, QoL or AE for this patient group. However, as the patients had completed linear growth they did not meet the inclusion criteria for this review and are therefore beyond the scope of this review.

Summary of previous systematic reviews

The searches for this systematic review identified three systematic reviews. One of these was the previous HTA report,[6] discussed above (see Comparison with previous review), and another was a Cochrane review related to that work.[134] The third reference was a new systematic review of GH in TS,[135] and this is discussed below.

The new systematic review was conducted in Canada in 2007 by the Canadian Agency for Drugs and Technologies in Health (CADTH).[135] The quality of the systematic review was good. Inclusion and exclusion criteria relating to the primary studies were reported. The review included RCTs or comparative observational studies that compared rhGH with placebo or no treatment, included females with TS, measured growth (FH, interim height, GV), AE and QoL. Those studies that included fewer than 20 patients, or administered rhGH for less than 1 year, were excluded. The Jadad scale and the Hailey scale were used in quality assessment, but no further details were reported.

The CADTH included 19 studies, 10 of which reported data from six RCTs.[135] Three of the six RCTs included in the CADTH review were excluded from the present systematic review. One was excluded as it was a conference abstract from 1991, another was excluded because its outcome measures did not match our inclusion criteria, and the third was excluded because it did not compare rhGH with a treatment arm that did not contain somatropin.

The CADTH authors judged the RCTs to be of good quality, and the observational studies of fair quality, using the Jadad scale. However, they do not describe this in detail in their report. The present systematic review used the CRD quality assessment criteria[83] rather than the Jadad scale. This, along with the difference in included studies, may explain this discrepancy in judgement of quality between the two reports.

The CADTH systematic review found that growth was accelerated and height increased in girls taking rhGH for TS. There were no SAEs reported in the included studies. The cost-effectiveness and cost–utility analyses (CUA) in the CADTH study are discussed in Chapter 4 (see Description of the identified studies). The CADTH study[135] concluded that the evidence suggested that rhGH is effective in improving growth and FH in girls with TS, but found no evidence available to suggest that rhGH improves QoL.

Chapter 4

Assessment of cost-effectiveness

Introduction

The aim of this section is to assess the cost-effectiveness of GH treatment in children with GHD, TS, PWS, CRI, SGA and SHOX-D compared with no treatment. The economic analysis comprises the following:

- a systematic review of the literature on the cost-effectiveness of GH treatment (see first section: Systematic review of existing cost-effectiveness evidence)
- a review of the HRQoL of people with GHD, TS, PWS, CRI, SGA, SHOX-D (see second section: Review of research on QoL)
- a review of the MSs to NICE (see third section: Review of manufacturers' submissions)
- a de novo Southampton Health Technology Assessments Centres (SHTAC) economic model and cost-effectiveness evaluation (see fourth section: SHTAC independent economic evaluation).

A previous HTA report has estimated the cost-effectiveness of GH treatment.[6] In that report, a cost-effectiveness model, which estimated lifetime treatment costs and benefits in terms of cost per centimetre gained, was constructed. Those analyses are extended in the present report by including QoL factors in the economic modelling.

Systematic review of existing cost-effectiveness evidence

Methods for the systematic review of cost-effectiveness

A systematic literature search was undertaken to identify economic evaluations for rhGH in children. The details of the search strategy for the cost-effectiveness studies are in Appendix 2. The MSs were reviewed for any additional studies. Titles and abstracts of studies identified by the search strategy were assessed for potential eligibility by two health economists. Full text versions of relevant papers were retrieved and checked by two health economists. Any differences in judgement were resolved through discussion. The quality of the cost-effectiveness studies was assessed using a critical appraisal checklist based on that by Drummond and Jefferson,[136] the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) checklist[137] and the NICE reference case.[138]

Results of the systematic review of cost-effectiveness

A total of 220 potentially relevant studies were identified in the cost-effectiveness searches and one in the QoL searches. Five full papers were retrieved with only two economic evaluations meeting the inclusion criteria. For all disease areas throughout the screening and data extraction process, differences in opinion were generally minor and easily resolved without the involvement of a third reviewer. The characteristics and results of the evaluations are discussed below.

Description of the identified studies

The literature search did not identify any economic evaluations conducted across the entire range of conditions of interest or any for the population of England and Wales. *Table 32* provides a summary of the characteristics and base-case findings for the two published North American economic evaluations for human GH for children with TS[135] and GHD.[139]

The cost-effectiveness studies were assessed against the critical appraisal checklist (*Table 33*). Generally, the CADTH study[135] was of a higher quality; the effectiveness of the treatment had been established through a systematic review, and the estimates for parameter values are more appropriate than the study by Joshi and colleagues.[139]

Modelling approach

Both economic evaluations presented cost-effectiveness analyses using simple deterministic decision-analytical models. Both assumed that the clinical benefit achieved as a result of the rhGH treatment in the patients' early years will

TABLE 32 *Characteristics of economic evaluations of rhGH treatment in children*

Study/Details	CADTH[135]	Joshi *et al.*[139]
Publication year	2007	2006
Organisation	Canadian agency for drugs and technologies in health	Novo Nordisk
Country	Canada	USA
Study type	CEA and CUA	CEA and CUA
Study perspective	Canadian health-care system	The US health-care payers' perspective
Study population	Female population aged 10 years at baseline with TS, receiving treatment for 5 years until 15 years old	1. Cohort 5 years old at baseline with GHD, receiving treatment for 11 years until 16 years old 2. Cohort 3 years old at baseline with GHD, receiving treatment for 15 years until 18 years old
Intervention	rhGH	rhGH (Norditropin)
Model type	Deterministic decision-analytical model	Deterministic decision-analytical model
Time horizon	Lifetime (assumed to be until age of 81 years)	Lifetime (assumed to be the age of 78 years for males and age 80 for females)[a]
Discounting	5% applied to both costs and benefits (QALYs)	3% applied to both costs and benefits (QALYs)
The primary clinical treatment effects modelled/ assessed	147.5 cm was the FH in the intervention group, 141 cm was the FH in the control group	The 'success' of treatment is defined as achieving 'normal height', i.e. FH within two SDs of the gender-specific population mean
Source of clinical evidence for the primary effect	Stephure and colleagues[86]	Not indicated. Appears to be an assumption. The probability of 'success' was assumed to be 90% if treatment started at age 3 and continued until age 18. The probability of 'success' was assumed to be 75% if treatment started at the age of 5 and continued until the age of 16
Health-benefit outcome	QALY	QALY
QoL gain, per year	0.042	0.189
Results	Individuals with rhGH treatment had an additional discounted cost of C$153,593 and an additional discounted benefit of 0.63 QALY. The cost-effectiveness was estimated as C$243,078 per QALY gained	For the cohort of 5–16 years, individuals with rhGH had an additional discounted cost of US$155,005 and an additional discounted benefit of 4.2 QALY. The cost-effectiveness was US$36,995 per QALY gained. For the cohort of 3–18 years, cost per QALY was US$42,556

CEA, cost-effectiveness analysis; CUA, cost–utility analysis; QALY, quality-adjusted life-year.
a The authors did not report a gender distribution at baseline and whether all-cause mortality rates were used in the calculations.

last through their lifetime. Joshi and colleagues[139] assumed that age-adjusted normal height was achieved after the first year of treatment. Subsequently, the benefits in terms of 'normal height years' and associated utility gain were assigned from the second year of treatment. Conversely, the CADTH study[135] did not assume that patients experienced any improvement in HRQoL during the treatment. The utility gain is associated with the completion of treatment rather than with achieving normal height, as normal height was not achieved in the review of clinical effectiveness.

The cohorts differed with respect to age at baseline, duration of treatment and probability of achieving normal height at the end of treatment (see *Table 32* above). The CADTH study[135] used the characteristics and clinical effectiveness data from the TS RCT,[86] whereas Joshi and colleagues[139] did not provide any clinical evidence for either the baseline characteristics of the two cohorts of patients with GHD or the assumed clinical effectiveness estimates.

Joshi and colleagues[139] assumed a 20% dropout rate after 12 months of treatment and related it to

TABLE 33 *Critical appraisal checklist of economic evaluation*

	Item	CADTH[135]	Joshi *et al.*[139]
1	Is there a well-defined question?	Yes	Yes
2	Is the patient group in the study similar to those of interest in UK NHS?	Yes	Yes
3	Is the correct comparator used that is routinely used in the UK NHS?	Yes	Yes
4	Is the study type and modelling methodology reasonable?	Yes	Yes
5	Is an appropriate perspective used for the analysis?	?	?
6	Is the health-care system or setting comparable to UK?	?	?
7	Is the effectiveness of the intervention established based on a systematic review?	Yes	No
8	Is the model structure appropriate and does it fit with the clinical theory of the disease process?	Yes	Yes
9	Are assumptions reasonable and appropriate?	Yes	No
10	Are health benefits measured in QALYs using a standardised and validated generic instrument from a representative sample of the public?	?	No
11	Are the resource costs used reasonable and appropriate for the UK NHS?	Yes	Yes
12	Are the health states and parameters used in the model described clearly and are they reasonable and appropriate for the UK NHS?	Yes	No
13	Is an appropriate discount rate used?	Yes	Yes
14	Has the model been validated appropriately?	?	?
15	Is sensitivity analysis undertaken and presented clearly?	?	?

?, unclear or partially true.

the slight pain experienced by patients, although no clinical evidence was presented to support this assumption. The CADTH study[135] did not adjust the final outcomes for the dropout rate, effectively assuming it to be zero. As none of the TS patients achieved normal height, the CADTH study[135] did not differentiate between partial and complete success of rhGH treatment. In contrast, Joshi and colleagues[139] assumed that those patients who completed treatment but did not achieve normal height still acquire a partial utility gain. However, no justification for this assumption is provided.

Discounting was appropriately applied to costs and benefits in both studies, although the discounting rates were different from the 3.5% recommended by NICE[138] (3% in the study by Joshi and colleagues[139] and 5% in the CADTH study[135]).

Estimation of final outcomes (QALYs)

Both studies highlighted the difficulty of translating intermediate (clinical) outcomes to final outcomes (QALYs). There is an apparent paucity of utility-based estimates of HRQoL in rhGH patients and an absence of such estimates obtained from children eligible for rhGH treatment (see below, Review of research on quality of life). Therefore, the authors chose alternative utility estimates that, despite acknowledged shortcomings, were judged to meet the requirements of their economic models. The utility increment associated with rhGH treatment reported in the two studies ranged from 0.04[135] to 0.189.[139]

Joshi and colleagues[139] adapted the QoL indexes presented in the Wessex Development and Evaluation Committee (DEC) report.[140] The indexes estimated in the report were not derived using one of the methodologically rigorous techniques for obtaining utility estimates, such as time trade-off (TTO) or standard gamble (SG)[141] and cannot therefore be interpreted as 'utilities'. Furthermore, the utility element of that report was a set of scenarios not based on primary or secondary data sources and thus could not be considered reliable or valid.[6] Joshi and colleagues[139] used utility estimates of 0.781 for the pretreatment and no treatment groups, although this is different to the value 0.884, reported in the DEC report. Those patients who achieved success, i.e. normal height, had a utility of 0.97 applied from the start of the second year of treatment. Patients with partial success were assumed to acquire a partial utility gain defined as 35% less than the full utility

gain associated with achieving normal height. The value was stated to be between 0.884 and 0.940.

The CADTH study[135] did not use absolute utility values associated with each health state but applied an incremental utility value of 0.04 for patients receiving treatment with rhGH. The utility increment was estimated from a TTO survey in a small sample of adults with TS[142] (see below, Review of research on qulity of life). The patients in the QoL study were asked how many years they would be willing to lose from their life to attain an average stature. The answers were translated into the incremental utility estimate of 0.04. The CADTH study[135] stated that TS patients do not attain an average stature, and so this estimate is likely to be an overestimate and bias the result of economic evaluation in favour of rhGH treatment.

Estimation of costs

Joshi and colleagues[139] included costs for paediatric consultations and rhGH treatment. The CADTH study[135] also included costs for X-ray examination. The unit costs reported in the economic evaluations reflect the difference in clinical practices in Canada and the USA, the price difference of the unit of resources expressed in Canadian and US dollars, and the difference in methodological approach adopted in the two studies. For example, the CADTH study[135] excluded the specialist visits as these do not differ between the intervention and the control groups. The total incremental cost reported varies according to the length of treatment but is consistent between the two studies.

Model results

The cost-effectiveness analysis in the CADTH study[135] used an incremental difference of 6.5 cm in FH between the intervention and control groups, based on their clinical review. They calculated the undiscounted cost-effectiveness as C$26,529 per centimetre of improved FH and the discounted incremental cost-effectiveness ratio (ICER) was C$23,630 per centimetre of improved FH. They estimated an ICER of C$243,078 per QALY gained. The authors concluded that for an average patient with TS, rhGH treatment is unlikely to be cost-effective unless the payer is willing to pay more than C$200,000 to obtain a QALY.

Joshi and colleagues[139] calculated the difference in 'normal height years' between the intervention and the control groups to estimate the incremental cost per normal height year. It was assumed that normal height was achieved by patients in the intervention group, but not in the control group. The incremental gain in 'normal height years' in the cohort of 5- to 16-year-olds was 17.4 (discounted). The corresponding value in the cohort of 3- to 18-year-olds was 21.1 (discounted), which translated into an incremental cost per additional year of normal height of $8900 (discounted) in the cohort of 5- to 16-year-olds and an incremental cost per additional year of normal height of $9300 (discounted) in the cohort of 3- to 18-year-olds. They estimated an ICER of about $37,000 per QALY gained for treating children with GHD from ages 5 to 16 years and an ICER of about $42,600 per QALY gained for treating children with GHD from ages 3 to 18 years. The authors concluded that the cost-effectiveness of rhGH compares favourably to accepted threshold values and represents reasonable value for money.

In both studies the deterministic one-way analyses indicated that the results were sensitive to variations in the utility estimate, the starting age of treatment, the duration of treatment and the daily dosage. The results were also sensitive to assumptions about clinical effectiveness[139] and to variations in the price of rhGH.[135]

The two economic evaluations arrived at opposite conclusions about the value for money of the rhGH treatment in children. The economic evaluation conducted for the CADTH study[135] may provide a more reliable estimate of the cost-effectiveness as it has used clinical data from a reasonable quality RCT and TTO utility estimates. In contrast, the assumptions about clinical effectiveness of rhGH treatment by Joshi and colleagues[139] did not seem to be supported by clinical evidence. Furthermore they also used indexes, interpreted as utility weights, which do not appear to be reliable or valid.

Summary and conclusion of the systematic review of cost-effectiveness studies

We undertook a systematic review of the literature in order to identify existing models in this area. The systematic review of published economic evaluations identified two North American studies relevant to the target population and no studies conducted in the UK. The results of the two identified studies produced two very different estimates of cost-effectiveness. This difference is largely due to the choice of utility estimates and

assumptions on the effectiveness. As discussed below (see next section, below, Review of research on QoL), there is a paucity of reliable estimates of utility gains associated with GH treatment. Therefore, the results of both studies should be treated with caution. In particular, Joshi and colleagues[139] adapted QoL indexes that were not derived according to the NICE reference case and could not be considered reliable or valid.[6] The literature study did not identify studies that we could use for this review and so a de novo independent economic model was required.

Review of research on QoL

Systematic review of HRQoL studies

A systematic review was undertaken to identify HRQoL studies for rhGH for children. The HRQoL searches were undertaken to populate a lifetime economic model with utilities to calculate QALYs, so studies with adults and children were eligible for inclusion. Titles and abstracts of studies identified by the search strategy were assessed for potential eligibility by two health economists. Full text versions of relevant papers were retrieved and checked by two health economists. Any differences in judgement were resolved through discussion. The details of the search strategy for QoL are in Appendix 2.

The titles and abstract of the studies identified by the search strategy were assessed on the basis of the following criteria:

- disease condition as defined in *Table 1* (Chapter 1) of this report
- primary research using a preference/utility based measure for the conditions interest
- primary research using a generic measure [i.e. Short Form questionnaire-36 items (SF-36)] that can be translated into a utility-based estimate
- primary research using a condition-/disease-specific QoL measure and an algorithm that allowed disease-specific QoL to be converted into utility values.

Exclusion criteria for the systematic literature search were:

- primary research reporting QoL that could not be converted into utility values using a validated mapping algorithm
- background or discussion papers that did not report a QoL measure for the conditions of interest
- papers reported in language other than English.

The search strategy identified 391 articles that were potentially relevant. After the abstracts had been screened, 24 articles were identified and full papers were retrieved for these articles. After checking the retrieved studies, six papers met the inclusion criteria. These are summarised in *Table 34*. A further targeted search linking height to HRQoL is reported below (see Height and health-related QoL).

Growth hormone deficiency

Three relevant studies were identified that met the inclusion criteria.[145,147,148] Sandberg and colleagues[148] used the SF-36 in participants with GHD. The study reported no baseline data, and reported SF-36 only after rhGH treatment had finished compared with non-GHD siblings and the general population. Therefore, the study was of no value in investigating the gain in HRQoL from rhGH treatment.

The second study, by Busschbach and colleagues,[145] used the TTO method, a preference-based approach that asks people to quantify the numbers of years of life they would be willing to give up to overcome a particular state of health. The participants were asked the number of years they were willing to trade off at the end of their life in order to obtain average stature. The TTO was completed by people with GHD, TS and CRI (see below for TS and CRI). There were 25 adults with isolated GHD included in the study. The sample of GHD men made only a negligible trade off (less than 2%), whereas the sample of GHD women were willing to make a slightly larger trade off of around 2% of their expected length of life to reach average height. The major drawbacks with this study were the small sample of between 17 and 25 people with each condition of interest, the retrospective design and the lack of a control group. Also it is unlikely that gaining average stature is a realistic possibility for most people with the conditions of interest. Furthermore, for one of the conditions of interest (GHD) the patients had received rhGH treatment, and for another condition (CRI) it was unclear whether they had or had not received rhGH treatment as children. It is likely that any rhGH treatment will underestimate the TTO made to gain average stature, as these participants have already benefited from an increase in extra height.

TABLE 34 *Characteristics of included QoL studies*

Study/ Details	Bannink et *al.*[143]	Bertella et *al.*[144]	Busschbach et *al.*[145]	Carel et *al.*[146]	Koltowska-Haggstrom et *al.*[147]	Sandberg et *al.*[148]
Publication year	2006	2007	1998	2005	2008	1998
Country	The Netherlands	Italy	The Netherlands	France	England and Wales	USA
Study type	QoL observational cohort study matched to normal population	QoL observational cohort study	QoL observational case–control study	QoL observational cohort study matched to normal population	Estimated utilities from a survey of general population in England and Wales, and mapped to an observational cohort study	QoL observational case–control study
Study population	49 participants with TS	13 participants with PWS	17 participants with CO renal failure 25 with TS 25 with GHD	568 participants with TS	894 participants with CO and AO GHD CO-onset GHD occurred in 21.6%	140 participants with GHD 53 participants with GHD who had siblings
Study population age	19.6 ± 3.0 years (14.8–25.8 years)	27.08 ± 4.55 years (20–33 years)	Between 24 years ± 4.1 (ISS) and 28 years ± 4.9 (TS)	22.6 ± 2.6 years	40 ± 16.5 years	26.1 ± 6.5 years (18.8–46.9 years)
Comparator population	Dutch general population	No comparator	44 normal short participants (not diagnosed with ISS)	French general population	England and Wales general population	53 controls (unaffected siblings)
Intervention (s)	GH treatment was for 7.1 ± 2.7 years	GH treatment in 5 participants, but had ceased treatment 1–4 years before being enrolled in the study	GHD treated with rhGH during childhood	GH treatment for 4.8 ± 2.2 years 72% received estrogen treatment	GH treatment	Pituitary-derived rhGH and recombinant GH. GHD treatment was for 4.5 ± 3.1 years (0.9 to 14.3)

Study/ Details	Bannink et *al.*[143]	Bertella et *al.*[144]	Busschbach et *al.*[145]	Carel et *al.*[146]	Koltowska-Haggstrom et *al.*[147]	Sandberg et *al.*[148]
Included QoL instrument used	SF-36	SF-36	TTO	SF-36	QoL-AGHDA with utility weights from EQ-5D	SF-36
Time period when HRQoL instruments administered	HRQoL evaluation occurred 2.8 (1.6) years after rhGH discontinuation	HRQoL evaluation at the beginning, during and after rhGH discontinuation	HRQoL evaluation in adulthood after rhGH discontinuation if applicable	HRQoL evaluation occurred 6 years after rhGH discontinuation	HRQoL evaluation at baseline and last reported visit follow up for 1–6 years	After rhGH discontinuation
Methodology of collecting QoL data	The SF-36 was administered after rhGH treatment had been discontinued for at least 6 months and FH had been reached	The SF-36 was administered at the beginning of the treatment and then again at intervals of 6, 12 and 24 months to patients and parents	TTO asked the participants the maximum number of years they were willing to give up in order to obtain average stature	A postal survey including the SF-36 and GHQ-12 sent to participants	Both the EQ-5D and QoL-AGHDA were completed by general population A regression model was used to estimate utility weights for QoL-AGHDA items in an observational study	Eligible GHD subjects completed SF-36 questionnaire over the telephone, in addition to same-sex siblings
Results	Women with TS treated with rhGH reported significantly better HRQoL in social functioning, role limitations, and emotional and bodily pain domains compared with normal population Other domains were roughly equal to normal population	PWS showed significant improvement during rhGH therapy on SF-36 in vitality, physical functioning, general health, social functioning, role limitation because of emotional problems, general mental health and total scale	The patients with GHD were hardly prepared to make a trade-off Participants with TS or renal failure had an estimated reduction in QoL of 2–4% Women with TS made an average TTO for their infertility of 9%	HRQoL was not statistically different from the reference values obtained for young French women from the general population	$QoL\text{-}AGHDA_{UTILITY}$ scores were higher in patients with CO than with AO, both at baseline 0.75 (SD 0.173) vs 0.64 and at the last reported visit) 0.82 (SD 0.167) vs 0.76. Patients with CO-GHD gained less than AO patients with regard to the total gain 0.18 (SD 0.488) vs 0.35	The GHD sample had only a significantly lower score from the sibling control group on general health scale ($p < 0.05$) The rest of the QoL domains showed not significant difference

AGHDA, adult growth hormone deficiency assessment; AO, adult onset; CO, childhood onset; EQ-5D, European Quality of Life-5 Dimensions; GHQ-12, General Health Questionnaire-12; ISS, idiopathic short stature.

It was decided that this study did not provide a robust enough estimate of preference of health states to be used in the model.

The third study, by Koltowska-Haggstrom and colleagues,[147] mapped European Quality of Life-5 Dimensions quality of life measure (EQ-5D) values to a disease-specific QoL assessment of GHD (QoL-AGHDA) instrument from a survey. This was then used to transform QoL-AGHDA scores from a cohort of patients from the Kabi International Metabolic Database (now Pfizer) (KIMS) database into utility-weighted QoL-AGHDA scores ($QoL\text{-}AGHDA_{UTILITY}$). A good response rate of 84% was achieved, and 921 individuals from the general population of England and Wales responded to the survey. A regression model was used to estimate utility weights for QoL-AGHDA ($R^2 = 0.42$). The EQ-5D responses were used as the dependent variable and the QoL-AGHDA responses were used as independent dummy variables with age as a covariate.

The patient cohort from the KIMS database consisted of 894 patients from England and Wales. However, only 21.6% had childhood-onset (CO)-GHD (applicable to the scope). The study was carried out in adults and it is unclear whether the CO-GHD group had had prior rhGH treatment. This may undervalue gain in HRQoL if this is the case. An inclusion criterion for the study was no treatment for rhGH for a minimum of 6 months prior to entry. The mean age for the whole cohort was 40 years old (SD16.5) at diagnosis and 45 years old (SD 14.3) at entry into KIMS. The study reported that patients with CO-GHD had a $QoL\text{-}AGHDA_{UTILITY}$ value of 0.75 (SD 0.173) at baseline compared to the last reported visit score of 0.82 (SD 0.166). The study reports mean gain in $QoL\text{-}AGHDA_{UTILITY}$ per year of 0.05 (SD 0.117). They also reported a total gain of 0.18 (SD 0.488), and it is assumed that this is the QALY gain over the study duration worked out using trapezoid formula compared to the baseline $QoL\text{-}AGHDA_{UTILITY}$ values. A last observation carried forward (LOCF) method was used. The average length of follow-up in the study for the CO-GHD was not reported and so is not possible to verify the QALY gain or gain per year.

In the combined cohort of adult-onset GHD (AO-GHD) (78%) and CO-GHD (22%) the greatest improvement in utility occurred within the first year of rhGH treatment. Subsequently, the QoL improvement is maintained when compared with the general population over a 6-year follow-up. It is unclear whether this benefit from rhGH treatment is maintained after treatment has stopped.

The limitations of this study were that it was observational with no control, and that the EQ-5D had not been conducted amongst the participants of the KIMS database. Furthermore, the regression model used to translate EQ-5D scores to disease specific measure explained less than one-half of the sample variation of the EQ-5D values. Nevertheless, the study provided an estimate of utility at baseline and at the last reported visit in one of the conditions of interest. The study's generalisability to the other conditions of interest is unclear and it was felt that any attempt to link utilities in this study to the other conditions of interest was difficult due to the difference in height outcomes.

Turner's syndrome

There were three studies that met the inclusion criteria for people with TS.[143,145,146] Two[143,146] of these were not useful as they reported SF-36 only scores after rhGH treatment had been completed compared to a cohort of women from the general population. Therefore, they could not be used to investigate the gain in HRQoL from rhGH treatment. Busschbach and colleagues[142] used a TTO method (described above) with 25 women with TS who had not received rhGH treatment as children. Their average TTO was small in the region of 4% of their life-years to reach an average height for the general population.

Prader–Willi syndrome

One study met the inclusion criteria.[144] This was potentially useful as it shows the gain in HRQoL from rhGH treatment over a 24-month period. However, the study had several limitations that make its results highly uncertain. It was a small study with only 13 Italian adult participants with PWS, of whom five had previously undergone rhGH treatment. There was no control group. At the last recorded observation (24 months) there were only nine participants left in the study. A new study mapping from SF-36 to a UK based EQ-5D preference-based utility index has recently been published, which provides an algorithm for this to be done.[149]

However, the PWS QoL study is for adults who have received rhGH and it is unclear how this relates to the QoL gain for a group of children, and whether this QoL benefit would be maintained throughout their lifetime.

CRI

One study was identified that met the inclusion criteria.[142] Busschbach and colleagues used a TTO approach for 17 adults who had childhood-onset renal failure. It is unclear whether the participants received any rhGH treatment prior to the TTO assessment. The participants were asked what percentage of the years of their expected life they were willing to trade to reach normal height and to not experience health states involving a kidney transplant and dialysis. The resulting TTO associated with renal failure was 4% to reach normal height.

SGA

No relevant HRQoL studies that were identified met the inclusion criteria.

SHOX-D

No relevant HRQoL studies that were identified met the inclusion criteria.

Height and health-related QoL

The NICE reference case clearly states that the measure of health outcome used in the cost-effectiveness analysis should be QALYs calculated with utilities derived from a validated, generic, preference-based measure of HRQoL.[138] The clinical effectiveness review in Chapter 3 found no RCTs that reported HRQoL measures as an outcome and the additional search for HRQoL studies (above) located only one relevant study by Koltowska-Haggstrom[147] in one of the conditions of interest (GHD) that was strictly applicable to the NICE reference case.[138]

Therefore, a targeted search was conducted to identify publications that reported gains and losses in utility in relation to variation in height, as height is one of the primary outcome measures of GH treatment. Details of the search are in Appendix 2. One full paper by Christensen and colleagues[150] was identified.

The study used the 2003 Health Survey for England, with 14,416 observations for adults (aged > 18 years).[151] HRQoL was measured using the EQ-5D with the UK tariff. Height was converted from centimetres to HtSDS using a UK population algorithm. Inter-relationships between variables were assessed using ordinary least squares (OLS) linear regressions, controlling for age, weight and gender. All OLS analyses were controlled for multicollinearity (close interaction between explanatory variables). Where there were any highly correlated variables (weight and BMI) then one variable was omitted from the regression. The regression analyses included two-level categorical variables ('sex', 'limiting longstanding illness' and 'social class') to explore the relationship between height and HRQoL while controlling for these confounding factors.[150]

There was a positive correlation between an increase in height and a participant's EQ-5D score. The mean EQ-5D scores were lower in the shorter compared with taller subjects, as well as lower than the overall population mean. The authors' report an analysis of variance (ANOVA) combined with post hoc Tukey's Honestly Significant Difference (HSD) test for homogeneous subgroups, which showed that the sample could be split into three meaningful subgroups, each significantly different ($p < 0.05$) from each other in terms of their EQ-5D scores. The first subgroup 'HtSDS ≤ –2.0' had significantly lower EQ-5D scores than the second group '–2.0 > HtSDS ≤ 0' and the third group 'HtSDS > 0'. The second subgroup had significant lower scores than the third group. A multivariate linear analysis using the previously identified subgroups was undertaken to predict the variation in HRQoL. The full model predicted only one-third of the sample variation in EQ-5D ($R^2 = 0.318$, 0.343 and 0.290) based on 11,946 observations.[150]

The model predicted that for those people shorter than –2.0 HtSDS, an improvement of 1 HtSDS will result in a change in EQ-5D score of 0.061. However, for the subgroup between –2.0 and 0 HtSDS the gain in EQ-5D is much reduced (a 1-HtSDS improvement increases EQ-5D score by only 0.010). One drawback to the Christensen study[150] is that the population used to elicit QoL values are not from the conditions of interest but from the general population.

Summary and conclusions of the QoL review

The systematic review of QoL identified six studies that met the inclusion criteria. None of the studies was in a childhood population. This is to be expected, given the difficulties in conducting preference-based QoL studies in children.[152] Three studies reported the SF-36 in adults but were not useful on further examination, as they reported SF-36 scores only after rhGH treatment. One poor-quality study reported SF-36 at baseline, 6 months, 12 months and 24 months for a small cohort of adult participants with PWS, and the scores from this study were mapped to a UK-based EQ-5D

preference-based utility index by a subsequent study.

There were only two studies that reported change in QoL using preference-based measures in the conditions of interest.[145,147] The first study[145] used TTO methodology for people with GHD, TS and CRI. The number of years that the participants were willing to trade to reach average height was in the range of 0–4%. However, there were several limitations to this study and it was felt that it did not generally provide a robust estimate of utility gain from rhGH treatment. The second study[147] used a regression model to give utility weights (based on the EQ-5D from a UK population) to the disease-specific QoL-AGHDA. The KIMS database was then used to transform patients QoL-AGHDA values into QoL-AGHDA$_{UTILITY}$ values. However, it was in an adult population and it is unclear whether they had previously had rhGH treatment as children. This study was specific to patients with GHD and is unlikely to be generalisable to the other conditions of interest.

An additional targeted search was undertaken for QoL in relation to height. One study was identified by Christensen and colleagues,[150] which provided utility estimates based on the EQ-5D for different HtSDS from the Health Survey for England for an adult general population. The study provides a common utility gain that could be compared across all of the conditions of interest that could be used with the clinical effectiveness outcomes from the RCTs.

Based on the review of the QoL literature, there is likely to be a small gain in utility for individuals receiving GH treatment. However, this is based on a proxy measure of gain in height from shorter people in the general population. This excludes many relevant potential benefits and disadvantages of rhGH treatment that it is not possible to capture without good-quality evidence from the conditions of interest. This is especially true for PWS as additional HRQoL gain from improved body composition is unlikely to be captured with this method. Furthermore, there is also uncertainty over the impact of extrapolating back into childhood with adult utility data.

Review of the manufacturers' submissions

Six of the seven manufacturers submitted evidence to be considered for this review. Five out of the six MSs consisted of a written report and an electronic model supporting the cost-effectiveness analyses. The sixth MS by Sandoz did not comply with the NICE template for the MTA and presented a description of the product (Omnitrope) and what appears to be a cost-minimisation analysis using Genotropin as a comparator (defined as a reference product). The collaborative submission is appraised below and a critique of the Sandoz submission is presented below (see Sandoz submission to NICE).

A de novo economic model has been used by the five collaborating manufacturers involved in the submission to the MTA of rhGH. Under Pfizer's leadership, a common modelling framework was developed and used in the cost-effectiveness analysis of treatment in children with GHD, TS, PWS, CRI and SGA. Each of the collaborating manufacturers presented essentially the same model with some minor modifications, for example changes in the unit price of rhGH. The model developed was based upon the previous HTA report[6] but has been extended to consider longer-term outcomes in order to estimate cost-effectiveness in terms of QALYs. One manufacturer, Merck Serono, produced its own version of the model and so the health benefits differ slightly to the other models.

The MSs also included a rapid review on QoL that was undertaken by Eli Lilly on behalf of the collaboration of manufacturers. The aim of the main review was to provide a rapid search to identify the key papers that explored the impact of short stature in childhood, and the impact of short stature in transition to adulthood and as adults. The overall conclusion from this review highlighted the inconsistent findings relating to the role of short stature in QoL and psychosocial functioning in both childhood and adulthood.

Modelling approach

In the MSs, the base-case analyses estimated the incremental cost of rhGH per centimetre of height gained relative to no treatment (in order to compare with previous HTA report[6]) and the incremental cost of rhGH per QALY gained relative to no treatment. The utility scores used in the model in children with GHD, TS, CRI and children who were SGA were based upon the study by Christensen and colleagues,[150] discussed above (see Description of the identified studies). A gain in height was assumed to be associated with QoL improvements, which was assessed using the EQ-5D utility scale. In patients with PWS the QoL gain

was based upon a small study of adult patients with PWS, together with an estimation of the benefits associated with a reduced risk of diabetes. The assumptions used to derive QoL utility improvements are discussed above (see Review of research on QoL).

The economic evaluation of rhGH treatment in conditions such as GHD, TS, SGA and CRI is based on a single clinical effect of additional height gained as a result of treatment. This clinical effect and many of the other parameters used in the model are estimated from the Kabi International Growth Study (KIGS) database,[153] which is a large-scale collaborative database developed by Pfizer for the safety and efficacy of treatment with rhGH. It includes data from more than 60,000 treated patients in over 50 countries for all licensed indications, i.e. GHD, TS, PWS, SGA and CRI. *Table 35* shows the input parameters used in the manufacturers' model that have been derived from the KIGS database. The costs used in the manufacturers' model were based upon those used in the previous HTA report, and inflated to current prices where appropriate.[6]

The cost-effectiveness analysis of rhGH treatment in PWS is based on an alternative structure of the model that estimates the utility gain based on a small study of 13 adult patients with PWS[144] (see Review of research on QoL, above) who received rhGH for 2 years and a further utility gain for reduced diabetes risk. However, the PWS QoL study is for adults who have received rhGH and it is unclear how this relates to the QoL gain for a group of children, and whether this QoL benefit would be maintained throughout their lifetime. Furthermore, the two methods[154,155] used by the Pfizer submission to translate SF-36 scores into utilities were not based on choice-based methods like TTO or SG, which produce utilities more rigorously.[141] The model assumes that individuals with PWS and diabetes would have a 10% lower QoL than those without. Based on Pfizer's submission to the Pharmaceutical Benefits Advisory Committee in Australia, it was assumed that the prevalence of diabetes in patients with PWS would reduce from 8% to 2%, although it was not possible to verify these assumptions in the reference provided.

An alternative model structure that allowed for the second clinical effect (a reduction in the risk of osteoporosis) was also presented in a scenario analysis for GHD. In this model it was assumed that a proportion of GHD children continue treatment until they reach the age of 25 years.

TABLE 35 *Input parameters from MSs from KIGS database (from Pfizer MS)*

Parameter	GHD	TS	PWS	CRI	SGA
No. of patients					
Start of treatment	7036	2749	485	806	990
Near adult height	2547	1349	75	157	127
Age					
Start	9.14	9.3	7.42	9	8.18
End	16.37	16.45	15.21	13.95	14.18
Dropout rate					
Percentage at 1 year	0.04	0.0273	0.02	0.117	0.03
Dose					
0–17 years of age (mg/kg/day)	0.03	0.04	0.03	0.04	0.04
Utility					
Treated	0.83	0.8	0.76	0.8	0.81
Untreated	0.69	0.69	0.67	0.69	0.69
HtSDS					
Treated	–1.17	–2.24	–1.36	–2.17	–2.01
Untreated	–2.99	–3.18	–2.22	–2.99	–3.23

The manufacturers' model makes the following assumptions:

1. Patients with conditions of interest have the same life expectancy as the general population of England and Wales in the treated and untreated groups.
2. Patients can continue rhGH treatment or discontinue treatment at the end of 1 year.
3. Untreated children do not gain any utility benefit throughout the course of the lifetime of the model.
4. Treatment costs and monitoring costs are applied over the treatment years. Health benefits, as measured by QoL associated with particular attained heights, are maintained over patients' lifetimes. The full utility value is applied after 2 years of treatment.
5. Compliance is assumed to be 90% in the base-case analysis and this was assumed to not impact efficacy.
6. Adverse events are not considered in the model for both the treated and non-treated patients.
7. In the base case, for all conditions except PWS, rhGH treatment affects only FH and does not affect the risk of morbidities, such as osteoporosis fracture or diabetes.
8. The MS estimated the average height at the end of treatment for the control group from the previous HTA report.

Appraisal of the manufacturer cost-effectiveness analysis

A summary of the MS compared with the NICE reference case requirements[138] is given in *Table 36* and indicates that the submission meets most of the requirements. See Appendix 9 for a tabulation of the critical appraisal of the submission against the Drummond and colleagues' checklist.[136]

Cost-effectiveness results

The mean daily per-patient cost for each of the manufacturer's GH treatments was based upon the unit cost shown in *Table 37*. Merck Serono stated that there will be a reduced cost of £20.87 through the use of the Merck Serono Easypod™, which they report will reduce vial wastage and increase compliance.

The base-case analyses for Pfizer, Eli Lilly, Ipsen and Merck Serono are shown in *Table 38*. Merck Serono produced their own version of the model and so the health benefits differ slightly from the other models.

The base-case results for the Novo Nordisk model using KIGS data are shown in *Table 39*. They also reported alternative ICERs using patient level data.

TABLE 36 *Assessment of MS against NICE reference case requirements*

NICE reference case requirements	Included in submission
Decision problem: as per the scope developed by NICE	✓
Comparator: no treatment alternative	✓
Perspective on costs: NHS and PSS	✓
Perspective on outcomes: all health effects on individuals	✓
Type of economic evaluation: cost-effectiveness analysis	✓
Synthesis of evidence on outcomes: based on a systematic review	No evidence synthesis
Measure of health benefits: QALYs	✓
Description of health states for QALY calculations: use of a standardised and validated generic instrument	✓
Method of preference elicitation for health-state values: choice-based method (e.g. TTO, SG, not rating scale)	✓
Source of preference data: representative sample of the public	✓
Discount rate: 3.5% p.a. for costs and health effects	✓

✓, yes. PSS, Personal Social Services.

TABLE 37 *Unit cost of rhGH for different manufacturers*

Manufacturer/product	Unit cost (£/mg)
Genotropin (Pfizer)	23.19
Humatrope (Eli Lilly)	18.00
NutropinAq (Ipsen)	20.70
Saizen (Merck Serono)	23.19
Norditropin SimpleXx (Novo Nordisk)	21.39

Manufacturers' conclusions

The authors suggested that many of the health benefits associated with rhGH treatment are not quantifiable and cannot be modelled easily. Many of these benefits would improve overall patient QoL and, possibly, duration of life. These benefits include self-esteem, improvements in sleep and concentration, and increased appetite as well as increases in LBM, total bone mass and muscle strength. These benefits may lead to reduced risk of diabetes, obesity and cardiovascular diseases.

TABLE 38 *Base-case results for Pfizer, Eli Lilly, Ipsen and Merck Serono*

Manufacturer		GHD continued[a]	GHD	TS	PWS	CRI	SGA
	Incremental QALY	3.48	3.48	2.83	2.30	2.53	2.98
	Height gain (cm)	32.24	32.24	7.95	25.59	4.48	21.92
Pfizer	Incremental cost (£)	72,003	61,124	84,078	74,849	40,325	54,088
	ICER (£/QALY)	20,673	17,552	29,757	32,540	15,962	18,167
	Cost per cm gain (£)	2233	1896	10,576	2925	9001	2467
Eli Lilly	Incremental cost (£)		57,043	65,654		31,574	42,340
	ICER (£/QALY)		16,176	36,237		12,498	14,221
	Cost per cm gain (£)		1747	8258		7048	1932
Ipsen	Incremental cost (£)	65,198	54,779	75,243		36,129	
	ICER (£/QALY)	18,721	15,730	26,630		14,301	
	Cost per cm gain (£)	2022	1699	9464		8065	
Merck Serono[b]	Incremental cost (£)	72,719		84,077		40,325	54,087
		65,711		*75,847*		*36,416*	*48,839*
	ICER (£/QALY)	20,881		29,757		15,962	18,167
		18,869		*26,844*		*14,414*	*16,404*
	Cost per cm gain (£)	2256		10,576		9001	2467
		2038		*9540*		*8129*	*2228*

a GHD continued is the scenario with rhGH treatment during childhood and a transition period.
b Figures in italics are for the EasyPod device.

TABLE 39 *Base-case results for Novo Nordisk using KIGS database*

	GHD continued[a]	GHD	TS	CRI	SGA
Incremental QALY	3.70	3.70	2.89	2.90	2.77
Height gain (cm)	27.45	27.45	7.95	3.65	5.67
Incremental cost (£)	71,264	58,637	79,976	41,388	51,745
Cost per QALY (£)	19,276	15,861	27,720	14,254	18,655
Cost per cm gain (£)	2596	2136	10,060	11,345	9123

a GHD continued is the scenario with rhGH treatment during childhood and a transition period.

The manufacturers concluded that their economic analyses demonstrated that rhGH is cost-effective for the treatment of short children with GHD, CRI and those born SGA, and borders on cost-effectiveness for the treatment of TS and PWS. They stated that the values for cost/centimetre compared favourably to those reported in the previous NICE assessment[6] and supported the recommendation of rhGH for children with GHD, TS and CRI, plus its extension to include SGA children.

Summary of general concerns

- Clinical effectiveness estimates for height gain were taken from an observational cohort rather than an RCT. It is not clear whether the subset of the KIGS database chosen was representative of the UK patient population or, for example, whether the subset chosen may be more severe.
- For three of the conditions (GHD, PWS and SGA) the estimates of height gain, in centimetres, were considerably higher than those shown in the trials due to the estimates used for end height in the control group.
- All conditions, except PWS, used mortality rates from the general population. It is likely that individuals with these conditions, in particular CRI, will have increased mortality compared with the general population.
- The manufacturers have used the Christensen study[150] for their HRQoL utility values but have not taken these from the regression analysis from this study. Instead, they have used the relationship between EQ-5D and height without controlling for other factors. Utility gain attributed to height is likely to be capturing the combined effects of other (unobserved) variables, such as age, longstanding illness and gender. For example, older generations generally have lower QoL because of their age. Not controlling for other factors, in particular age, results in the overestimation of the utility values. Furthermore, the group with the lowest height and QoL (< –3 SDS) had few observations and individuals in this group were generally elderly (mean age > 70 years).
- Treatment cost is calculated by rounding up to the nearest whole year of treatment.
- There is high uncertainty associated with the assumptions and sources used to estimate QoL gain in the PWS model. These were based on a small study of adult patients with PWS and it is unclear how this relates to the QoL gain for a group of children, and whether this QoL benefit would be maintained throughout their lifetime. The methods used to derive values from the SF-36 for utilities were based on rating scales and therefore did not use choice-based methods, such as the SG and TTO. QoL gain also estimated utility gain from reduced diabetes prevalence but this evidence could not be verified. There are considerable difficulties extrapolating the benefit from treating children with rhGH to their health benefits as adults.

Sandoz submission to NICE

Sandoz presented an analysis comparing Omnitrope with Genotropin. The MS contained a comparison of the annual cost of treatment with Omnitrope and with Genotropin in patients with GHD and TS. However, the MS did not comply with NICE guidance for a MTA,[138] as QALYs were not estimated and a cost-effectiveness analysis was not presented. The MS attempted a cost-minimisation analysis, implicitly suggesting that treatment with Omnitrope is equally effective as treatment with Genotropin (in terms of additional height in children with GHD and TS) but is associated with less cost to the UK NHS. A critical appraisal of the Sandoz MS is given in Appendix 10.

SHTAC independent economic evaluation

Overview

A comparison of the costs and benefits of rhGH compared with no treatment in cohorts of children with GHD, TS, PWS, CRI and SHOX-D and children who are SGA was made using decision-analytical models. Models were constructed in Microsoft EXCEL according to standard modelling methods.[138] To identify data to populate the model, systematic searches were conducted to locate studies on the natural history and epidemiology of the indicated conditions, HRQoL and costs.

Costs were derived from published studies (where available), and from national and local NHS unit costs. The model was from the perspective of the NHS and PSS, as only these direct costs were included. The model estimates the lifelong costs and benefits from rhGH treatment. The costs and benefits were discounted at 3.5%, as recommended by NICE.[138] The base year for the costs was 2008. The intervention effect in terms of improvement in HtSDS was derived from the systematic review of effectiveness reported in Chapter 3. The outcome

of the economic evaluation is reported as cost per QALY gained and cost per centimetre gained.

Description of the model

A decision-analytical model was designed for the economic evaluation of rhGH for treatment of GHD, TS, PWS, CRI, SGA and SHOX-D, and was based upon one developed in the previous HTA report.[6] The current model compares a cohort of patients receiving rhGH during their childhood with a cohort of patients who were not treated with rhGH. The state transition Markov model has a cycle length of 1 year and a lifetime horizon. A Markov model was used as these are suitable for lifetime analyses with few health states.[156] The base-case decision-analytical model includes health states for alive and dead. The England and Wales population mortality rates are applied in each cycle for patients, with an adjustment using the SMRs for each of the conditions.

The model assumes that a daily subcutaneous injection of rhGH is administered for the duration of treatment, unless a patient from the treatment cohort drops out of treatment or dies. The parameters of the model that determine the age at the start of treatment, the duration of treatment and the annual dropout rates are estimated from the KIGS database described in the MS or based upon advice from our clinical advisory group, and vary between conditions. A daily dose is calculated according to the child's weight. The dose regimen corresponds to the licensed indication of rhGH in children (and adults, in a scenario analysis of the GHD cohort).

Health-care resources included for the cost of patient monitoring apply to both the treatment and no treatment cohorts. The cost categories and unit costs are consistent with the costs used in the previous HTA report for rhGH.[6] The discount rate of 3.5% is applied to both costs and final outcomes.

Patients from the treatment cohort who stay in treatment receive a benefit of an additional height gain relative to patients in the no treatment cohort. Patients who drop out of treatment stop accumulating height gain, so their growth progression is no different from the height gain in the no treatment cohort. In each yearly cycle, individual HRQoL is estimated based upon their height gain. Individuals are assumed to maintain the same HRQoL after treatment has stopped for the rest of their lifetime. In each cycle, the total costs and QALYs are calculated by multiplying the individual costs and HRQoL by the number of people in the cohort still alive for the treatment and no treatment cohorts. The total lifetime costs and QALYs are calculated for the treated and non-treated groups by aggregating the costs and QALYs in each cycle. The total discounted QALY gain, and cost of treatment for the treatment and no treatment cohorts are calculated. Thus, the cost-effectiveness of rhGH is calculated:

$$\text{Cost-effectiveness} = \frac{\text{Cost for treatment cohort} - \text{Cost for no treatment cohort}}{\text{QALYs for treatment cohort} - \text{QALYs for no treatment cohort}}$$

Parameters used in the model and the data sources used to derive them are described in more detail below (see Model validation).

A list of the model assumptions is given below. Assumptions are applied to all conditions unless explicitly stated otherwise. All assumptions were tested in sensitivity analyses.

- The diagnostic costs were not included in the analysis as they were assumed to be the same for both rhGH-treated and no-treatment patients.
- The base case assumes no dropout or discontinuation of treatment. This was based upon advice from our clinical advisory group that this was likely to be a relatively rare occurrence. The base-case model therefore evaluates just rhGH treatment versus no treatment.
- There are two health states for alive or dead in the model, and the transition between them is based on age-related mortality data.
- The mortality rates were assumed to be higher than for the England and Wales general population estimates for untreated and treated cohorts for all conditions.
- It was assumed that there would be no reduction in mortality as a result of rhGH treatment. There is a lack of data to assume otherwise.
- The model time horizon is 100 years and all individuals are assumed to die by this age.
- Effectiveness estimates for the conditions were based on selection of the best-quality evidence from the clinical effectiveness review in Chapter 3. RCTs were only selected if the follow up length was at least 2 years after the start of treatment. Where there were no appropriate RCTs, long-term observational

studies were considered. In the case of SGA, the most appropriate RCT was for only 1 year.
- Compliance was assumed to be 85% in the base case, with no loss of efficacy for rhGH treatment.[157]
- An additional scenario was undertaken for the GHD condition where treatment continued for a transition phase into adulthood to age 25. This was only applicable for 34% of the GHD population.[158] No additional benefit, in terms of height gained, was assumed from this additional treatment.
- In the treatment and no-treatment cohorts, all children are monitored until they reach adulthood, assumed to be the age of 17 years.

Evaluation of uncertainty

The evaluation of the cost-effectiveness of GH treatment is based on uncertain information about variables, such as clinical effect, HRQoL and resource use. This uncertainty was evaluated using deterministic and probabilistic sensitivity analyses. One-way deterministic sensitivity analyses were conducted to evaluate the influence of individual parameters on the model results and to test the robustness of the cost-effectiveness results to variations in the structural assumptions and parameter inputs (see Sensitivity analyses, below).

Multiparameter uncertainty in the model was addressed using probabilistic sensitivity analysis (PSA) (see below).[159] In PSA, probability distributions are assigned to the point estimates used in the base-case analysis. The model is run for 1000 iterations, with a different set of parameter values for each iteration, by sampling parameter values at random from their probability distributions. The uncertainty surrounding the cost-effectiveness of the GH treatment is represented on a cost-effectiveness acceptability curve (CEAC) according to the probability that the intervention will be cost-effective at a particular willingness-to-pay threshold. Appendix 12 reports the parameters included in the PSA, the form of distribution used for sampling each parameter, and the upper and lower limits assumed for each variable.

Model validation

The Southampton Health Technology Assessments Centre (SHTAC) model was validated by checking the model structure, calculations and data inputs for technical correctness. The completed cost-effectiveness model was verified by another health economist. The SHTAC model was checked for internal consistency against the MS economic models by running the SHTAC model with the inputs used in MS models to ensure similar results. The robustness of the model to changes in input values was tested using sensitivity analyses to ensure that any changes to the input values produced changes to the results of the expected direction and magnitude. Finally, the model results were compared with those from previous studies including the previous HTA report and this is discussed in more detail in Chapter 6.

Data sources

Life expectancy

Several studies have attempted to assess the mortality rate of adults with the conditions of interest. Nielsen and colleagues[160] conducted a meta-analysis to assess overall SMR for men and women with benign pituitary disease. Six studies were included in the meta-analysis of sex-specific mortality. Studies (total 5412 patients) reported SMR for men of 2.06 (CI 1.94 to 2.2) and women 2.8 (CI 2.59 to 3.02). However, these analyses were for hypopituitarism rather than GHD.

Shoemaker and colleagues[161] followed up 3439 women in the UK, who were diagnosed with TS between 1959 and 2002, to the end of 2006. Mortality in women with TS is three times higher than in the general population, is raised for almost all major causes of death, and is raised at all ages. SMR was 3.9 in women aged 15–44 years old and 2.6 in women aged 45–84 years.

Population-based morbidity and mortality data for PWS are not available, except from regional cross-sectional surveys.[162] A recent regional survey in England indicates high morbidity and mortality rates. Lifetime mortality rates were roughly three times higher than the general population. Within these studies the data are insufficient to construct survival curves.

Mortality and causes of death in treatment for children with end-stage renal disease was estimated in a Dutch cohort study between 1972 and 1992.[163] Of all 381 patients, 85 had died. The SMR was 31.0 over this period and 21.0 in the last cohort between 1992 and 2002.

Kajantie and colleagues[164] studied the relationship between small size at birth and all-cause and non-cardiovascular mortality in 13,830 individuals born between 1924 and 1944 in Helsinki, Finland. They found that small size at birth is associated with increased all-cause mortality at all ages among adult women but only with premature death in adult men.

We were unable to find any information on mortality rates for SHOX-D.

Using UK life tables, we estimated the life expectancy of adults with these conditions using the SMRs described above. Normal adult life expectancy was estimated to be 75 years for men and 79 years for women. Life expectancy for patients with hypopituitarism was reduced to 68 years for men and 70 years for females. Life expectancy with TS was reduced to 70 years for females. We estimated the life expectancy with CRI to be reduced to 35 years for men and 42 years for females, using the end-stage renal disease mortality rates as a proxy in the absence of any available data for CRI. This may underestimate life expectancy, as not all patients with CRI will go on to develop end-stage renal disease.

In the base-case model, we assume that for all conditions the life expectancy is lower than that of the general UK population, and investigate general population life expectancy in sensitivity analyses.

Effectiveness data

The start and end age of treatment, and the duration of treatment, are shown in *Table 40*. For GHD, CRI, PWS and SGA there are no RCTs with a duration of more than 3 years, so we used data from the KIGS database.[153] SHOX-D was not included in the KIGS database and so we assumed that these children start treatment at the same age as those in the Blum RCT[49] and continue treatment for the same duration as for children with TS in the KIGS database. For the purposes of the model we rounded the start age and treatment duration.

For GHD, some children continue to receive rhGH treatment into adulthood. This is shown as an additional scenario for GHD, for which it is assumed that 34% of GHD patients continue treatment[158] until age 25 years with a dose of 0.4 mg/day.[6] These individuals do not receive any additional benefit associated with height gain from this treatment in the model.

The clinical effect of rhGH was taken from the systematic review in Chapter 3. Where possible the clinical effect was taken from the best-quality RCT, for which children had treatment for a sufficiently long time to capture HtSDS height gain, which we assumed would be at least 2 years. For GHD, these data were not available, as the only available RCT was for only 1 year, and so we have used observational data (KIGS database)[153] to estimate the clinical effect (*Table 41*). For SGA, there were no RCTs available for the licensed dose and so we used a study with 1-year treatment.[114] For TS, height gain was reported in terms of age-specific TS HtSDS, but the mean age-specific value was not reported. We assumed that the age-specific TS HtSDS was that reported in the KIGS database.[153] Several studies have not reported the height gain in centimetres, and for these studies we converted HtSDS values to centimetres, using the height table from the Health Survey for England (HSE) 2003.[151]

A review of compliance with rhGH was conducted by Merck Serono as part of the MSs. It found that estimates for compliance ranged from 69% to 95% for the studies identified. One study estimated concordance in 75 children by using data on GP prescriptions over 12 months.[157] Between one and two injections/week were missed by 16% of the children, and 23% missed more than two injections/week. Based on this study, we assumed a compliance of 85%.

Health-related quality of life

There was a lack of good-quality HRQoL data expressed in terms of utility in the RCTs and other QoL studies for most of the conditions of interest (see Review of research on QoL, above). Only one study was found that was appropriate to the conditions of interest and this was for GHD.[147] However, it was in an adult population and it was uncertain whether the participants had already benefited from GH as children; the QoL utility gain from this study was similar to that from the Christensen and colleagues study[150] for GHD. For the other studies the most appropriate utility

TABLE 40 *Input parameters used in the SHTAC model*

	GHD	TS	PWS	CRI	SGA	SHOX-D
Source	KIGS[153]	CGHAC[86]	KIGS[153]	KIGS[153]	KIGS[153]	Blum[49]
Starting age (years)	9	10	7	9	8	7
Age at end of treatment (years)	16	16	15	14	14	14
Treatment duration (years)	7	6	8	5	6	7
Sex (males, %)	70	0	50	71	60	48

TABLE 41 *Clinical effect for rhGH used in the SHTAC model*

Parameter	GHD	TS	PWS	CRI	SGA	SHOX-D
Source	KIGS[153]	CGHAC[86]	[a]de Lind van Wijngaarden *et al.*[93]	Fine *et al.*[108]	Philip *et al.*[114]	Blum *et al.*[49]
Treatment cohort						
Starting HtSDS	–2.99	–3.4[b]	–2.0	–2.9	–3.1	–3.3
Final HtSDS	–1.17	–1.8[b]	–0.5	–1.6	–2.3	–2.1
Control cohort						
Starting HtSDS	–2.99	–3.3[b]	–2.5	–2.9	–3.1	–3.3
Final HtSDS	–2.99	–3.0[b]	–2.6	–2.9	–3.0	–3
Treatment effect						
Treatment height gain (SDS)	1.82	1.3	1.6	1.3	0.7	0.9
Treatment height gain (cm)	12.8[c]	9.3	11.1[c]	9.2[c]	3.3	5.9
QoL gain	0.069	0.069	0.021	0.059	0.043	0.055

a Results reported as median values.
b Estimated, based on age-specific turner SDS score, converted to SDS score using KIGS database.[153]
c HtSDS gain converted to centimetres using HSE 2003.[153]

measurement was from the study by Christensen and colleagues,[150] which measured QoL using the EQ-5D in a large sample of the general UK population (HSE). The utility values are not from the conditions of interest; nevertheless it does provide a common utility gain that could be compared across all the conditions of interest and that could be used with the clinical effectiveness outcomes from the RCTs. It was assumed for children that the adult gain in utility from increased height derived from the Christensen and colleagues study would be the same as a utility gain in children.

This study assessed HRQoL estimates through the use of ordinary least squares (OLS) linear regression, which controlled for age, weight and gender. More details on the study are reported above (see Height and health-related QoL, above). We assumed that individuals in the treated and untreated cohorts would have no difference in terms of age, gender, social class, weight and longstanding illness. The differences in HRQoL utility estimates between the treated and untreated cohorts are therefore derived from their differences in height. According to the regression, for those people shorter than –2.0 HtSDS an improvement of 1 HtSDS will result in a change in HRQoL utility of 0.061; for the subgroup between –2.0 and 0 HtSDS, a 1 HtSDS improvement increases utility by 0.01. These values were used in the SHTAC estimation of cost-effectiveness.

For patients with PWS there may be an additional health benefit associated with improved body composition. Any improvements in body composition may lead to reduced risk of diabetes and cardiovascular disease. However, there is considerable difficulty estimating the magnitude of this effect and extrapolating short-term treatment in childhood to lifelong benefit. There was one study of poor quality in adults with PWS but this was not considered to be a robust estimate of QoL benefit (see Review of research on QoL). The MS estimated a QoL benefit from reduced diabetes risk but it was not possible to verify this evidence. Due to the high uncertainty around the estimates of QoL benefit, we assumed no benefit due to body composition in the base case and then conducted sensitivity analyses using the studies mentioned above.

Estimation of costs

The costs used in the SHTAC model were based upon those used in the previous HTA report.[6] The annual cost of monitoring associated with each condition was calculated for each arm of the model using treatment pathways described in that report. Treatment costs are calculated on the basis of mean dose of rhGH. Unit costs for drugs were taken from the *British National Formulary* (BNF)[165] and, for consultations, outpatient visits and procedures, from *NHS Reference Costs*.[166] The base year used for the analysis was 2008; where necessary, costs were inflated to that year.

Based on advice from our clinical advisory group, the resource use was the same as for the previous HTA report except for nurse visit time was assumed to be the same for all conditions and patients would have two outpatient visits per year. Furthermore, patients would no longer have a hand X-ray at the end of treatment. The resource use is similar for all conditions, except GHD where 20% of treated children have a pituitary test each year. The unit costs applied to the resource use estimates for monitoring tests were provided by the finance department at Southampton University Hospital Trust [personal communication, Southampton University Hospitals Trust: unit costs (unpublished database), 2008]. The hourly cost of community nursing is taken from the *Unit Costs of Health and Social Care*.[167] All children are monitored until they reach adulthood, assumed to be at the age of 17 years old. The unit costs and resource use are shown in *Tables 42* and *43*, respectively.

TABLE 42 *Unit costs used in the SHTAC model*

Costs component	Cost (£)	Source
Cost per outpatient attendance first contact face-to-face paediatric endocrinology (HRG code 302F)	206.28	NHS ref costs 2007/8[166]
Cost per outpatient attendance subsequent contact face-to-face paediatric endocrinology (HRG code 302F)	127.97	NHS ref costs 2007/8[166]
Specialist community nurse per patient contact (1 hour)	73	PSSRU 2008[167]
Community nurse per patient visit (1 hour)	64	PSSRU 2008[167]
Blood tests (for full blood count, chemical profile, thyroid and IGF)	51	SUHT 2008
X-ray, hand (BA test)	28.64[a]	NHS ref costs 2006/7[166]
Pituitary function test (glucagon, insulin stress test), includes 2 hours' nurse time	207.50	SUHT 2008

a Original cost of £27.71 inflated to 2008 costs.
HRG, Healthcare Resource Group; PSSRU, Personal Social Services Research Unit; SUHT, Southampton University Hospitals Trust.

TABLE 43 *Administration and monitoring resource use*

	GHD	TS, PWS, CRI, SGA, SHOX-D
No treatment monitoring		
Outpatient visit	2	2
Blood test	1	1
Treatment 1st year		
Specialist nurse home visit (hours)	1	1
Community nurse home visits (hours)	4	4
Outpatient visit	2	2
Blood test	1	1
Pituitary function test	0.2	0
GH treatment subsequent year		
Outpatient visit	2	2
Blood test	1	1
Hand X-ray	1	1
Pituitary function test	0.2	0
End of treatment		
Outpatient visit	1	1

The unit cost of the drug used in the manufacturers' models varies between £18.00 and £23.19 per milligram. As this review is for the cost-effectiveness of somatropin, rather than being dependent on manufacturers' different device costs, we have assumed an rhGH cost in the base case that is the average of the six manufacturers' unit cost of rhGH given in the BNF *58* (*Table 44*). This gives an average price of £21.06. This was done for consistency between the different conditions, despite the average cost of rhGH for each condition actually varying depending on which and how many manufacturers have a licence for the condition of interest. The maximum and minimum price of rhGH will be used in a sensitivity analysis. Drug costs are calculated according to the dosage used (*Table 45*) and the weight of the child.[165] The weight of children at different ages was taken from a long-term observational database (Appendix 13).[153]

Estimation of cost-effectiveness

This section reports the cost-effectiveness results for a cohort of children for each of the conditions of interest who received rhGH treatment. Results for costs and QALYs are presented for children in the cohort for a treated and untreated cohort, with costs and benefits discounted at 3.5%. The cost-effectiveness of rhGH compared to no treatment is presented as incremental cost per QALY and incremental cost per centimetre gained. The results are shown in *Table 46* for each condition. In the base-case analysis, all conditions, except GHD, used the clinical benefit seen in the best-quality RCT for each condition (see Chapter 3). The cost-effectiveness of rhGH versus no treatment varied from £23,196 for GHD to £135,311 for PWS per QALY gained.

The incremental cost per QALY gained for PWS is very high despite a similar or greater height gain compared with the other conditions as a result of rhGH treatment. This is due to the PWS cohort having a starting HtSDS that is much closer to population norms with most of the gain in height occurring between –2.0 and 0 HtSDS. Therefore, using the Christensen regression estimates, this is associated with a lower utility gain (see Health-related quality of life, above) and a smaller QALY gain when compared with the other conditions. With the exception of PWS, all conditions have an ICER lower than £41,000 per QALY gained.

A further analysis was undertaken to see the effect of continuation of rhGH treatment into adulthood for 34% of the original cohort until the age of 25 years. The incremental cost per QALY was £28,244 (*Table 47*).

TABLE 44 *Individual prices of rhGH and the average cost used in the cost-effectiveness analyses*

rhGH	BNF 58 price (£) (per mg)
Genotropin	23.19
Humatrope	18.00
Norditropin	21.39
Saizen	23.18
Nutropin	20.70
Zomacton	19.92
Average cost	21.06

Sensitivity analyses

Cost-effectiveness of rhGH treatment – deterministic sensitivity analysis

One-way deterministic sensitivity analyses were performed, in which model parameters were systematically and independently varied, using a realistic minimum and maximum value. The sensitivity analysis investigated the effect of uncertainty around the model structure and for variation in parameters on the cost-effectiveness results, in order to highlight the most influential parameters. The effects of uncertainty in multiple parameters were addressed using PSA, which is

TABLE 45 *Drug dosage*

	Condition					
	GHD	TS	PWS	CRI	SGA	SHOX-D
Drug dosage (mg/kg/day)	0.025	0.045	0.035	0.045	0.035	0.045

TABLE 46 *Cost-effectiveness results for the base-case analysis*

Condition	Treatment	Costs (£)	QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)	Gain (cm)	ICER (£/cm)
GHD	No rhGH	2211	16.8					
	rhGH	38,031	18.4	35,820	1.54	23,196	12.80	2798
TS	No rhGH	1965	15.9					
	rhGH	62,752	17.4	60,787	1.54	39,460	9.30	6536
PWS	No rhGH	2646	17.6					
	rhGH	67,794	18.1	65,148	0.48	135,311	11.10	5869
CRI	No rhGH	1876	11.6					
	rhGH	35,877	12.4	34,001	0.87	39,273	9.20	3696
SGA	No rhGH	2432	17.1					
	rhGH	34,431	18.1	31,999	0.97	33,079	3.30	9697
SHOX-D	No rhGH	2646	16.8					
	rhGH	53,434	18.1	50,788	1.25	40,531	5.90	8608

Inc., incremental.

TABLE 47 *Cost-effectiveness results for continuation of rhGH treatment into adulthood for patients with GHD*

Condition	Treatment	Costs (£)	QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)	Gain (cm)	ICER (£/cm)
GHD continuers	No rhGH	2211	16.8					
	rhGH	45,826	18.4	43,615	1.54	28,244	12.80	3407

Inc., incremental.

reported later in this section. Where possible, the parameters were varied according to the ranges of the CIs of these parameters, based on the published estimate. Where these data were not available an alternative suitable range was chosen. The same ranges were used in the deterministic and probabilistic sensitivity analyses and these are described in Appendix 12.

Table 48 shows the results for each of the conditions using the KIGS database[153] for estimate of the clinical benefit. The KIGS database, a large observational study of children treated with rhGH, was used for the effectiveness of GHD in the base case reported above. According to these results, an ICER of rhGH versus no treatment varied from an ICER of £18,980 per QALY gained for SGA to £144,050 per QALY gained for PWS. Results are of a similar magnitude to the base case with the exception of the SGA analyses. The ICER for SGA is much lower in this analysis because the incremental clinical height gain is lower in the RCT effectiveness data than in the KIGS effectiveness data.

The discount rates used for the analyses have a large effect on the results, due to the upfront costs and the health outcomes stretching over the life time of the model. *Table 49* shows the results using the discount rates used in the previous HTA report, i.e. costs 6% and benefits 1.5%. Using these discount rates, rhGH treatment is more cost-effective. For all conditions, except PWS, the ICER reduces to less than £30,000 per QALY.

Tables 50–55 report the results of the deterministic sensitivity analyses for the conditions for the most influential parameters. Other variables were varied in sensitivity analyses but were found to only have a negligible effect on the results. The cost-effectiveness results are fairly sensitive to the variation in parameters included in the deterministic sensitivity analysis. For all of the conditions the model results are most sensitive to

TABLE 48 *Cost-effectiveness results with clinical benefit from KIGS database*

Condition	Treatment	Height (HtSDS)	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
TS	No rhGH	–3.18	1965	15.8			
	rhGH	–2.24	62,752	17.1	60,787	1.28	47,553
PWS	No rhGH	–2.22	2646	17.4			
	rhGH	–1.36	67,794	17.9	65,148	0.45	144,050
CRI	No rhGH	–2.99	1876	11.5			
	rhGH	–2.17	35,877	12.2	34,001	0.74	46,245
SGA	No rhGH	–3.23	2432	16.8			
	rhGH	–2.01	34,431	18.4	31,999	1.69	18,980
SHOX-D	No rhGH	–3.18	2646	16.6			
	rhGH	–2.24	53,434	17.9	50,788	1.31	40,531

TABLE 49 *Cost-effectiveness results with alternative discount rates*

Condition	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Gain (cm)	ICER (£/cm)
GHD	32,407	2.49	12,999	12.80	2532
TS	55,753	2.49	22,358	9.30	5995
PWS	58,075	0.79	73,836	11.10	5232
CRI	31,609	1.22	25,804	9.20	3436
SGA	29,362	1.57	18,690	3.30	8898
SHOX-D	45,937	2.05	22,436	5.90	7786

treatment start age and length, compliance and utility gain.

The deterministic sensitivity results for GHD are shown in *Table 50*. The results varied between £19,187 and £35,917 per QALY gained and were most sensitive to dosage.

The deterministic sensitivity results for TS are shown in *Table 51*. The results varied between 30,505 and £48,778 per QALY gained and were most sensitive to utility gain.

The deterministic sensitivity results for PWS are shown in *Table 52*. The results varied between £111,560 and £159,062 per QALY gained and were most sensitive to compliance.

The deterministic sensitivity results for CRI are shown in *Table 53*. The results varied between £28,080 and £54,105 per QALY gained and were most sensitive to the treatment start age and length of treatment.

The deterministic sensitivity results for SGA are shown in *Table 54*. The deterministic sensitivity results varied between £25,675 and £41,180 per QALY gained and were most sensitive to utility gain.

The deterministic sensitivity results for SHOX-D are shown in *Table 55*. The deterministic sensitivity results varied between £33,406 and £50,457 per QALY gained and were most sensitive to utility gain.

For patients with PWS there may be an additional health benefit associated with improved body composition, which may reduce the risk of diabetes and other morbidities. In addition, there is considerable difficulty estimating the magnitude of this effect and extrapolating short-term treatment in childhood to lifelong benefit. In the base case we have assumed that there is no HRQoL benefit associated with changes in body composition. In this section we present a scenario analysis for additional changes in body composition. However, there is a difficulty linking changes in lean FM to changes in utility, as there are no utility studies for lean FM. For this reason we have focused on changes in BMI.

TABLE 50 *Deterministic sensitivity analyses for GHD*

Parameter	Baseline	Upper value	Lower value	ICER (£/QALY)		
				Upper value	Lower value	Range
Dosage (mg/kg)	0.025	0.039	0.023	35,917	21,379	14,538
Utility gain per HtSDS	0.061	0.073	0.049	19,776	28,047	8271
Compliance (%)	85	100	70	27,205	19,187	8018
Treatment age (years)	9–16	11–16	7–16	19,279	25,659	6380
Cost of rhGH treatment (£/mg)	21.06	23.19	18.00	25,493	19,895	5598
Utility benefit spread over	2 years	1 year	7 years	22,732	25,638	2906
SMR	2.4	2.4	1	23,196	22,184	1012

TABLE 51 *Deterministic sensitivity analyses for TS*

Parameter	Baseline	Upper value	Lower value	ICER (£/QALY)		
				Upper value	Lower value	Range
Utility gain per HtSDS	0.061	0.073	0.049	33,131	48,778	15,647
Treatment age (years)	10–16	12–16	8–16	30,505	45,105	14,600
Compliance	85%	100%	70%	46,376	32,544	13,832
Cost of rhGH treatment (£/mg)	21.06	23.19	18.00	43,424	33,766	9658
Dosage (mg/kg)	0.045	0.05	0.4	43,815	35,106	8709
Utility benefit spread over	2 years	1 year	6 years	38,672	42,753	4081
SMR	2.4	2.4	1	39,460	37,308	2152

TABLE 52 *Deterministic sensitivity analyses for PWS*

Parameter	Baseline	Upper value	Lower value	ICER (£/QALY)		
				Upper value	Lower value	Range
Compliance (%)	85	100	70	159,062	111,560	47,502
Cost of rhGH treatment (£/mg)	21.06	23.19	18.00	148,924	115,755	33,169
Treatment age (years)	7–15	9–15	5–15	119,036	144,159	25,123
Utility benefit spread over (years)	2	1	8	132,645	152,275	19,630
Dosage (mg/kg)	0.035	0.035	0.03	135,311	116,084	19,227
Utility gain per HtSDS	0.061	0.073	0.049	128,030	143,471	15,441
SMR	2.4	2.4	1	135,311	129,640	5671

Picot and colleagues[168] conducted a targeted search to identify published utility estimates for the BMI values relevant to an adult obese population. The search aimed to identify estimates of the change in utility scores based on the unit change in BMI values. Utility estimates were considered only where they used a validated, multiattribute utility scale (e.g. EQ-5D) or appropriate methodology (e.g. SG or TTO techniques) and provided a clear definition of utility scores. They suggest the values reported by Hakim and colleagues[169] represent the most methodologically sound estimates derived from subjects across a wide range of obesity levels. Hakim and colleagues[169] found that a one-unit decrease in BMI, over a period of 1 year, was associated with a gain of 0.017, which was independent of age or gender.

TABLE 53 *Deterministic sensitivity analyses for CRI*

Parameter	Baseline	Upper value	Lower value	ICER (£/QALY)		
				Upper value	Lower value	Range
Treatment age (years)	9–14	11–14	7–14	28,080	46,477	18,397
Utility benefit spread over	2 years	1 year	5 years	38,253	54,105	15,852
Utility gain per HtSDS	0.061	0.073	0.049	33,188	48,091	14,903
Compliance (%)	85	100	70	46,181	32,365	13,816
SMR	21	21	1	39,273	28,820	10,453
Cost of rhGH treatment (£/mg)	21.06	23.19	18.00	43,232	33,585	9647
Dosage (mg/kg)	0.045	0.05	0.04	43,623	34,923	8700

TABLE 54 *Deterministic sensitivity analyses for SGA*

Parameter	Baseline	Upper value	Lower value	ICER (£/QALY)		
				Upper value	Lower value	Range
Utility gain per HtSDS	0.061	0.073	0.049	27,641	41,180	13,539
Treatment age (years)	8–14	10–14	6–14	25,675	37,921	12,246
Compliance (%)	85	100	70	38,888	27,270	11,618
Cost of rhGH treatment (£/mg)	21.06	23.19	18.00	36,408	28,296	8112
Dosage (mg/kg)	0.035	0.04	0.035	37,781	33,079	4702
Utility benefit spread over	2 years	1 year	6 years	32,422	35,818	3396
SMR	2.4	2.4	1	33,079	31,657	1422

TABLE 55 *Deterministic sensitivity analyses for SHOX-D*

Parameter	Baseline	Upper value	Lower value	ICER (£/QALY)		
				Upper value	Lower value	Range
Utility gain per HtSDS	0.061	0.073	0.049	33,868	50,457	16,589
Compliance (%)	85	100	70	47,657	33,406	14,251
Treatment age (years)	7–14	9–14	5–14	33,787	44,666	10,879
Cost of rhGH treatment (£/mg)	21.06	23.19	18.00	44,615	34,664	9951
Dosage (mg/kg)	0.045	0.05	0.04	45,018	36,045	8973
Utility benefit spread over	2 years	1 year	7 years	39,733	44,729	4996
SMR	2.4	2.4	1	40,531	38,822	1709

In Chapter 3 (see Body composition), RCTs for PWS reported mixed results for changes in BMI with a maximum BMI difference of 1.8 kg/m^2 between treated and untreated groups after 2 years' treatment. Assuming this change in BMI is maintained lifelong, and therefore there is an additional utility of 0.031, the cost-effectiveness of PWS would be £54,800 per QALY gained.

Probabilistic sensitivity analyses

In the probabilistic sensitivity analyses (PSAs) the main parameters were sampled probabilistically from an appropriate distribution using similar ranges as used in the deterministic sensitivity analyses. The parameters sampled were: starting age, length of treatment, dose, HtSDS at the start and end of treatment for both the rhGH and no

treatment cohorts, utility increment for gains in height and all costs used in the base case excluding the cost of rhGH.

The distribution assigned to each variable included in the PSA and the parameters of the distribution are reported in Appendix 12. One thousand simulations were run for each condition of interest in this analysis. *Table 56* reports the mean costs and outcomes from the PSA and the ICER for rhGH compared with no treatment, based on the mean values generated in the PSA. *Table 57* shows the 2.5% and 97.5% percentiles for the PSA.

The cost-effectiveness results from the PSA are slightly lower than those from the deterministic analyses for GHD, TS, CRI, SGA and SHOX-D (which were £23,196, £39,460, £39,273, £33,079 and £40,531, respectively). The cost-effectiveness results from the PSA for PWS, however, are much lower than the deterministic estimates. This is due to non-linearity in the PWS model as a result of the baseline starting HtSDS for the treated group being at –2.0 HtSDS. This is also the height at which the utility gain per unit HtSDS changes and thus an individual with a starting height slightly lower than –2.0 HtSDS will have much higher utility gain than one with a starting height slightly higher than –2.0 HtSDS. This non-linearity results in a higher incremental QALY in the PSA results, therefore decreasing the ICER in the PSA.

Scatter plots are shown for the incremental cost and incremental QALYs for each of the conditions in *Figures 2*–*7*. The difference in the dispersion of costs and QALY data points between the six conditions reflects the different levels of uncertainty in each condition. The spread of costs and to a greater extent QALYs is more compact in GHD than for the other conditions. This is because the standard errors are much smaller due to the effectiveness data coming from the KIGS database, which has a large number of observations. This

TABLE 56 *Costs and outcomes from the PSA*

Condition	Treatment	QALYs	Costs (£)	Inc. QALYs	Inc. costs (£)	ICER (£/QALY)
GHD	No rhGH	16.81	2277			
	rhGH	18.36	37,719	1.543	35,517	23,019
TS	No rhGH	15.89	1952			
	rhGH	17.43	62,128	1.546	60,176	38,931
PWS	No rhGH	17.61	2639			
	rhGH	18.19	67,716	0.576	65,076	113,075
CRI	No rhGH	11.57	1874			
	rhGH	12.44	35,702	0.868	33,828	38,951
SGA	No rhGH	17.09	2429			
	rhGH	18.06	34,283	0.966	31,854	32,963
SHOX-D	No rhGH	16.80	2633			
	rhGH	18.07	53,027	1.267	50,394	39,781

Inc., incremental.

TABLE 57 *Range of results from the PSA (2.5% and 97.5% percentiles)*

	Incremental QALYs		Incremental costs (£)		ICERs	
Condition	Min.	Max.	Min.	Max.	Min.	Max.
GHD	1.27	1.83	25,306	46,043	15,752	31,309
TS	0.77	2.35	43,478	77,707	21,758	81,026
PWS	–0.33	1.43	49,419	78,677	–838,603	1,055,815
CRI	0.43	1.30	21,580	44,294	21,553	77,929
SGA	0.52	1.48	23,179	40,773	19,945	64,614
SHOX-D	0.53	2.12	37,854	62,023	21,524	95,600

Max., maximum; Min., minimum.

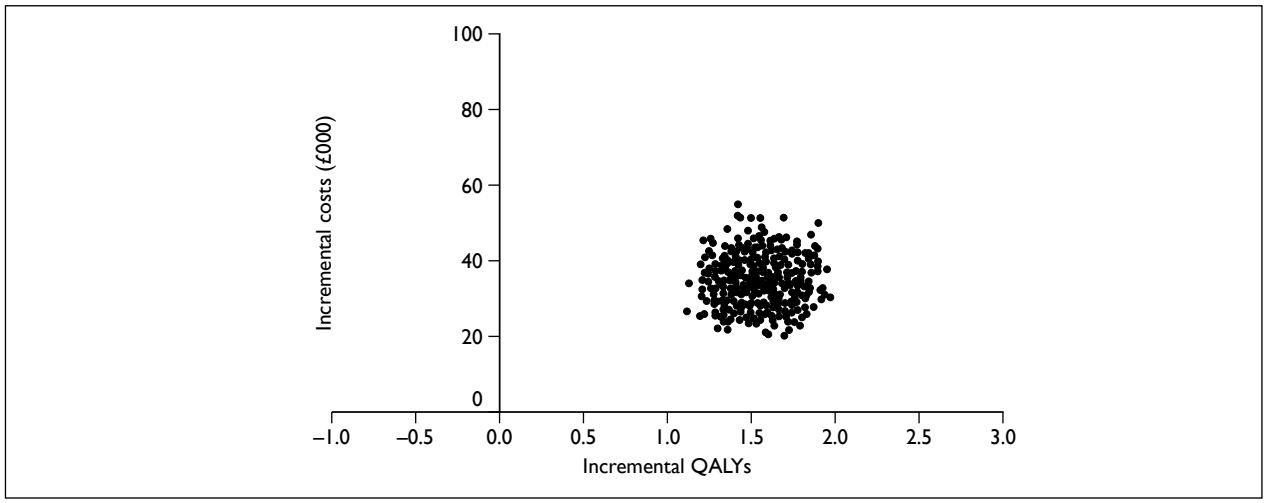

FIGURE 2 *Cost-effectiveness plane – incremental cost and incremental QALYs for rhGH treatment and no treatment in growth hormone deficiency.*

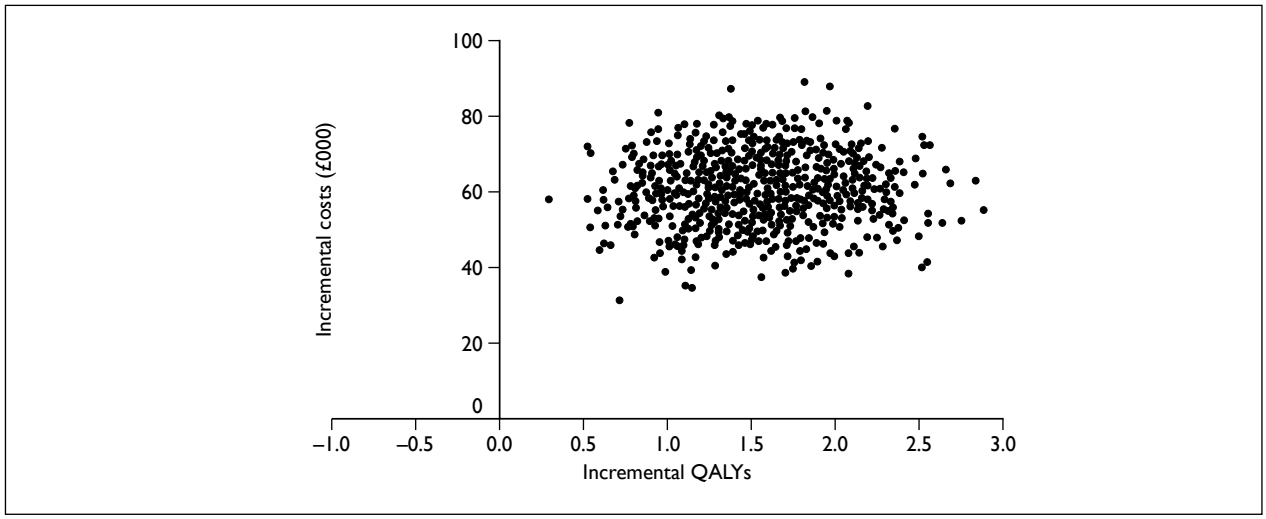

FIGURE 3 *Cost-effectiveness plane – incremental cost and incremental QALYs for rhGH treatment and no treatment in Turner syndrome.*

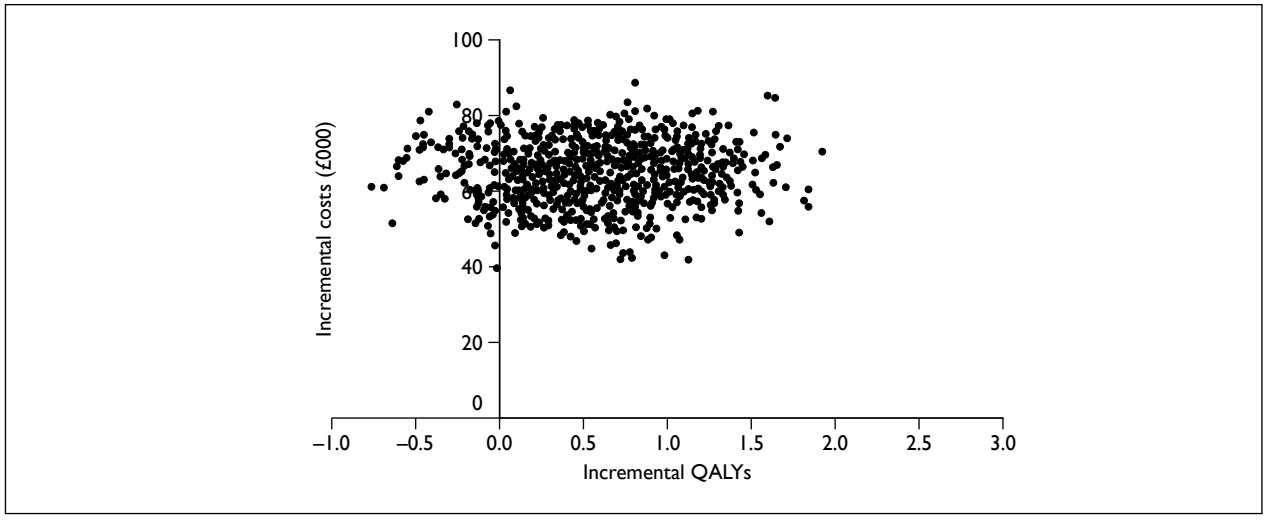

FIGURE 4 *Cost-effectiveness plane – incremental cost and incremental QALYs for rhGH treatment and no treatment in Prader–Willi syndrome.*

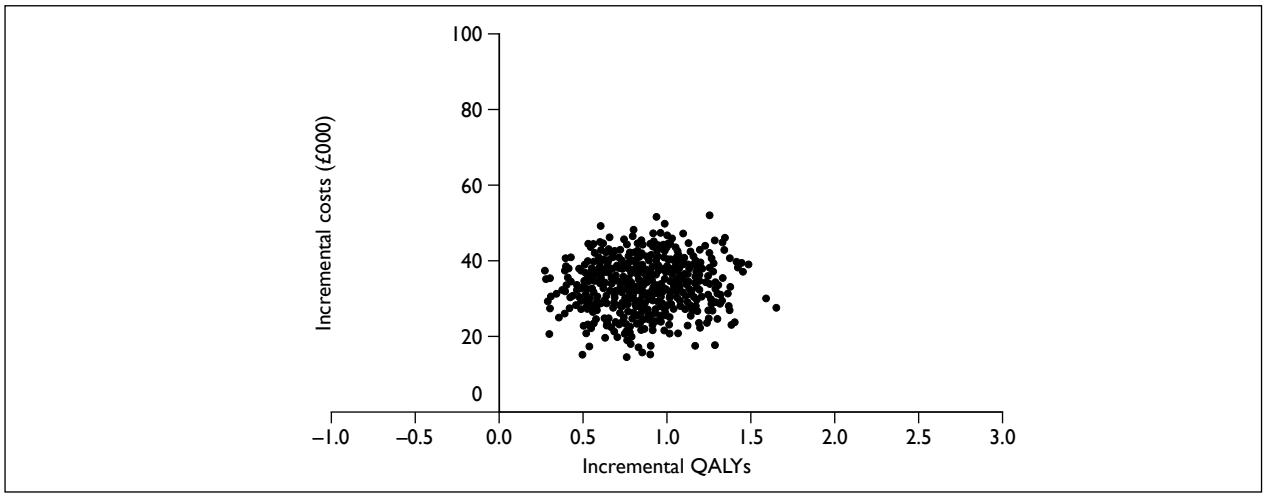

FIGURE 5 *Cost-effectiveness plane – incremental cost and incremental QALYs for rhGH treatment and no treatment in chronic renal insufficiency.*

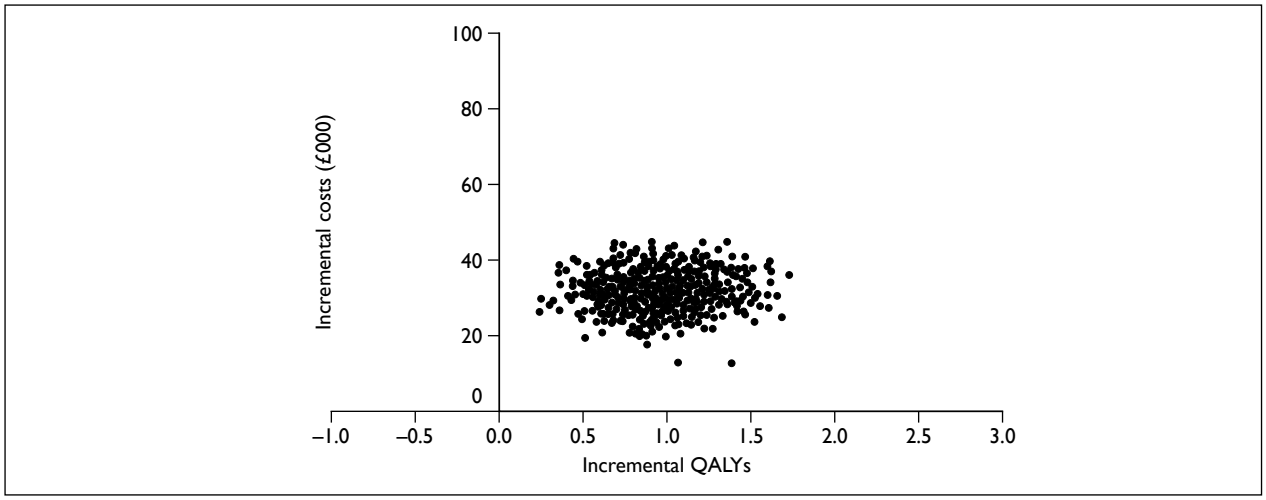

FIGURE 6 *Cost-effectiveness plane – incremental cost and incremental QALYs for rhGH treatment and no treatment for the condition 'small for gestational age'.*

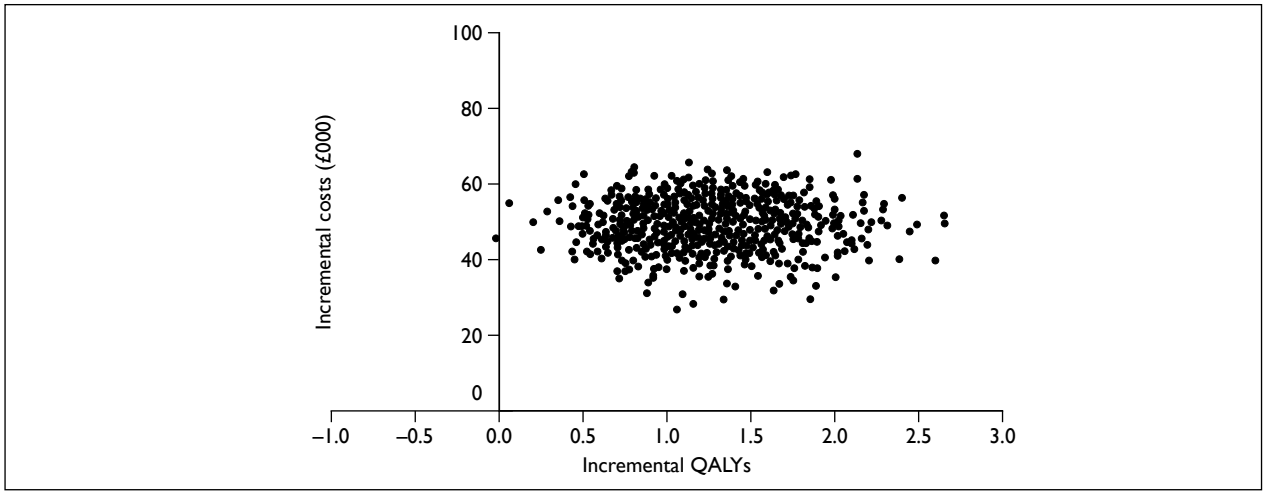

FIGURE 7 *Cost-effectiveness plane – incremental cost and incremental QALYs for rhGH treatment and no treatment in short stature homeobox-containing gene deficiency.*

creates a tighter probability distribution around the mean value.

In addition, a CEAC was also derived, representing the proportion of simulations when GH treatment is cost-effective for a range of willingness-to-pay thresholds, up to £100,000, see *Figure 8*.

In this analysis, rhGH treatment had the probability of being cost-effective at willingness-to-pay thresholds of £20,000, £30,000 and £50,000 per QALY as: 22%, 95% and 100% for GHD, 2%, 19% and 78% for TS, 0%, 1% and 8% for PWS, 2%, 16% and 80% for CRI, 4%, 38% and 90% for SGA, and 1%, 15% and 74% for SHOX-D, respectively.

Summary of cost-effectiveness

- A systematic search of the literature found two fully published economic evaluations of rhGH treatment for TS and GHD. The results from the studies varied due to the choice of utility estimates and assumptions on the effectiveness.
- A systematic search for published studies of QoL for patients with individuals with the conditions of interest who had rhGH identified six studies, although none of these was in children. These were generally small studies of poor quality. One study was considered of reasonable quality.[147] This study estimated HRQoL for adults with GHD.
- An additional targeted search was undertaken for QoL in relation to height, which identified one study[150] that provided utility estimates based on the EQ-5D for different HtSDS from HSE.
- Six of the seven manufacturers submitted evidence to be considered for this review. One MS by Sandoz did not comply with the NICE template for MTA and presented a description of the product (Omnitrope) and what appears to be a cost-minimisation analysis using Genotropin as a comparator (defined as a reference product). The other five out of the six MSs consisted of a written report and an electronic model supporting the cost-effectiveness analyses. This model was used by the five collaborating manufacturers involved in the submission to the MTA of rhGH in the cost-effectiveness analysis of treatment in children with GHD, TS, PWS, CRI and SGA.
- Each of the collaborating manufacturers presented essentially the same model with some minor modifications. The model developed was based upon the previous HTA report[6] but has been extended to consider longer term outcomes in order to estimate cost-effectiveness in terms of QALYs.
- The utility scores used in the MS model in children with GHD, TS, CRI and SGA were based upon the study by Christensen and colleagues,[150] which estimates QoL associated with height for a general population survey. However, they used the utility point estimates, based only on height, instead of the regression analysis from the study, which controlled for other key variables.
- In the manufacturers' base case, the cost-effectiveness results for all conditions were less than £30,000 per QALY gained. They

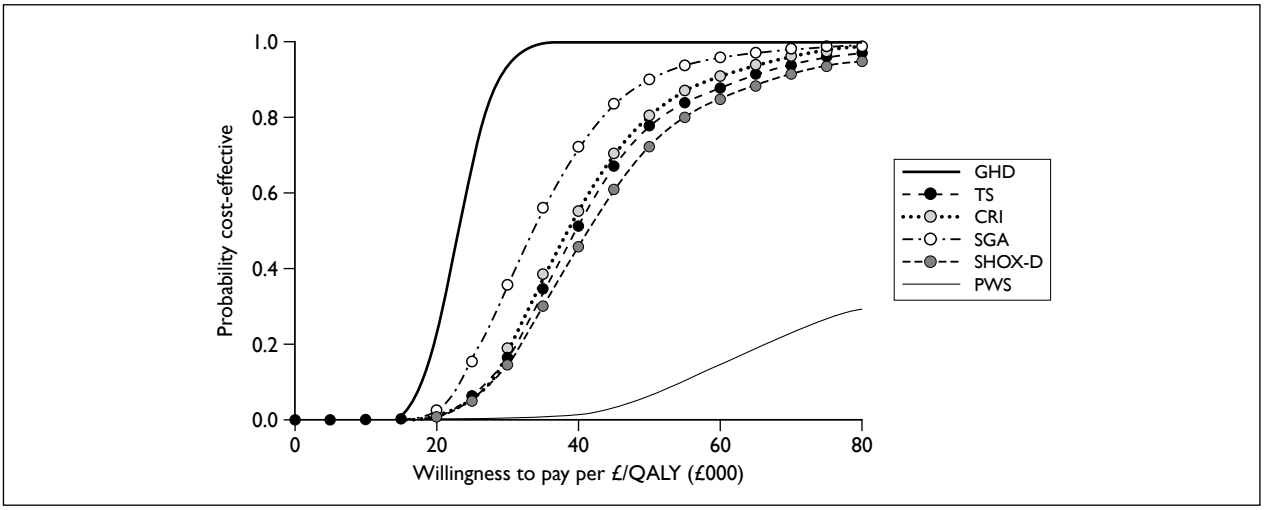

FIGURE 8 *Cost-effectiveness acceptability curve for rhGH treatment and no treatment for all the conditions.*

estimated ICERs of: £17,552 for GHD, £29,757 for TS, £32,540 for PWS, £15,962 for CRI, and £18,167 for SGA per QALY gained.

- The authors of this report developed an independent model, based upon the previous HTA report, and extended to consider longer term outcomes in order to estimate cost-effectiveness in terms of QALYs.
- From this independent model, the incremental cost per QALY estimates of rhGH compared to no treatment were: £23,196 for GHD, £39,460 for TS, £135,311 for PWS, £39,273 for CRI, £33,079 for SGA and £40,531 for SHOX-D. A further analysis was run for PWS, which included a lifelong improvement of body composition of 1.8 kg/m^2 BMI and an associated additional utility of 0.031. Under these assumptions there was a more favourable ICER of £54,800 per QALY gained.
- The effect of a range of parameter values in the economic model were evaluated in sensitivity analyses. The model results were found to be most sensitive to the discount rate used. When the previous NICE discount rate of 6% for costs and 1.5% for benefits was used, all conditions were cost-effective for a willingness-to-pay threshold of £30,000 per QALY. The model results are also sensitive to treatment start age and length, compliance and utility gain.
- The PSA estimated the probability of each of the conditions to be cost-effective at £30,000 to be: 95% for GHD, 19% for TS, 1% for PWS, 16% for CRI, 38% for SGA and 15% for SHOX-D.

Chapter 5

Assessment of factors relevant to the NHS and other parties

Guidance from NICE already recommends treatment with rhGH for children who have short stature that is associated with GHD, TS, PWS and CRI. Prescriptions associated with these conditions are therefore already part of primary care trusts' (PCTs') budgets, and are unlikely to increase significantly. However, advice from our clinical advisory group indicates that many families of children with PWS are now seeking treatment in infancy rather than in mid-childhood, and there may also be some increase in the number of prescriptions for GHD associated with oncology, as greater numbers of children are surviving childhood cancers. The newly licensed conditions SHOX-D and SGA are not covered by NICE guidance at the time of writing. Of the estimated 4758 UK patients currently receiving rhGH,[74] a breakdown by diagnosis for 3951 of them found that only 5.2% (205 patients) were receiving treatment for short stature that was associated with being born SGA. Advice from our clinical advisory group indicates that there is unlikely to be a large increase in prescriptions for children who were SGA.

The BSPED survey[74] did not include patients with SHOX-D, and it is not clear how many children with this condition are currently receiving treatment. Children with short stature due to unknown causes, or with other conditions, such as LWS, not currently covered by NICE guidance, might have an underlying SHOX-D. The availability of prescriptions to these new groups of patients could therefore have a budgetary impact. However, these conditions are very rare, so there is unlikely to be a large increase in people requiring treatment.

Chapter 6
Discussion

Statement of principal findings

Growth hormone deficiency

The use of rhGH as replacement therapy is well established in children who have a deficiency of the natural hormone. Therefore, most clinicians would consider it unethical to withhold treatment and there is a corresponding lack of RCT evidence in the literature. Only one trial[84] met the inclusion criteria for the review of rhGH in children with GHD, and this did not report FH. No details were reported on randomisation or allocation to treatment groups or blinding. The included patients ($n = 19$) were part of a larger study, which was generally poorly reported. After a year's treatment, HtSDS was statistically significantly higher in treated than in untreated children, although actual height was not reported. Children who received rhGH for 1 year had grown at a mean velocity of 2.7 cm/year faster than untreated children, which was statistically significantly faster. The low patient numbers mean that the evidence base for GHD is weak. Thus, there is very limited evidence of a slight increase in growth for children with GHD treated with GH, based on one study of mixed quality. Estimates of height gain in the previous HTA report[6] suggested FH gains of approximately 1.3–1.6 SDS (i.e. within 2 SDs of the normal mean) with rhGH treatment. However, these figures were from retrospective single-cohort studies that were not included in the present review.

The cost-effectiveness estimate of rhGH treatment in GHD is about £23,200 per QALY gained or £2,800 per centimetre gained. As there were no appropriate RCTs, the KIGS database was used for the estimate of height gain from rhGH.[153] This estimate for height gain was higher than for the other conditions. The previous HTA report[6] estimated a cost per centimetre gained of £6000 using 8 years' treatment compared to the 7 years used in our analysis and a slightly lower height gain from the KIGS database.[153] The cost-effectiveness estimate for the cohort of GHD who continue rhGH treatment into adulthood was £28,200 per QALY gained and £3400 per centimetre gained.

Turner syndrome

Six trials met the inclusion criteria for the review of GH for growth disturbance in patients with TS.[12,85,86,88–90] There is some evidence of effectiveness across all reported growth outcomes for girls with TS. However, these results are reported in studies of poor reporting and methodological quality, and in some cases of short duration. Of the six included studies, none of the included trials used an ITT analysis, one reported adequate randomisation to treatment groups,[85] one study described adequate concealment of treatment allocation,[85] and one adequately blinded the patient to treatment by administering placebo.[89]

In a large RCT that followed girls until FH, children in the rhGH group grew an average of 9.3 cm more from baseline than those in the untreated group.[86] In a study of younger children over 2 years, the difference was 7.6 cm.[85] Both of these were statistically significant results. Weight and WtSDS were found to be significantly greater in the treated group in one study of younger girls with TS.[85]

The searches for this study identified a new systematic review, conducted in Canada in 2007.[135] The review concluded that rhGH is effective in improving growth and FH in girls with TS, but found no evidence available in the clinical trials to suggest that rhGH improves QoL. The evidence discussed in the present review reflects this, as we found some evidence for increased height but no RCT evidence for improvements in QoL.

In summary, there is some evidence of effectiveness across all reported growth outcomes for girls with growth disturbance as a result of TS. There is also evidence of improved body composition. These results are reported in studies of poor reporting and methodological quality, and, in some cases, short duration, issues that may affect the validity of these findings. The previous HTA report[6] found that treated girls' FH was approximately 5 cm taller than untreated controls. The full publication of the large Canadian RCT[86] since the earlier HTA report[6] has shown a slightly larger difference in FH of 9.3 cm, as reported in the present review.

The cost-effectiveness estimate of rhGH treatment in TS is about £39,500 per QALY gained, or £6500 per centimetre gained. The estimate of cost-effectiveness compares with the estimate of about £130,000 per QALY (at current exchange rates) from CADTH,[135] which used a lower QoL benefit for rhGH of 0.042 than used in our analysis. The previous HTA report estimated a less favourable cost per centimetre gained of £16,000 as a lower estimate for height gain of 3.9 cm (compared with 9.3 cm) was used.

PWS

Eight small, rather poorly reported RCTs were included for PWS.[22,91–102] Participants' average ages ranged from 13 months to 10 years. Only the crossover study[102] used a placebo injection; the parallel-group RCTs had no treatment as the comparison arm.

Treated patients grew an average of 3–5 cm/year faster than untreated patients. Only one[22] of the studies reported actual change in height, with infants treated with rhGH growing an average of 6.1 cm more than untreated patients during 1 year. HtSDS was statistically significantly greater in treated patients than in untreated patients after 1 year (1–1.5 SDS higher) or 2 years of rhGH treatment (> 2 SDSs).

Four[22,95,96,102] trials reported a statistically significantly lower percentage of body fat (between 1% and 10% lower) in patients treated with rhGH than in those receiving placebo or no treatment. Three[93,95,96,102] trials reported that patients treated with rhGH had statistically significantly higher LBM or a larger improvement in LBM than untreated patients. Clinical advice indicates that rhGH characteristically increases LBM and reduces FM, although weight and BMI do not always change. This is reflected in the RCTs' findings, where changes in BMI were statistically significant in two studies,[91,102] there were no statistical differences in two other studies,[93,95,96] and results were similar between groups in the other two studies.[92,100,101]

In summary, patients treated with rhGH grew faster than untreated patients, and tended to have lower body fat percentages. Measurements in treated patients were reported to be statistically significantly better than in untreated patients in several studies, but the included studies were rather small and did not report power calculations or specify a primary outcome, so it is not clear whether they were adequately powered. These findings were comparable with growth and body composition outcomes reported in the previous HTA review.[6] However, the previous review also reported an uncontrolled, single-cohort study of 16 children, which suggested that rhGH treatment normalised FH.

The cost-effectiveness estimate of rhGH treatment in PWS is about £135,300 per QALY gained or £5,900 per centimetre gained. The ICER values for PWS were higher due to the majority of the height gain occurring within –2 HtSDS of average height where a lower utility gain is experienced. The previous HTA report[6] presented a cost per HtSDS gained of £40,815 and this compares with the current report's estimate of £44,718.

For PWS patients, there may be an additional health benefit associated with improved body composition, which may reduce the risk of diabetes and other morbidities. There is considerable difficulty with extrapolating between childhood treatment and adult morbidity and QoL.

In the clinical effectiveness review, RCTs for PWS reported mixed results for changes in BMI, with a maximum BMI difference of 1.8 between treated and untreated groups after 2 years' treatment. Assuming this change in BMI is maintained lifelong, and therefore there is an additional utility of 0.031, the cost-effectiveness of PWS would be £54,800 per QALY gained.

Chronic renal insufficiency

The evidence for rhGH in children with CRI came from six RCTs,[103–108] three of which had fewer than 25 participants,[103–105] and these might not have been sufficiently powered to test for a real difference between groups. Three[103,105,107] of the studies included children who had received renal transplants, and three[104,106,108] were for children with CRI who had not had a transplant.

One study[106] reported that treated children grew an average of 3.6 cm more than untreated children in 1 year, with HtSDS being statistically significantly better in treated children than in untreated children in two studies. Growth was statistically significantly faster in treated children than in untreated children, with between-group differences in velocity ranging from 3.2 cm/year to 4.2 cm/year in the parallel-group trials.[103,106–108] Children treated with rhGH showed statistically significant improvements in weight gain or WtSDS compared

with untreated children in three studies.[103,106,108] No QoL data were reported for prepubertal children with CRI. Two rhGH-treated patients in one study[91,102] experienced acute rejection episodes but both reversed after treatment with methylprednisolone. There were no SAEs reported.

In summary, treatment with rhGH led to small but statistically significant improvements in growth in children with CRI in two trials,[106,107] one of which included post-transport patients and the other included children with CRI who had not received a transplant. The previous HTA review[6] reported differences in HtSDS of approximately 0.8 SD and 1.3 SD for 1 and 2 years of treatment, respectively. The present review found slightly greater differences, favouring rhGH, of approximately 1 SDS for 1 year and just over 2 SDSs for 2 years' treatment.

The cost-effectiveness estimate of rhGH treatment in CRI is about £39,300 per QALY gained or £3,700 per centimetre gained. The previous HTA report estimated a cost per centimetre gained of £7,403 and this was based upon treatment for only 3 years compared with 5 years in this analysis. CRI has a lower QALY gain than the other conditions as we assumed that children with CRI would have a much shorter life expectancy than the general population due to their renal failure.

SGA

The licensing criteria for rhGH in children born SGA with growth disturbance state that eligible children need to have a current HtSDS ≤–2.5, a parental-adjusted HtSDS ≤–1, a birth weight/length SDS ≤–2 SDS, and have failed to show catch-up growth, defined as GV SDS < 0 during the previous year, by 4 years of age or later. None of the RCTs screened for this review met the inclusion criteria; these were therefore modified, retaining the current height and birth weight/length SDS criteria. Studies' inclusion criteria were required to state that no catch-up growth had taken place by 3 years of age but no specific criteria were used for this. The amended inclusion criteria did not require any definition of parental height.

This could affect the generalisability of the results as it is possible that the trials included children with a genetic factor for short stature. However, such children would presumably have a shorter target height than children whose parents are closer to the population mean. So children who meet the marketing authorisation may actually have a greater possibility for increased growth than those in the clinical trials. The other difference between the marketing authorisation criteria and the adapted inclusion criteria used in this review was that the included trials had children as young as 3 years of age, whereas the licensed population in the UK is children over the age of 4 years. It is possible that an early start for treatment could lead to better results than would be generalisable to the licensed population. However, in practice, the mean age of the children in the included studies was over 4 years of age for all the trials, so results should be generalisable to the licensed population.

Six trials met the modified inclusion criteria for this review of growth disturbance in children born SGA.[109–114] However, only one of the studies used the licensed dose for rhGH;[26] the others all used two or three times the licensed dose. Several trials did not meet the inclusion criteria for this review as they included patients with heights of < –2 SDS rather than < –2.5 SDS as stated in the marketing authorisation. These are listed in Appendix 5, with reason for exclusion given as 'wrong patient group'.

One trial reported AH,[111] and patients who had received rhGH gained an extra 4 cm of height compared with the control group. The difference between treated and untreated patients was statistically significant, as was the difference in adult HtSDS. Another study[114] reported that patients who received 0.033 mg/kg/day rhGH (the licensed dose) gained an additional 3.3 cm height compared with untreated children, and those who received 0.1 mg/kg/day gained 6.5 cm of additional height after 1 year's treatment. HtSDS was found to be greater in children treated with GH in the four studies that reported this outcome.[110,111,113,114]

Weight standard deviation score was higher in treated than in untreated groups after both 1 and 2 years of treatment in three studies reporting this outcome.[109,110,113] Lean mass was reported in one study, being greater in the treated group.

There is very limited evidence of a slight increase in AH gained in centimetres and SDS, and some evidence of an increase in HtSDS in children receiving rhGH in these studies. There is also limited evidence of improved body composition outcomes, including a statistically significant mean difference in WtSDS between treated and untreated children. This evidence is from trials that did not meet the licensed inclusion criteria exactly, used higher than the licensed dose in all but one

study, and were generally of poor quality, with few participants in many cases.

The cost-effectiveness estimate of rhGH treatment in SGA is about £33,000 per QALY gained or £9700 per centimetre gained. The height gain from the clinical review indicated that the gain for SGA was smaller than for the other conditions.

SHOX deficiency

Only one study[49] reported the use of rhGH in children with SHOX-D, and this was open label and generally poorly reported. Treated children grew approximately 2 cm/year faster than their untreated counterparts after 2 years of treatment, with a rate of 3.5 cm/year quicker than untreated children during the first year. After 2 years of treatment, children were approximately 6 cm taller than the control group and HtSDS was statistically significantly higher in treated than in untreated patients. Treatment with rhGH raised IGF-1 and IGFBP-3 levels to the upper-normal range, but there were no SAEs reported during the study.

The ICER estimate of rhGH treatment in SHOX-D is about £40,500 per QALY gained or £8000 per centimetre gained.

General discussion

This review updates a previous assessment report.[6] The criteria for this extended review were broadened to include children with SHOX-D or who were born SGA, as well as those with GHD, TS, PWS or CRI. In addition, we actively searched for all outcome measures including growth, body composition, biochemical markers and QoL.

The review focuses on increase in height as 'centimetres gained' and also as HtSDS, i.e. a comparison with average heights for the child's peer group. One goal of treatment is to prevent future loss of height, i.e. a child may remain short compared with their peers, but still be taller than they would have been without treatment. This is an important outcome, especially where attainment of average AH is sometimes an unrealistic possibility. Unrealistic expectations of height gain have been shown to affect QoL. For example, a French survey of young women with TS found that higher expectations from treatment were associated with lower QoL scores.[146] This review identified a paucity of evidence for QoL data in children receiving rhGH, and as such it is difficult to quantify the way in which a child's life can be changed by treatment other than in terms of centimetres of height gained.

In the previous HTA report,[6] a cost-effectiveness model was constructed that estimated lifetime treatment costs and benefits in terms of cost per centimetre gained. Those analyses are extended in the present report by including QoL factors in the economic modelling. The cost-effectiveness of rhGH has been evaluated by decision-analytical models using clinical trial data for the gain in height, apart from GHD, which used KIGS data.[153] The analysis presented both cost-per-QALY outcomes and cost per centimetre height gained for comparison with the previous HTA report, as shown in *Tables 58–60*.

The cost-effectiveness results from the SHTAC model for rhGH treatment vary widely between conditions, from about £23,000 for GHD to £135,000 for PWS per QALY gained. The ICERs for TS, CRI and SGA and SHOX-D were between about £33,000 and £40,500 per QALY gained. This indicates that rhGH is unlikely to be cost-effective for TS, PWS, CRI, SGA and SHOX-D at a willingness-to-pay threshold of £20,000 to £30,000. However, the results were sensitive to the discount rate used. All conditions, except PWS, would be cost-effective at a £30,000 willingness-to-pay threshold using the previous NICE discount rate of 6% for costs and 1.5% for benefits. For all the conditions, the model results are most sensitive to treatment start age and length, compliance and utility gain.

The cost-effectiveness results in the current report varied from those in the MS and the previous HTA report.[6] The incremental costs reported are generally consistent between the three models, with slight variations due to different dose, cost, and treatment start age and duration. In general, the results, presented in terms of centimetres gained, are more favourable in the current analyses than in the previous HTA report.[6] This is due to higher estimates in height gain and lower incremental costs in the current report. The height gains in the MS for GHD, PWS and SGA appear extremely high and inconsistent with those found in the review of clinical effectiveness. The ICERs in the MS are considerably more favourable than the current analysis, due to higher estimates of utility gain. The current analyses and the MS have chosen utility estimates from the same study.[150] However, the manufacturers have not taken these values from the regression analysis from this study. Instead they

TABLE 58 *Base-case results for the SHTAC cost-effectiveness model*

	GHD	TS	PWS	CRI	SGA	SHOX-D
Incremental QALYs	1.54	1.54	0.48	0.87	0.97	1.25
Incremental costs (£)	35,820	60,787	65,148	34,001	31,999	50,788
ICER (£/QALY)	23,196	39,460	135,311	39,273	33,079	40,531
Height gain (cm)	12.8	9.3	11.1	9.2	3.3	6.3
Cost per cm gain (£)	2798	6536	5869	3696	9697	8062

TABLE 59 *Base-case results for Pfizer*

	GHD	TS	PWS	CRI	SGA
Incremental QALYs	3.48	2.83	2.3	2.53	2.98
Incremental costs (£)	61,124	84,078	74,849	40,325	54,088
ICER (£/QALY)	17,552	29,757	32,540	15,962	18,167
Height gain (cm)	32.24	7.95	25.59	4.48	21.92
Cost per cm gain (£)	1896	10,576	2925	9001	2467

TABLE 60 *Base-case results for the previous GH HTA[6]*

	GHD	TS	PWS[a]	CRI
Incremental costs (£)	53,373	61,770	56,663	54,009
Height gain (cm)[b]	8.85	3.9	1.36	7.29
Cost per cm gain (£)	6029	15,997	40,815	7403

a Height gain expressed in terms of HtSDS gained.
b Discounted and adjusted for dropouts.

have used the relationship between EQ-5D and height without controlling for other factors.

In general, the incremental costs consist primarily of the rhGH drug costs, while other costs have little effect on model results. For the cost-effectiveness results, the key issue is the choice of utility values. The utility gain from rhGH is assumed to last over the patients' lifetimes and hence most of the QALY gain is in adulthood.

The results were sensitive to the length of treatment, for example by treating children from an earlier age. Current best practice is usually regarded as treating children as early as possible and this is likely to mean a longer treatment duration, which increases the cost of treatment and thus the ICER. It is unclear whether there will be an associated extra increase in height as most of the RCTs followed up children for a short time period, for less than 3 years. The previous HTA report suggested that height gains were greatest in the first year or two of treatment but stopping treatment before achieving FH generally leads to loss of growth gains, and so should not be advised.

The results were sensitive to the clinical effect. The treatment effect has been obtained, where possible, from the best-quality RCT available. However, as indicated in Chapter 3 (see Results), these trials were generally of poor quality and were not long-term trials. We also used the clinical treatment effect from the KIGS observational study but the results were largely similar to those reported from the RCTs.

There are limitations to the QoL estimates used in the model. There was a lack of good QoL studies conducted in the conditions of interest. Therefore, evidence based on these studies was not used in the main analysis. The utility estimates were based upon a study that estimated utility in the general adult population according to height. The study provides a common utility gain that could

be compared across all the conditions of interest. Furthermore, it also provided the possibility the outcomes from the RCTs identified in the clinical effectiveness could be used. However, this still remains a major source of uncertainty in the model.

The QoL gains were highest for individuals with lower starting height; for those with starting height < –2 HtSDS the QoL gain was minimal. For example, those with PWS had a starting height of –2 HtSDS, and so for this group of patients the health gain is small and therefore rhGH has high ICER values compared with no treatment. Patients with PWS may experience an improvement in body composition due to rhGH but this was difficult to quantify, especially in the long term, due to lack of long-term data.

The current analysis assumes in the base case that all children with the conditions of interest will have reduced life expectancy. This was based upon some evidence to suggest that these children would have a lower life expectancy due to increased risk of cardiovascular disease, due to abdominal obesity and raised blood pressure. Furthermore, those children with CRI have a much reduced life expectancy. We have used the end-stage renal disease mortality rates as a proxy in the absence of any available data for CRI. This may underestimate life expectancy and overestimate ICER values, as not all patients with CRI will go on to develop end-stage renal disease. Bengtsson[170] suggests that rhGH can rectify most of the cardiovascular abnormalities associated with GHD, although there appear to be few long-term observational studies that confirm this claim. Therefore, we assumed that rhGH will not increase life expectancy.

Apart from as a scenario analysis for PWS, the current analysis has not considered other benefits in addition to height gain within the model. The base case does not include possible benefits from changes in body composition, such as reduced risk of diabetes or cardiovascular disease, which may even result in increases in life expectancy. At this stage, these health gains would be purely speculative and it is not possible to verify if they exist or quantify them. It is also possible that there may be additional psychological benefits such as improved self-esteem.

Strengths and limitations of the assessment

Strengths

- The systematic review and economic evaluation were carried out independently, with no vested interest, and results are presented in a consistent and transparent manner.
- Evidence for clinical effectiveness came from RCT data, considered to be the highest level of evidence.
- The project followed established methodology and principles for conducting a systematic review. The methods used were defined a priori in a research protocol (see Appendix 1), and this was circulated to clinical experts and agreed with NICE before the project started.
- A clinical advisory group reviewed and commented on drafts of the protocol and the final report.
- A de novo economic model was developed following recognised guidelines.

Limitations and uncertainties

As specified in the protocol, the systematic review was restricted to RCTs, because these provide the highest level of evidence for clinical effectiveness. The majority of the studies included in this review lasted for between 6 months and 2 years, with very few continuing long term or to AH. Many of the trials excluded patients from analyses due to incomplete follow-up data or patient withdrawal. The short duration of the RCTs means it is difficult to assess effectiveness of rhGH in the context in which it would be prescribed in real life, i.e. for many years in some cases.

None of the RCTs included in this review reported any assessment of QoL issues, and the literature has conflicting conclusions regarding the effect of short stature on QoL. It is therefore difficult to make any judgement about the impact of rhGH on the quality of a person's daily life. Many of the children with the health conditions covered in this review will have a variety of other physical problems. While rhGH treatment can help to improve growth, height and body composition to some extent, QoL issues associated with underlying health problems will continue to affect some children.

Given the lack of QoL data for this patient group, it is possible that QALYs do not capture all the benefits of treatment for these children.

We did not identify any RCTs that met the original inclusion criteria for children born SGA. Following discussion with NICE, we therefore amended the criteria as detailed in Chapter 3 (Inclusion and data extraction process). The main difference was that we included studies of children who failed to show catch-up growth by 3 years of age (rather than 4 years) but did not specify exact criteria for this. Although this will have allowed slightly younger children to be included, the evidence presented in this report is still relevant to the UK SGA population. We also removed the reference to parental height, so it is possible that children in the included trials were naturally shorter than those in the general population. Only one of the included trials used the licensed dose, so results from the other five could overstate the effectiveness of rhGH treatment for this patient group.

We found only one RCT of rhGH in children with GHD,[84] so the evidence base for this condition is rather weak. However, the previous HTA report[6] also included observational studies for GHD, TS, PWS and CRI. Non-randomised evidence for this condition has therefore been summarised previously in the literature and is publicly available.

The included trials were generally poorly reported, and often had low numbers of participants. Primary outcomes were not clearly specified, and few studies reported power calculations. It is therefore possible that some trials were underpowered to detect 'real' differences between the treatment groups, even where such differences were reported to be statistically significant.

The included studies were heterogeneous in terms of participants, dosages and study duration. The results are therefore presented as a narrative summary, and it was not appropriate to meta-analyse the data.

The review did not assess publication bias or selective reporting of outcomes, so it is not possible to comment on the degree to which these affect the evidence base.

The economic model used the suggested doses given in the BNF.[165] However, the RCTs used doses that were sometimes outside the licensed doses.

Chapter 7
Conclusions

Implications for service provision

Guidance from NICE already recommends treatment with rhGH for children who have short stature that is associated with GHD, TS, PWS and CRI, so prescriptions associated with these conditions are already in place. Advice from our clinical advisory group indicates that there may be a trend towards earlier prescribing for PWS, and many families are now seeking treatment in infancy rather than in mid-childhood. There may also be an increase in treatment associated with acquired GHD as the proportion of children surviving cancers and associated treatment increases.

The newly licensed conditions SHOX-D and SGA are not covered by NICE guidance at the time of writing. Of the estimated 4758 UK patients currently receiving rhGH, only approximately 5% were receiving treatment for short stature associated with being born SGA. A recent survey by BSPED found that there had been little change in the number of prescriptions in recent years.[74]

It is not clear how many children with SHOX-D are currently receiving treatment. The availability of prescriptions to these new groups of patients could theoretically have a budgetary impact. However, the number of children with this condition is small so there is unlikely to be a large increase in prescriptions.

Suggested research priorities

- There is a lack of RCT evidence for the effects of rhGH treatment on FH, as it is impractical to run such long studies. However, longer studies beyond 2 years would be helpful in improving the evidence base for long-term treatment, even if near-FH rather than final AH were reported.
- None of the included RCTs reported measures of HRQoL. There is a need to develop and validate a standardised QoL assessment that is specifically designed for children and adults. Future RCTs should include this as an outcome measure in order to assess the impact of small increases in height on daily QoL. This would also be helpful for developing utilities for cost-effectiveness analysis of rhGH treatment for these conditions.
- Good-quality trials of continuation/discontinuation of rhGH in children who have finished growing are required, which report consistent and clinically relevant outcomes, and which are standardised in terms of dose.
- Good-quality trials are needed of GH in children born SGA, where the children included and the dose administered match the licensing criteria.
- It was difficult to establish when treatment is initiated for the different disease areas, as this depends on age at diagnosis. Further work to survey national practices or policies would be helpful in terms of providing information for future updates of this review and economic evaluation.
- Although figures for the use of renal replacement therapy are available, there is little epidemiological data available on the incidence and prevalence of CRI. Epidemiological studies would therefore be useful.
- Good-quality observational studies are needed, which show the long-term effects of rhGH, particularly the effect of treatment on body composition, psychological benefits (such as improved self-esteem), long-term morbidities (such as diabetes or cardiovascular disease) and life expectancy, particularly for PWS.
- Further research is also necessary to establish the QoL benefits associated with rhGH in adults and children with these conditions. Well-conducted qualitative studies could provide data to inform future developments in this area.
- Monitoring of AEs associated with long-term rhGH treatment is required, with a central register to record the effects of long-term elevations in IGF-1 levels.
- More research is needed to assess the long-term effect on QoL for individuals who had rhGH as children.

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Appendix 1
Protocol methods

A review of the evidence for the clinical effectiveness and cost-effectiveness of somatropin will be undertaken systematically following standard guidelines from the NHS Centre for Reviews and Dissemination (CRD).[83] An expert advisory group of clinical experts and service users where appropriate will support the review team at key stages of the project.

Search strategy

A search strategy will be developed and tested by an experienced information scientist. The strategy will be designed to identify studies reporting clinical effectiveness, cost-effectiveness, HRQoL, resource use and costs, epidemiology and natural history.

The draft clinical effectiveness search strategy for MEDLINE is shown in Appendix 2. This will be adapted for other databases.

A number of electronic databases will be searched including: The Cochrane Database of Systematic Reviews (CDSR); The Cochrane Central Register of Controlled Trials; NHS CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE) and the NHS Economic Evaluation Database (NHS EED); MEDLINE (Ovid); EMBASE (Ovid); National Research Register; Current Controlled Trials; ISI Proceedings; Web of Science; and BIOSIS. Bibliographies of related papers will be assessed for relevant studies where possible.

The MSs to NICE will be assessed for any additional studies that meet the inclusion criteria.

Experts will be contacted to identify additional published and unpublished references.

Searches will be carried out from the inception date of the database. Although this will involve duplication of searches carried out for the previous review, it will be necessary to identify trials reporting body composition as an outcome measure, as these may not have been identified for all conditions in the previous review. For databases of abstracts and conference presentations searches will only be carried out for the past 2 years to capture any research that has not yet been fully published. All searches will be limited to the English language, and will be updated around February 2009.

Inclusion and exclusion criteria

Patients

Children with growth disturbance, as per licensed indication for each preparation available.

Interventions

Recombinant human growth hormone (somatropin).

Comparators

Management strategies without somatropin.

Outcomes

The following outcomes will be included, where data are available:

- final height gained
- height standard deviation score
- growth velocity
- growth velocity standard deviation score
- body composition, and biochemical/metabolic markers as appropriate
- adverse effects of treatment
- HRQoL.

Types of studies

- Fully published RCTs or systematic reviews of RCTs will be included. Indicators of a systematic review include: explicit search strategy, inclusion criteria, data extraction and assessment of quality. Where we judge it necessary and appropriate, we will consider the inclusion of evidence from other non-randomised studies. Full economic evaluations (cost-effectiveness studies, cost–utility studies, cost–benefit studies) and reviews of economic evaluations will be included in the review of cost-effectiveness.

- Studies published only as abstracts or conference presentations will be included only in the primary analysis of clinical effectiveness and cost-effectiveness if sufficient details are presented to allow an appraisal of the methodology and assessment of results.
- Non-English language studies will be excluded.

Inclusion and data extraction process

- Two reviewers will assess the titles and abstracts of studies identified by the search strategy for potential eligibility.
- The full text of relevant papers will be requested for further assessment, and these will be screened independently by two reviewers.
- Data will be extracted by one reviewer using a standard data extraction form and checked by a second reviewer.
- At each stage, any discrepancy will be resolved by discussion, with involvement of a third reviewer where necessary.

Quality assessment

The quality of included clinical effectiveness studies will be assessed using NHS CRD (University of York) criteria.[83] The methodological quality of the economic evaluations will be assessed using accepted frameworks such as the international consensus-developed list of criteria developed by Evers and colleagues[171] and Drummond and colleagues.[141] For any studies based on decision models we will also make use of the checklist for assessing good practice in decision-analytical modelling (Philips and colleagues).[172]

Quality criteria will be applied by one reviewer and checked by a second reviewer, with differences in opinion resolved by discussion and involvement of a third reviewer where necessary.

Methods of analysis/synthesis

- Clinical effectiveness and cost-effectiveness studies will be synthesised through a narrative review with tabulation of results of included studies.
- Where data are of sufficient quality and homogeneity, a meta-analysis of the clinical effectiveness studies will be performed using appropriate software.
- Quality-of-life studies will be synthesised using the same methods as above, i.e. narrative review and meta-analysis as appropriate.

Appendix 2

Literature search strategies

Search strategies for MEDLINE are shown below. Strategies for other databases are available from the authors.

rhGH clinical effectiveness

MEDLINE: all years 1950–2008, search date: 23 June 2009.

1. growth disorders/
2. growth failure.ti,ab.
3. growth deficien*.ti,ab.
4. Prader-Willi Syndrome/
5. prader-willi.ti,ab.
6. turner syndrome/
7. (Turner*2 adj syndrome).ti,ab.
8. growth hormone deficien*.ti,ab.
9. GH deficien*.ti,ab.
10. GHD.ti,ab.
11. exp renal insufficiency chronic/
12. (chronic adj2 (renal or kidney*) adj2 (failure or insufficien*)).ti,ab.
13. (CRI or CRF).ti,ab.
14. "small for gestational age".ti,ab.
15. "short for gestational age".ti,ab.
16. infant small for gestational age/
17. "short stature homeobox-containing gene". ti,ab.
18. "short stature homeobox".ti,ab.
19. SGA.ti,ab.
20. SHOX.ti,ab.
21. PHOG.ti,ab.
22. "Pseudoautosomal homeobox-containing osteogenic gene".ti,ab.
23. or/1-22
24. human growth hormone/or growth hormone/
25. (somatropin* or somatotropin* or somatotrophin* or genotropin* or saizen* or zomacton* or nutropin* or norditropin* or omnitrope* or humatrope*).ti,ab.
26. 24 or 25
27. exp child/or exp adolescent/or exp infant/
28. child preschool/
29. (child* or infant* or adolescen* or girl* or boy* or prepubert* or pre-pubert*).ti,ab.
30. or/27-29
31. 23 and 26 and 30
32. randomized controlled trial.pt.
33. controlled clinical trial.pt.
34. exp Randomized Controlled Trial/
35. exp Randomized Controlled Trials as Topic/
36. exp random allocation/
37. Double-Blind Method/
38. Single-Blind Method/
39. ((singl* or doubl* or trebl*) adj9 (blind* or mask*)).ti,ab.
40. placebo*.ti,ab,sh.
41. random*.ti,ab.
42. (medline or medlars or embase or scisearch or cinahl).ti,ab,sh.
43. (systematic* adj5 review*).mp.
44. (systematic adj5 overview*).mp.
45. (methodolog* adj5 review).mp.
46. (methodolog* adj5 overview).mp.
47. (methodolog* adj5 research*).mp.
48. meta analysis.pt.
49. meta-analysis.sh.
50. (meta-analys* or meta analys* or metaanalys*). mp.
51. ((hand adj5 search*) or (manual* adj5 search)). mp.
52. (electronic* database* or bibliographic* database* or computer* database* or online database*).mp.
53. (Health Technology Assessment* or Medical Technology Assessment*).ti,ab,in.
54. or/32-53
55. 31 and 54
56. limit 55 to (english language and humans)
57. kidney transplantation/
58. (renal or kidney*).ti,ab.
59. 57 or 58
60. 26 and 30 and 54 and 59
61. 60 not 56
62. growth hormone/or human growth hormone/
63. 30 and 54 and 59 and 62
64. 63 not 56
65. 61 or 63
66. limit 65 to (english language and humans)
67. 55 or 66
68. (editorial or letter or comment).pt.
69. 67 not 68
70. from 69 keep 1-13,21-22

Cost-effectiveness

MEDLINE: all years 1950 to current, search date 24 June 2009.

1. exp economics/
2. exp economics hospital/
3. exp economics pharmaceutical/
4. exp economics nursing/
5. exp economics medical/
6. exp "Costs and Cost Analysis"/
7. Cost Benefit Analysis/
8. value of life/
9. exp models economic/
10. exp fees/and charges/
11. exp budgets/
12. (value adj2 (money or monetary)).tw.
13. (economic adj2 burden).tw.
14. (expenditure* not energy).tw.
15. budget*.tw.
16. (economic* or price* or pricing or financ* or "fee" or "fees" or pharmacoeconomic* or pharma economic* or pharmaco-economic*).tw.
17. (decision adj1 (tree* or analys* or model*)).tw.
18. Resource Allocation/
19. (unit cost or unit-cost or unit-costs or unit costs or drug cost or drug costs or hospital costs or health-care costs or health care cost or medical cost or medical costs).tw.
20. ((value or values or valuation) adj2 (money or monetary or life or lives or costs or cost)).tw.
21. (cost adj2 (util* or effective* or efficac* or benefit* or consequence* or analys* or minimi* or saving* or breakdown* or lowering or estimate* or variable* or allocation* or control* or illness* or affordable* or instrument* or technolog* or fee* or charge* or charges)).tw.
22. Markov Chains/
23. Monte Carlo Method/
24. exp Decision Support Techniques/
25. (resource adj2 (use* or utili* or allocat*)).tw.
26. or/1-25
27. growth disorders/
28. growth failure.ti,ab.
29. growth deficien*.ti,ab.
30. Prader-Willi Syndrome/
31. prader-willi.ti,ab.
32. turner syndrome/
33. (Turner*2 adj syndrome).ti,ab.
34. growth hormone deficien*.ti,ab.
35. GH deficien*.ti,ab.
36. GHD.ti,ab.
37. exp renal insufficiency chronic/
38. (chronic adj2 (renal or kidney*) adj2 (failure or insufficien*)).ti,ab.
39. (CRI or CRF).ti,ab.
40. "small for gestational age".ti,ab.
41. "short for gestational age".ti,ab.
42. infant small for gestational age/
43. "short stature homeobox-containing gene".ti,ab.
44. "short stature homeobox".ti,ab.
45. SGA.ti,ab.
46. (SHOX or PHOG).ti,ab.
47. "idiopathic short stature".ti,ab.
48. "Pseudoautosomal homeobox-containing osteogenic gene".ti,ab.
49. or/27-48
50. human growth hormone/
51. (somatropin* or somatotropin* or somatotrophin* or genotropin* or saizen* or zomacton* or nutropin* or norditropin* or omnitrope* or humatrope*).ti,ab.
52. or/50–51
53. 26 and 49 and 52
54. growth disorders/ec or growth hormone/ec
55. 53 or 54
56. limit 55 to (human and english language)
57. (editorial or letter).pt.
58. 56 not 57
59. "growth hormone".ti,ab.
60. 26 and 49 and 59
61. 58 or 60
62. limit 61 to (english language and humans)

Quality-of-life searches

Searched 30 September 2008.

1. "Quality of Life"/
2. (hql or hqol or "h qol" or hrqol or "hr qol").ti,ab.
3. ("hye" or "hyes").ti,ab.
4. (euroqol or "euro qol" or "eq5d" or "eq 5d").ti,ab.
5. Quality-Adjusted Life Year/
6. "quality adjusted life".ti,ab.
7. (qaly$or qald$or qale$or qtime$).ti,ab.
8. "disability adjusted life".ti,ab.
9. "quality of wellbeing".ti,ab.
10. "quality of well being".ti,ab.
11. daly$.ti,ab.
12. (SF-36 or SF-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.
13. health$year$equivalent$.tw.
14. disutil*.ti,ab.
15. "Value of Life"/
16. rosser.ti,ab.

17. willingness to pay.tw.
18. standard gamble$.tw.
19. time trade off.tw.
20. time tradeoff.tw.
21. health utilit*.ab.
22. exp Health Status/
23. exp Health Status Indicators/
24. "Activities of Daily Living"/
25. "Patient Acceptance of Health Care"/
26. "health-related quality of living".ti,ab.
27. "health-related quality of life".ti,ab.
28. (patient* adj2 (preference* or satisfaction or acceptance)).ti,ab.
29. (health adj ("state" or "status" or "states")).ti,ab.
30. or/1-29
31. growth disorders/
32. growth failure.ti,ab.
33. growth deficien*.ti,ab.
34. Prader-Willi Syndrome/
35. prader-willi.ti,ab.
36. turner syndrome/
37. (Turner*2 adj syndrome).ti,ab.
38. growth hormone deficien*.ti,ab.
39. GH deficien*.ti,ab.
40. GHD.ti,ab.
41. exp renal insufficiency chronic/
42. (chronic adj2 (renal or kidney*) adj2 (failure or insufficien*)).ti,ab.
43. (CRI or CRF).ti,ab.
44. "small for gestational age".ti,ab.
45. "short for gestational age".ti,ab.
46. infant small for gestational age/
47. "short stature homeobox-containing gene".ti,ab.
48. "short stature homeobox".ti,ab.
49. SGA.ti,ab.
50. SHOX.ti,ab.
51. PHOG.ti,ab.
52. "Pseudoautosomal homeobox-containing osteogenic gene".ti,ab.
53. or/31-52
54. human growth hormone/
55. (somatropin* or somatotropin* or somatotrophin* or genotropin* or saizen* or zomacton* or nutropin* or norditropin* or omnitrope* or humatrope*).ti,ab.
56. 54 or 55
57. 30 and 53 and 56
58. limit 57 to (english language and humans)
59. (edtorial or letter or comment).pt.
60. 58 not 59
61. HIV.ti,ab.
62. 60 not 61

Appendix 3

Quality assessment

Criteria	Judgement
1. Was the assignment to the treatment groups really random?	Adequate/partial/inadequate/unknown
2. Was the treatment allocation concealed?	Adequate/inadequate/unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported/unknown
4. Were the eligibility criteria specified?	Adequate/partial/inadequate/unknown
5. Were outcome assessors blinded to the treatment allocation?	Adequate/inadequate/unknown
6. Was the care provider blinded?	Adequate/partial/inadequate/unknown
7. Was the patient blinded?	Adequate/partial/inadequate/unknown
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate/partial/inadequate/unknown
9. Did the analyses include an ITT analysis?	Adequate/inadequate

Appendix 4

Data extraction tables

GHD data extraction forms

Reference and design	Intervention	Participants	Outcome measures
Soliman *et al.* 1996[84] *Country*: Egypt *Study design*: RCT *Number of centres*: not stated *Funding*: not reported	(*Group 1 not data extracted as dose–response arm*) 1a. GH 30 U/m^2/week as a daily s.c. dose 1b. GH 15 U/m^2/week as a daily s.c. dose 2a. GH 15 U/m^2/week as a daily s.c. dose 2b. No treatment (*Group 3 not data extracted as not GHD*) 3a. GH 15 U/m^2/week as a daily s.c. dose 3b. No treatment *Duration of treatment*: 1 year	*Target population*: prepubertal children with GHD *Number of participants*: total 77 (19 in group 2) 1. *Group 1*: 34 children with peak GH response to provocation < 7 μg (not data extracted as dose–response arm) 2. *Group 2*: 19 children with peak GH response to provocation between 7 and 10 μg/l (2a: 9, 2b: 10) 3. *Group 3*: 24 children with normal peak GH response (not data extracted as not GHD) *Sample attrition/dropout*: none reported for group 2 *Inclusion criteria for study entry*: Inclusion criteria not clearly stated Subjects were prepubertal, and BA was < 10 years at initiation of therapy, and < 3rd percentile height for chronological age None of the children had haemoglobinopathy, hepatic or renal impairment. No child had a reduced weight relative to height, other systemic disease, history of head trauma or cranial irradiation, malnutrition, psychosocial dwarfism or hypothyroidism	*Primary outcomes*: not stated *Secondary outcomes*: GV, HtSDS, BA delay, IGF-1, glucose, FT4, TSH, GH *Method of assessing outcomes*: height measured on a stadiometer, normal population data were according to Tanner, skeletal age examined yearly according to Greulich and Pyle, height determined at 3-month intervals, and height GV calculated from height at beginning and end of therapy. HtSDS calculated using age-matched population mean height and SD

BA, bone age; FT4, free thyroxine; TSH, thyroid-stimulating hormone; s.c., subcutaneous; U, unit.

Characteristics of participants: growth parameters and hormonal data

Characteristic	GH 15 U/m^2/week (*n* = 9)	No treatment (*n* = 10)	Overall
Age (years)	7.1 ± 1.9	6.6 ± 1.6	6.8 ± 2.1
GV (cm/years)	3.65 ± 1.1	4.3 ± 1	3.9 ± 1.1
HtSDS (–)	3.4 ± 0.8	3.1 ± 0.6	2.8 ± 1
BA delay	2.1 ± 0.8	1.8 ± 0.65	1.9 ± 1
GH peak after clonidine (μg/l)			8.4 ± 1.3
GH peak after insulin (μg/l)			8.1 ± 1.6
IGF-1 (ng/ml)	58.5 ± 42.5	52.4 ± 21.3	59 ± 33
Glucose (mmol/l) 0 min	3.6 ± 0.6	4.1 ± 0.5	
Glucose (mmol/l) 120 min	5.4 ± 0.5	4.9 ± 0.45	

FT4 (pmol/l)	16.5 ± 2.1	14.6 ± 1.4	
TSH (μIU/ml)	1.4 ± 0.4	1.6 ± 0.3	

Results

Outcomes	**GH 15 U/m²/week (*n* = 9)**	**No treatment (*n* = 10)**	***p*-value**
GV (cm/years)	8.4 ± 1.4[a,b]	5.7 ± 1.8	
HtSDS (–)	2.3 ± 0.45[a,b]	2.8 ± 0.45	
BA delay	2.25 ± 0.8	1.93 ± 0.75	
GH peak after clonidine (μg/l)	8.6 ± 1.1	8.2 ± 1	
GH peak after insulin (μg/l)	8.5 ± 1.4	8.3 ± 1.2	
IGF-1 (ng/ml)	91.2 ± 30.4[a,b]	49.4 ± 19	
Glucose (mmol/l) 0 min	4.3 ± 0.6	4.5 ± 0.8	
Glucose (mmol/l) 120 min	5.1 ± 0.4	4.4 ± 0.6	
FT4 (pmol/l)	17.4 ± 2.2	15.6 ± 1.4	
TSH (μIU/ml)	2.4 ± 0.5	2.2 ± 0.5	

a $p < 0.05$ before vs after 1 year.
b $p < 0.05$ 'a' vs 'b' subgroups.

Methodological comments

Allocation to treatment groups: Three groups of children were identified and recruited according to their peak GH response to provocation then subsequently allocated 'at random' to two subgroups within that group. No further details on randomisation were provided.

Blinding: Blinding is not reported.

Comparability of treatment groups: Treatment groups appear comparable, but no *p*-value is reported.

Method of data analysis: Data are presented as mean ± SD.

Sample size/power calculation: None reported.

Attrition/dropout: None reported for group 2, although *n* = 4 excluded from group 1b due to lack of compliance.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Inadequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Inadequate
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Adequate
10. Were withdrawals and dropouts completely described?	Adequate

TS data extraction forms

Reference and design	Intervention	Participants	Outcome measures
Quigley *et al.* 2002[12] *Country*: USA *Study design*: RCT, dose response *Number of centres*: 50 *Funding*: author/group appear to be employed by Eli Lilly & Co.	1. Growth hormone (GH) (Humatrope) 0.27 mg/kg/week, with oral placebo (GH 0.27/Pla) 2. GH 0.27 mg/kg/week with LDE (GH 0.27/LDE) (not data extracted) 3. GH 0.36 mg/kg/week with oral placebo (GH 0.36/Pla) 4. GH 0.36 mg/kg/week with LDE (GH 0.36/LDE) (not data extracted) 5. Placebo injection with oral placebo (Pla/Pla) *GH/placebo injections*: s.c., in equally divided doses, initially 3 times per week; oral placebo given daily *Duration of treatment*: Placebo group for first 18 months of the study; subjects completed the full study when HV was less than 2 cm/year and BA ≥ 15 year *Other interventions used*: Ethinyl E2 daily, 25–200 ng/kg/day depending on age	*Target population*: prepubertal girls with TS (first 18 months of the study data extracted, as placebo group joined group 3 after this time) *Number of participants*: total = 232, stratified by age and randomised. 224 completed 180 days' active therapy and have baseline data reported 1. 45 2. 47 3. 49 4. 42 5. 41 *Sample attrition/dropout*: No further details on withdrawals are given ($n = 8$) *Inclusion criteria for study entry*: Karyotypically proven TS ≥ 5 years old BA ≤ 12 years Prepubertal < 10th percentile for height on NCHS standard HV < 6 cm/year *Exclusion criteria for study entry*: Presence of any Y chromosomal component in karyotype Concurrent treatment with agent that might influence growth Clinically significant systemic illness	*Primary outcomes*: NFH (cm) (no placebo group), changes in HtSDS from baseline to end point (no placebo group) *Secondary outcomes*: changes in: BA, height (cm), impact of GH dose, effect of LDE *Method of assessing outcomes*: subjects were assessed every 3 months for first 6 years then 6 months until study completion: height using stadiometer, weight and pubertal status. Blood chemistry and thyroid function tests at every visit. Glucose and insulin every 6 months. IGF-1 every 3 months for first 18 months, at 24 months then annually. X-ray of the left wrist and hand for BA performed every 6 months for 24 months then annually. HtSDS calculated with reference to general population and to Lyon TS growth data *Length of follow-up*: 18 months for placebo-controlled study

BA, bone age; LDE, low-dose estrogen; NCHS, National Center for Health Statistics; Pla, placebo.

Characteristics of participants

Baseline (mean ± SD)	GH 0.27/Pla ($n = 45$)	GH 0.36/Pla ($n = 49$)	Pla/Pla ($n = 41$)
Age (years)	9.7 ± 2.7	9.8 ± 2.9	9.4 ± 2.7
BA (years)	7.9 ± 2.3	7.9 ± 2.3	7.9 ± 2.4
Height (cm)	119.2 ± 13.6	118.6 ± 12.5	117.6 ± 13.6
HtSDS (NCHS)	–2.7 ± 0.9	–2.9 ± 0.9	–2.9 ± 0.9
HtSDS (NCHS)	0.3 ± 1.0	0.2 ± 0.8	0.2 ± 0.9
Mid-parental height (cm)	164.6 ± 6.1	162.9 ± 5.9	162.4 ± 5.0
Mid-parental height SD score	0.27 ± 0.93	0.00 ± 0.91	–0.08 ± 0.77
Prestudy GV	4.1 ± 1.2	4.0 ± 1.2	4.1 ± 1.2

Results

Outcomes	GH 0.27/Pla ($n = 45$)	GH 0.36/Pla ($n = 49$)	Pla/Pla ($n = 41$)	*p*-value
GV 0–18 months (cm/year)	6.6 ± 1.1	6.8 ± 1.1	4.2 ± 1.1	< 0.001[a]

a Compared with placebo.
The 6-monthly GV results are presented on a difficult-to-read graph – could not data extract. Authors state that HV declined slightly in all GH groups after the initial peak but was significantly greater than that of the placebo group.

Adverse effects	GH	Placebo	*p*-value
Otitis media (occurrence/ worsening)	54/186 (29%)	6/46 (13%)	0.037

Comments

Ear pain and ear disorder were not different in frequency between groups. Otitis media was reported in 41% of subjects overall, ear pain in 27% and hypothyroidism in 16% and oedema in 3%. There were no disorders that occurred significantly more frequently in subjects receiving the higher dose. Serious AEs (defined as death, life-threatening cancer, hospitalisation, permanently disabling, drug overdose or resulting in congenital anomaly in an offspring) were reported for 47 out of 232 subjects; 31/47 of these were hospitalised for surgical procedures, either for elective management of conditions associated with TS or related to accidental injury; 11 were hospitalised for other reasons: infectious illness/ dehydration $n = 5$, psychosis $n = 1$, abnormal liver function tests $n = 1$, vaginal bleeding $n = 1$, haematuria $n = 1$, cardiac failure $n = 1$, hypertension $n = 1$; and the remaining five were reported to have accidentally overdosed on the study drug. AEs that were considered unexpected and possibly related to the study drug were reported for 5/232 subjects (2%): hypertension $n = 2$ (in 1 subject this had been present for 11 years), surgical procedures $n = 2$, scoliosis $n = 1$. There were no reports of deaths, cancer or neoplasia.

Methodological comments

Allocation to treatment groups: Authors state that subjects were randomised in a double blind fashion, but no further details are given.

Blinding: States double blind. Placebo is given by injection. BA radiographs were read by a single observer who was blinded to treatment status.

Comparability of treatment groups: Treatment groups appear similar at baseline.

Method of data analysis: Data obtained during the initial 18-month placebo-controlled phase are reported for each of the five original randomisation groups. ITT performed for all subjects who received 180 days of active treatment.

Sample size/power calculation: Not reported.

Attrition/dropout: Withdrawals not discussed; eight patients were randomised but did not complete treatment.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Unknown
7. Was the patient blinded?	Partial
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Inadequate

Reference and design	Intervention	Participants	Outcome measures
Stephure and The Canadian Growth Hormone Advisory Committee[86] and Rovet *et al.* 1993[87] (no extractable data, so no further information extracted here) *Year*: 2005 *Country*: Canada *Study design*: RCT *Number of centres*: multicentre *Funding*: Eli Lilly Canada Inc.	*Intervention*: (GH group) rhGH (Humatrope, Eli Lilly Canada) by daily s.c.i. 6 times weekly (0.30 mg/kg/week, maximum weekly dose 15 mg) *Control*: no GH treatment *Other interventions used*: girls with primary ovarian failure received standardised sex steroid replacement: ethinyloestradiol 2.5 μg/day at age 13, 5.0 μg/day at age 14, and 2.0 μg on days 1–24 with medroxyprogesterone acetate 10 mg on days 15–24 of each month at age 15 and thereafter	*Target population*: prepubertal girls, aged 7–13 years, with a diagnosis of TS documented by peripheral blood karyotype *Number of participants*: 154 (95 in Rovet) prepubertal girls *Intervention*: 76 (51 in Rovet) *Control*: 78 (44 in Rovet) *Sample attrition/dropout:* Overall, 15 withdrew from GH; 35 from control: addendum follow-up 8 from GH; 9 from control 1997 follow-up only, 5 from GH; 13 from control core protocol data only, 2 from GH; 13 from control *Sample crossovers*: N/A *Inclusion criteria for study entry*: Height less than the 10th percentile for chronological age on the growth charts of the NCHS of the USA An annualised GV less than 6.0 cm/year during a 6-month prerandomisation period Diagnosis of TS documented by peripheral blood karyotype. Phenotypic females with identifiable Y chromosome eligible to participate if had undergone prior gonadectomy *Exclusion criteria for study entry*: Clinically significant chronic systemic illness, prior treatment with GH, anabolic steroids, estrogens, craniospinal radiation or inadequate thyroxine replacement for hypothyroidism were excluded A spontaneous or stimulated serum GH level was 8.0 μg/l or greater in all subjects	*Primary outcomes*: BA (years), height (cm), HtSDS (age specific/adult Turner), change in height (cm), change in HtSDS (age-specific Turner) *Secondary outcomes*: *Method of assessing outcomes*: routine haematology, biochemistry and thyroid function studies were monitored every 3 months (every 6 in control after first year), BA interpreted by central reader using Greulich and Pyle annually. Age-specific and AH SD scores (SDS, height SD score) and the change in height SD scores at protocol completion and follow-up relative to baseline were calculated according to published standards for girls with TS *Length of follow-up*: subjects returned for follow-up every 3 months until study completion, protocol completion criteria required annualised GV less than 2 cm/year and BA 14 years or greater Addendum follow-up = height and safety follow-up at least 1 year following latest core protocol visit

Characteristics of participants (mean ± SD)

Baseline characteristics	GH ($n = 61$)	No treatment ($n = 43$)	*p*-value
Age	10.3 ± 1.8	10.9 ± 1.7	
Baseline BA (years)	8.8 ± 1.4	8.9 ± 1.3	
Baseline height (cm)	119.1 ± 8.5	122.0 ± 7.8	
Baseline HtSDS (age-specific Turner)	–0.2 ± 0.9	–0.1 ± 0.8	
Adjusted mid-parental height (cm)[a]	160.7 ± 6.2	159.3 ± 5.8	
45,X karyotype (%)	62.3	58.1	

Comments

a Adjusted mid-parental height = [(father height – 13 cm) + mother height]/2.
Baseline results for patients who completed the protocol. Baseline data for patients who also had follow-up are very similar. No baseline characteristics differed at $p < 0.05$.

Results: protocol completion characteristics (mean ± SD)

Primary outcomes	GH (*n* = 61)	No treatment (*n* = 43)	GH effect:[b] mean (95% CI)	*p*-value
Age (years)	16.0 ± 0.8	16.5 ± 0.9	[c]	0.002
Time since randomisation (years)	5.7 ± 1.6	5.7 ± 1.6		
BA (years)	14.4 ± 0.8	14.5 ± 0.9	–0.1 (0.5 to 0.3)	ns
Height (cm)	147.5 ± 6.1	141.0 ± 5.4	7.2 (6.0 to 8.4)	< 0.001
HtSDS (age-specific Turner)	1.4 ± 1.0	0.2 ± 0.9	1.2 (1.0 to 1.5)	< 0.001
HtSDS (adult Turner)	0.7 ± 0.9	–0.3 ± 0.8	1.1 (0.8 to 1.3)	< 0.001
Change in height (cm)	28.3 ± 8.9	19.0 ± 6.1	7.2 (6.0 to 8.3)	< 0.001
Change in HtSDS (age-specific Turner)	1.6 ± 0.6	0.3 ± 0.4	1.3 (1.1 to 1.5)	< 0.001

ns, not significant.
b ANCOVA model with treatment, baseline HtSDS, baseline HtSDS by treatment interaction, baseline age, and baseline age by treatment interaction. Explanatory variables were removed from the model when not significant. GH effect is estimated by differences of least-squares means for treatment.
c Age at protocol completion was significantly different between control and GH, p=0.002, this reflects the similar numerical difference at baseline and completion, and the lower SD at completion due to the narrower age range.
Protocol completion criteria required an annualised GV of less than 2 cm/year and a BA of 14 years or greater.

Results: addendum follow-up characteristics (mean ± SD)

Primary outcomes	GH (*n* = 40)	No treatment (*n* = 19)	GH effect:[b] mean (95% CI)	*p*-value
Age (years)	20.7 ± 2.5	21.2 ± 2.0		
Time since randomisation (years)	10.6 ± 1.7	10.7 ± 1.4		
BA (years)	15.1 ± 1.0	15.2 ± 1.0	0.0 (–0.6 to 0.6)	ns
Height (cm)	149.0 ± 6.4	142.2 ± 6.6	73. (5.4 to 9.2)	< 0.001
HtSDS (age-specific Turner)	0.9 ± 0.9	–0.1 ± 1.0	1.1 (0.8 to1.4)	< 0.001
HtSDS (adult Turner)	0.9 ± 0.9	–0.1 ± 1.0	1.1 (0.8 to 1.4)	< 0.001
Change in height (cm)	30.3 ± 8.3	21.6 ± 6.2	7.3 (5.4 to 9.1)	< 0.001
Change in HtSDS (age-specific Turner)	1.1 ± 0.5	0.0 ± 0.5	1.1 (0.8 to 1.4)	< 0.001

Comments

As for completion characteristics.

Adverse event	GH (*n* = 74)	No treatment (*n* = 64)	*p*-value
Surgical procedures	37	17	0.005
Otitis media	35	17	0.014
Ear disorder	15	4	0.024
Joint disorder	10	2	0.036
Respiratory disorder	8	1	0.037
Sinusitis	14	4	0.041
Goitre	0	4	0.004
Death (ruptured aortic aneurysm)	0	1	nr
Elevated transamine levels[d]	1	0	nr
Intracranial hypertension	1	0	nr

Comments

d Leading to withdrawal from study.
After protocol completion there was no significant difference in auditory acuity (conductive or neurosensory) between groups (data not shown).

There were no significant between group differences in change from baseline to end point in fasting blood glucose, glycated haemoglobin (HbA_{1c}), serum T4 or TSH (data not shown).

Methodological comments

Allocation to treatment groups: Eligible subjects were stratified for height relative to chronological age at entry and randomly assigned.

Blinding: Unblinded – control received no treatment. No mention of blinding of assessors.

Comparability of treatment groups: No statistically significant differences between groups at baseline (stated, *p*-values not given).

Method of data analysis: Data are reported as mean ± 1 SD unless stated otherwise. Differences between groups at baseline and end point for characteristics such as age and duration of therapy were assessed by one-way ANOVA or Fisher's exact test, as appropriate. No ITT analysis.

Sample size/power calculation: Not calculated.

Attrition/dropout: Dropout is discussed: 15 withdrew from the GH group; 35 from the control. Addendum follow-up: eight from GH, nine from control; 1997 follow up only: five from GH, 13 from control; core protocol data only: two from GH, 13 from control.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Inadequate (no treatment)
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
Davenport *et al.* 2007[85] *Country*: USA *Study design*: RCT, open label *Number of centres*: 11 *Setting*: US paediatric endocrine centres *Funding*: Supported by Eli Lilly (EL) & Co., along with grants from universities; four of the authors are employed by EL, most of the authors have received grant support from EL, as well as consulting and lectureship fees from EL and other pharmaceutical companies in the past	1. Recombinant growth hormone (Humatrope) daily s.c.i. of 50 μg/kg/day 2. No treatment *Duration of treatment*: 2 years *Other interventions used*: none	*Target population*: girls with TS, aged 9 months to 4 years *Number of participants*: total: 89 (The efficacy data exclude 1 subject who was found after study entry to have a 46,XX karyotype) 1. 45 2. 44 *Sample attrition/dropout*: Overall dropouts 10, GH group 4, no treatment 6 *Reasons for discontinuation*: Control: Parents' decision $n = 2$ Scheduling problems $n = 1$ Request for GH $n = 2$ Lost to follow-up $n = 1$ GH: Relocation $n = 1$ Lost to follow-up $n = 3$ Compliance rated as excellent by authors: 95% of subjects received 80% of scheduled injections *Inclusion criteria for study entry*: Aged 9 months to 4 years Karyotype proven TS Normal urinalysis, haemoglobin and thyroid stimulating hormone Adequate thyroid hormone replacement for at least 6 months in those with hypothyroidism Written informed consent from legal guardians *Exclusion criteria for study entry*: Presence of Y-chromosomal component in the karyotype in subjects with gonads in situ Autosomal abnormality Concurrent treatment that might influence growth Clinically relevant systemic illness *No specific eligibility criteria based on height or GV*	*Primary outcomes*: change in SDS for length or height (depending on age) from baseline to 2 years. A height gain of at least 0.5 was considered clinically significant *Secondary outcomes*: serum IGF-I, IGFBP-3, bone tumour markers, identify factors associated with treatment response, determine whether outcome could be predicted by regression model using these factors, assess safety of GH treatment in young cohort *Method of assessing outcomes*: Age-appropriate measures were obtained at each visit for length using infant measuring box (children < 2 years or older, children for whom accurate standing measurements could not be obtained) Standard wall-mounted stadiometer (children older than 2 years) Both length and height measured for girls between 2 and 3 years old; length measurements in these cases were used for the analyses Length/HtSDS were calculated on the basis of data for aged matched girls from the US Centers for Disease Control Mid-parental height calculated as follows: (father's height – 13 cm + mother's height)/2 and converted to SDS using normative height data for women at 20 years of age Serum IGF-1, IGFBP-3 and bone turnover markers were measured at baseline, 4 months, 1 year and 2 years SDSs were calculated using Esoterix's data for healthy controls BA radiographs obtained at baseline, 1 year, and 2 year and read by blinded independent assessors Safety was assessed on each visit based on reported AE, detailed history and physical examinations *Length of follow-up*: 4-monthly intervals for the 2 years of treatment

Baseline characteristics of participants (mean ± SD)

Variable	GH (*n* = 45)	No treatment (*n* = 43)	*p*-value
Chronological age (years)	1.98 ± 1.01	1.97 ± 1.01	nr
BA (years)[a]	1.95 ± 0.89	1.88 ± 0.96	nr
BA–CA	–0.06 ± 0.56	–0.14 ± 0.42	nr
Length/height (cm)	78.9 ± 8.6	77.6 ± 8.7	nr
Length/HtSDS	–1.42 ± 1.00	–1.76 ± 1.07	nr
MPH (cm)[b]	164.4 ± 5.0	164.4 ± 4.7	nr
MPH SDS[b]	0.17 ± 0.77	0.16 ± 0.73	nr
Weight (kg)	10.35 ± 2.28	9.92 ± 2.47	nr
WtSDS	–1.31 ± 1.18	–1.77 ± 1.46	nr
BMI (kg/m^2)	16.48 ± 1.37	16.24 ± 1.29	nr
Head circumference (cm)[c]	47.2 ± 2.4	46.7 ± 2.1	nr
Head circumference SDS[c]	0.09 ± 1.05	–0.14 ± 1.19	nr
Karyotype distribution: 45,X	27/45 (60%)	29/43 (67%)	
Karyotype distribution: 45,X/46,XX	7/45 (16%)	7/43 (16%)	
Karyotype distribution: other	11/45 (24%)	7/43 (16%)	
IGF-1 SDS[d]	–0.25 ± 0.85	–0.39 ± 0.95	nr
IGFBP-3[d]	–0.66 ± 1.08	–0.83 ± 1.05	nr

CA, chronological age.

a Baseline BA missing for two subjects in each group.
b Father's height missing for one GH subject at both baseline and end point.
c Baseline data missing for one subject in each group; one control subject had an erroneous value at baseline, so the value was not used; end point data missing for two control subjects.
d Baseline data missing for eight control subjects and three GH-treated subjects; end point data missing for four control subjects and seven GH subjects.

Results (mean ± SD)

Outcomes	GH (*n* = 41)	No treatment (*n* = 37)	*p*-value
Chronological age (years)	4.03 ± 1.05	4.03 ± 1.03	0.9944
BA (years)[a]	4.24 ± 1.35	3.38 ± 1.11	0.0033
BA–CA	–0.64 ± 0.80	0.21 ± 0.96	< 0.0001
Length/height (cm)	99.5 ± 7.6	91.9 ± 7.2	< 0.0001
Length/HtSDS	–0.34 ± 1.10	–2.16 ± 1.22	< 0.0001
MPH (cm)[b]	164.7 ± 4.9	164.1 ± 4.9	0.5608
MPH SDS[b]	0.22 ± 0.76	0.12 ± 0.76	0.5607
Weight (kg)	16.62 ± 2.86	13.81 ± 2.50	< 0.0001
WtSDS	0.20 ± 1.06	–1.37 ± 1.36	< 0.0001
BMI (kg/m^2)	16.72 ± 1.70	16.24 ± 1.29	0.1724
Head circumference (cm)[c]	51.1 ± 1.5	49.9 ± 1.4	0.0004
Head circumference SDS[c]	1.17 ± 1.03	0.30 ± 0.99	0.0004
IGF-1 SDS[d]	1.26 ± 0.72	–0.69 ± 0.84	< 0.0001
IGFBP-3[d]	0.97 ± 0.94	–1.12 ± 1.13	< 0.0001

Comments

For table footnotes, see corresponding notes above, under Baseline characteristics of participants.

The between group difference for change in HtSDS after 2 years was 1.6 ± 0.6, $p < 0.001$ – this analysis was performed on data from the 78 subjects with karyotype proven TS who completed the 2-year study. The between-group difference was significant by 4 months and increased progressively. Total 2-year height gain was 13.6 ± 3.5 cm for the control group, vs 20.4 ± 3.3 cm for the GH group ($p < 0.001$). Data are reported as mean ± SD unless noted otherwise.

	No treatment (*n* = 37)	**GH (*n* = 41)**	***p*-value**
First-year GV[e] (cm/year)	8.0 ± 2.4	11.7 ± 2.4	< 0.0001
Second-year GV (cm/year)	5.5 ± 1.8	8.4 ± 1.6	< 0.0001
First-year GV SDS	–0.83 ± 0.95	1.75 ± 1.25	< 0.0001
Second-year GV SDS	–1.63 ± 1.29	0.70 ± 1.11	< 0.001

e Numbers in groups not known for first-year results; data are reported as mean ± SD unless noted otherwise. At the 2-year time point (when heights of both groups were compared with US standards), only 7% of GH-treated subjects remained below –2.0 SDS (~2.3 percentile); in contrast, 57% of the control subjects were below –2.0 SDS at 2 years ($p < 0.0001$).

Outcome	**GH (*n* = 41)**	**No treatment (*n* = 37)**	***p*-value**
Baseline to 2-year change: IGF-I SDS	1.53 ± 0.93	–0.09 ± 0.87	nr

Adverse effects

Adverse effects	**GH (*n* = 45)**	**No treatment (*n* = 44)**
Serious AE, *n* (%)[f]	4 (9)	4 (9)
Treatment-emergent AE[g]	42 (93)	43 (98)

f *Control group*: one subject each was hospitalised for surgical repair of an atrial septal defect, croup/bronchiolitis, gastroenteritis and dehydration. *GH*: one subject each was hospitalised for gastroenteritis/dehydration, bacterial pneumonia, persistent bleeding after tonsillectomy and hypoxaemia after adenoidectomy.

g Events or conditions that began or worsened after study entry: many of these events were related to ear disorders. There was no detrimental effect of GH treatment on frequency of episodes of otitis media, rates of ear tube insertion, middle ear function or hearing. Most other events reported with a high frequency were typical childhood illnesses that were considered unlikely to have been related to GH treatment. There were no significant changes or between-group differences in serum TSH. AEs have been reported for the full group numbers.

Methodological comments

Allocation to treatment groups: Children were stratified by age (9 months to 2.5 years and > 2.5–4 years) and then randomised using a blinded phone in process, in a 1 : 1 ratio.

Blinding: Assessors of BA radiographs were blinded; it is not reported if assessors of other outcomes were blinded. Control group did not receive placebo injections.

Comparability of treatment groups: The two groups appear broadly similar at baseline. BA–chronological age, length/HtSDS, IGF-1 SDS and IGFBP-3 SDS were slightly lower in the GH group at baseline. Weight measures were slightly higher in this group. No *p*-value, so unknown if these differences are minimal.

Method of data analysis: The primary efficacy analysis was conducted on the baseline–2-year change in HtSDS for all subjects who had measurements at both time points (not ITT) using an ANOVA model with treatment group and baseline age group as explanatory variables. For analyses of changes in HtSDS, 1-sided tests were used, with the significance level set at 0.05. All other analyses of efficacy variables were conducted using 2-sided tests, with the significance level set at 0.05. Serious AEs, treatment-emergent AEs and laboratory data were summarised for all subjects who entered the study. Data are reported as mean ± SD unless noted otherwise.

Sample size/power calculation: No calculation.

Attrition/dropout: Overall dropouts 10, GH group 4, no treatment 6.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Inadequate
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
Gravholt *et al.* 2005[88] *Country*: Denmark *Study design*: Randomised, placebo-controlled crossover study *Number of centres*: not reported *Funding*: Government grant to Novo Nordisk Centre for Research in Growth and Regeneration. One author recipient of honoraria from Pharmacia and Novo Nordisk, and a second author is recipient of a research grant from Eli Lilly, Novo Nordisk and Roche	1. GH 0.1 IU/kg/day s.c. 2. Placebo Age-matched control group studied once (not data extracted) *Duration of treatment*: 2 months in each arm. No washout period between the two study periods *Other interventions used*: At least 6 months before inclusion in the study all girls had received GH (0.1 IU/kg/day)	*Target population*: girls with TS *Number of participants*: total 12; numbers allocated to each group not given *Sample attrition/dropout*: not reported *Inclusion/exclusion criteria for study entry*: not stated	*Primary outcomes*: not stated *Secondary outcomes*: body composition, insulin sensitivity, other biochemical/metabolic markers, markers of ovarian function (not data extracted) *Method of assessing outcomes*: Participants studied at the end of every 2-month period, IGF-1, IGFBP-3 and IGFBP-1 and other biochemical markers tested at the end of every study period. Body composition measured by whole body DEXA *Length of follow-up*: 4 months

DEXA, dual-energy X-ray absorptiometry.

Characteristics of participants: 12 girls with TS, aged 9.5–14.8 years (median 12.9) – not reported

Outcomes	GH 0.1 IU/kg/day s.c.	Placebo	*p*-value
FM arms (g/kg total body weight)	32.9 ± 8.2	36.0 ± 8.6	0.12
FM legs (g/kg total body weight)	98.7 ± 18.7	104.9 ± 17.8	0.340
FM trunk (g/kg total body weight)	80.7 ± 27.4	88.1 ± 35.4	0.1
FM head (g/kg total body weight)	18.7 ± 3.3	18.7 ± 3.1	0.5
FM total (g/kg total body weight)	231.0 ± 49.5	247.8 ± 58.1	0.04
BMC arms (g/kg total body weight)	3.6 ± 0.8	3.5 ± 0.7	0.6
BMC legs (g/kg total body weight)	10.5 ± 1.7	10.6 ± 1.8	0.3
BMC trunk (g/kg total body weight)	7.9 ± 1.5	8.0 ± 1.4	0.4
BMC head (g/kg total body weight)	7.9 ± 1.1	8.0 ± 1.2	0.9
BMC total (g/kg total body weight)	29.6 ± 3.6	30.1 ± 3.6	0.1
LBM arms (g/kg total body weight)	62.9 ± 6.4	60.5 ± 6.6	0.1
LBM legs (g/kg total body weight)	205.7 ± 23.7	202.0 ± 25.9	0.2
LBM trunk (g/kg total body weight)	378.8 ± 17.4	369.3 ± 29.6	0.046
LBM head (g/kg total body weight)	78.0 ± 15.2	78.8 ± 13.6	0.5

LBM total (g/kg total body weight)	725.4 ± 44.8	710.5 ± 54.6	0.05
IGF-1 (μg/l)	380.5 ± 116.3	179.8 ± 79.4	< 0.0005
IGFBP-1 (μg/l)	3.1 ± 2.4	7.3 ± 4.7	0.002
IGFBP-3 (μg/l)	5982 ± 1557	4344 ± 787	0.002
IGF-1/IGFBP-3 ratio	0.065 ± 0.014	0.041 ± 0.013	< 0.0005
Fasting glucose (mmol/l)	4.28 ± 0.59	4.02 ± 0.44	0.046
Fasting insulin (pmol/l)	17.17 ± 8.30	8.58 ± 4.27	0.007[a]
Fasting glucagon (ng/l)	97.8 ± 43.4	79.2 ± 23.3	0.08
ISIcomp	10.3 ± 9.8	20.9 ± 16.0	0.003
R_{HOMA}	3.34 ± 1.70	1.56 ± 0.87	0.001
AUC insulin (pmol/l/24 h)	61 344 ± 28 547	40 868 ± 16 112	0.006
AUC glucose	6922 ± 570	6707 ± 464	0.3
AUC lactate (mmol/l/540 min)	5255 ± 1224	4589 ± 1165	0.2
AUC alanine (μmol/l/540 min)	2230 ± 548	2081 ± 368	0.4
AUC glycerol (μmol/l/540 min)	648 ± 208	527 ± 104	0.1
AUC BOH (μmol/l/540 min)	1215 ± 1486	589 ± 385	0.2
AUC lactate OGTT (mmol/l/120 min)	11569 ± 2438	10239 ± 1674	0.09
AUC alanine OGTT (μmol/l/120 min)	2848 ± 730	2665 ± 459	0.3
AUC glycerol OGTT (μmol/l/120 min)	444 ± 83	408 ± 96	0.2
AUC BOH OGTT (μmol/l/120 min)	564 ± 812	319 ± 268	0.3
AUC FFA OGTT (μmol/l/120 min)	2.43 ± 0.77	2.06 ± 0.91	0.1

Comments

AUC, area under the curve; BOH, 3-hydroxybutyrate; FFA, free fatty acids; HOMA, homeostasis model assessment index; ISIcomp, composite whole-body insulin sensitivity index; OGTT, oral glucose tolerance test; R, fasting insulin ($22.5 \times e^{-\ln \text{fasting glucose}}$).

a Wilcoxon two-tailed test. Numbers entered into each group unclear.

Adverse effects

Not reported.

Methodological comments

Allocation to treatment groups: States randomised, but no other details. No details of numbers allocated to groups.

Blinding: States placebo used, no other details given.

Comparability of treatment groups: Appear comparable, but unclear if the details are from baseline.

Method of data analysis: Groups were compared using Student's two-tailed paired *t*-test, independent *t*-test, Mann–Whitney *U*-test or Wilcoxon test as appropriate. States that all data were tested for period as well as carry-over effects: authors state this did not affect significance. Results expressed as mean ± SD. Statistical significance was assumed for $p < 5\%$.

Sample size/power calculation: Not reported.

Attrition/dropout: Not reported/discussed, no numbers allocated to groups specified.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Unknown
4. Were the eligibility criteria specified?	Inadequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Unknown
7. Was the patient blinded?	Unknown
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Inadequate

Reference and design	Intervention	Participants	Outcome measures
Gravholt *et al.* 2005[89] *Country*: Denmark *Study design*: randomised, placebo-controlled, crossover trial *Number of centres*: not reported *Funding*: Government grant to Novo Nordisk Centre for Research in Growth and Regeneration	All girls were treated with placebo + placebo, GH + placebo or GH + 17β oestradiol (this latter group's results are not data extracted) for a 2-month period each completed by a 24-h blood sampling period. The treatment regimen was given sequentially and in random order *Doses*: 1. GH [1.3 ± 0.3 (0.7–1.8)] mg/day [mean ± SD (range)] 2. 17β oestradiol [0.39 ± 0.16 (0.25–0.6)] mg/day A pubertal stage-matched healthy control group (n = 10) was studied once (not data extracted) *Duration of treatment*: 6 months *Other interventions used*: At least 5 months before inclusion in the study all TS girls received GH [1.3 ± 0.3 (0.7–1.8)] mg/day [mean ± SD (range)] and 17β oestradiol [0.39 ± 0.16 (0.25–0.6)] mg/day	*Target population*: girls with TS *Number of participants*: total 9; no numbers given for treatment groups *Sample attrition/dropout*: One girl was excluded for non-compliance with study protocol *Inclusion/exclusion criteria for study entry*: all girls with TS previously verified by chromosomal karyotyping. No other criteria stated	*Primary outcomes*: not stated *Secondary outcomes*: insulin sensitivity, glucose tolerance, body composition *Method of assessing outcomes*: participants were studied at the end of every 2-month period. IGF-1, IGFBP-3 and IGFBP-1 tested at each study visit. Body composition measured by DEXA *Length of follow-up*: 8 months (including initial observation period of 2 months)

Characteristics of participants: baseline data given for Turner participants as 1 group; did not extract data for healthy controls

	TS	*p*-value
Age (years)	15.9 ± 1.8	
Weight (kg)	49.1 ± 11.0	
Height (cm)	148.3 ± 4.0	
BMI (kg/m^2)	22.2 ± 4.0	

Results

Outcomes	GH	Placebo	*p*-value
FM arms	41.2 ± 10.2	46.3 ± 12.9	Unclear which groups the *p*-values in the paper are referring to: not data extracted here
FM legs	122.4 ± 22.2	135.1 ± 30.2	
FM trunk	96.2 ± 27.9	116.6 ± 38.7	
FM head	14.7 ± 2.1	14.8 ± 2.5	
FM total	274.5 ± 55.5	312.9 ± 74.7	
BMC arms	4.5 ± 0.4	4.2 ± 0.3	
BMC legs	11.7 ± 0.8	11.9 ± 0.9	
BMC trunk	9.0 ± 1.1	8.9 ± 0.7	
BMC head	7.3 ± 1.2	7.2 ± 1.2	
BMC total	32.5 ± 2.6	32.1 ± 2.0	
LBM arms	61.2 ± 6.5	56.5 ± 10.4	
LBM legs	213.2 ± 24.1	197.2 ± 29.0	
LBM trunk	356.8 ± 20.9	339.9 ± 30.4	
LBM head	61.6 ± 10.7	61.3 ± 10.4	
LBM total	692.8 ± 55.5	655.2 ± 73.7	

IGF-1 (μg/l)	661 ± 192	288 ± 69
IGFBP-1 (μg/l)	1.8 ± 1.2	4.2 ± 2.8
IGFBP-3 (μg/l)	5157 ± 741	4146 ± 573
Fasting glucose (mmol/l)	4.46 ± 0.40	4.04 ± 0.47
Fasting insulin (pmol/l)	147.1 ± 54.0	86.1 ± 41.0
Fasting glucagon (ng/l)	37.4 ± 12.6	43.0 ± 26.1
ISIcomp	7.0 ± 3.7	14.7 ± 8.7
RHOMA	4.12 ± 1.60	2.24 ± 1.31
AUC insulin (pmol/l/24 h)	8710 ± 4728	5848 ± 4312
AUC glucose	119 ± 10	111 ± 13
AUC lactate (nmol/l/480 min)	4853 ± 1520	5532 ± 2120
AUC alanine (μmol/l/480 min)	1864 ± 627	2230 ± 543
AUC glycerol (μmol/l/480 min)	516 ± 245	491 ± 220
AUC BOH (μmol/l/480 min)	947 ± 1372	338 ± 437
AUC lactate OGTT (mmol/l/120 min)	3614 ± 976	3718 ± 948
AUC alanine OGTT (μmol/l/120 min)	855 ± 190	840 ± 159
AUC glycerol OGTT (μmol/l/120 min)	117 ± 56	99 ± 42
AUC BOH OGTT (μmol/l/120 min)	96 ± 96	57 ± 68
AUC FFA OGTT (μmol/l/120 min)	0.83 ± 0.18	0.75 ± 0.27

AUC, area under the curve; BOH, 3-hydroxybutyrate; FFA, free fatty acids; HOMA, homeostasis model assessment index; ISIcomp, composite whole-body insulin sensitivity index; OGTT, oral glucose tolerance test; R, fasting insulin ($22.5 \times e^{-\ln \text{fasting glucose}}$).

Adverse effects

Not reported/discussed.

Methodological comments

Allocation to treatment groups: Unclear whether allocation to treatment groups has taken place, or whether participants all took the same combination of drugs in the same time period.

Blinding: No details given, although is stated that placebo + placebo given and GH + placebo in those groups.

Comparability of treatment groups: Not reported – baseline information given for TS participants as a whole.

Method of data analysis: Groups were compared using Student's two-tailed paired *t*-test and an independent *t*-test when normally distributed, Mann–Whitney and Wilcoxon used for non-parametric data. Results expressed as mean ± SD. Statistical significance was assumed for $p < 5\%$.

Sample size/power calculation: Not reported.

Attrition/dropout: One patient excluded for non-compliance with study protocol. No further details given.

No washout period. Unclear on whether is randomised or treatment simply given 'in a random order' (p. 617).

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	nr
4. Were the eligibility criteria specified?	Inadequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Unknown
7. Was the patient blinded?	Adequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
Johnston *et al.* 2001[90] *Country*: UK *Study design*: RCT *Number of centres*: six *Funding*: Pharmacia & Upjohn	1. GH 28–30 IU/m^2 surface area/week daily s.c.i. 2. Low-dose estrogen: ethinyloestradiol 1.0 μg/day for < 10 years and 2.0 μg/day for > 10 years (approx 50–75 ng/kg body weight daily) 3. Combined ethinyloestradiol and GH (not data extracted) *Duration of treatment*: 1 year in these groups (group 2 changed to group 3 after the first year, not data extracted, and treatment continued until height increases had fallen below 1 cm/year) *Other interventions used*: not stated for year 1	*Target population*: girls with TS *Number of participants*: total 58 1. 22 2. 13 3. 23 *Sample attrition/dropout*: 7 withdrawals, 5 girls reallocated from estrogen to GH: it is unclear at what point this occurred *Inclusion criteria for study entry*: not stated *Exclusion criteria for study entry*: other growth-limiting disorders, prior hormone therapy	*Primary outcomes*: height gain at AH *Secondary outcomes*: growth-enhancing effect of LDE (not data extracted), change in HSDS *Method of assessing outcomes*: standing height, sitting height, and weight were measured at 3-month intervals; HtSDSs were derived from published Turner height standards, BA was initially determined at yearly intervals and calculated using the Tanner–Whitehouse RUS method applicable to normal female population. Various biochemical measures performed at study entry and annually, including triglycerides, cholesterol and TSH *Length of follow-up*: 1 year

RUS, radius, ulna and finger (or short) bones.

Characteristics of participants

Characteristic	GH 28–30 IU/m^2 surface area/week (*n* = 22)	Low-dose estrogen: ethinyloestradiol (*n* = 13)	*p*-value[a]
Age (years)	9.0 (5.2 to 15.4)	9.1 (6.0 to 13.7)	
BA (years)	8.0 (3.3 to 13.5)	7.9 (3.0 to 13.7)	
Height (cm)	113.2 (93.2 to 135.1)	114.0 (94.6 to 140)	
HSDS for CA	–0.3 (–2.1 to 1.2)	–0.1 (–1.5 to 1.8)	
HSDS for BA	0.6 (–0.8 to 3.3)	1.0 (–0.6 to 2.4)	
Mid parental HSDS	–0.2 (0.8)	–0.3 (1.1)	

a Not extracted, as unclear which groups of the three to which this refers.
Results are expressed as mean (range) or (SD).

Results

Outcomes	GH 28–30 IU/m^2 surface area/week (*n* = unclear)	Low-dose estrogen: ethinyloestradiol (*n* = unclear)	*p*-value
Change in HSDS in first year	+0.7 (0.7)	+0.4 (0.9)	< 0.05

Adverse effects

Three of 58 girls ceased GH early because of serious health events not directly related to GH or LDE: one each with hypertension, ulcerative colitis and brain tumour. One patient in group 3 died from aortic dissection shortly after treatment cessation. Compliance problems led to the withdrawal of four patients. Seven others developed coincidental disorders but these were not considered sufficient to invalidate continued participation in the study. Five girls from group 2 were allocated to LDE were re-allocated to GH due to concerns over early breast development at age range 6.2–8.9 years.

Methodological comments

Allocation to treatment groups: States randomised, no other details given. Five girls reallocated from estrogen to GH; it is unclear at what point this occurred.

Blinding: Unknown, no details given.

Comparability of treatment groups: Authors state that the groups were similar for the main monitoring parameters.

Method of data analysis: Within-group results were compared using the paired Student's *t*-test. Between-group results were compared using analysis of variance. Parental HtSDS values were calculated using normal population data.

Sample size/power calculation: Not reported.

Attrition/dropout: Seven withdrawals: three out of 58 girls ceased GH early because of serious health events not directly related to GH or LDE. Compliance problems led to the withdrawal of four patients. Treatment centres had the option of stopping ethinyloestradiol therapy if girls showed unacceptable premature breast development or excessive bone maturation: this occurred in five cases. Group numbers for FH data are lower; for the 1-year data they are unclear.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Inadequate
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Inadequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Unknown
7. Was the patient blinded?	Unknown
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Inadequate

PWS data extraction forms

Reference and design	Intervention	Participants	Outcome measures
Lindgren *et al.* 1997,[100] 1998,[101] *Countries*: Sweden and Denmark *Study design*: RCT *Number of centres*: multicentre *Funding*: Pharmacia & Upjohn	1. 0.1 IU/kg/day GH by s.c.i. 2. No treatment *Duration of treatment*: 2 years (only year 1 data extracted, as no control arm in year 2) *Other interventions used*: special dietary instructions more than 1 year before start of treatment and throughout the study period to ensure constant energy intake per kilogram of body weight	*Target population*: prepubertal children aged 3–12 years with PWS *Number of participants*: total *n* = 29 1. *n* = 15 2. *n* = 14 An additional group of non-PWS obese children was also studied, but data from this group were not data extracted *Sample attrition/dropout*: Two control group patients excluded from analysis *Inclusion criteria for study entry*: fulfilled diagnostic criteria for PWS and had either a paternal deletion or maternal disomy of chromosome region 15q11-13; projected FH < 165 cm (boys) and 154 cm (girls)	*Primary outcomes*: not stated *Secondary outcomes*: HtSDS; GV SDS, BMI SDS, lean mass, % body fat *Method of assessing outcomes*: height and WtSDS calculated with reference to the standard for healthy Swedish children; BA was assessed according to Tanner–Whitehouse 2/ RUS; % body fat estimated by DEXA QoL questionnaires completed (but no extractable data reported) *Length of follow-up*: 1 year

Characteristics of participants

Mean (range)	0.1 IU/kg/day GH (*n* = 15)	No treatment (*n* = 12)	*p*-value
Age (years)	6.8 (3.6 to 11.9)	6.4 (3.3 to 11.7)	
BA (years)	6.6 (3.3 to 13.0)	5.4 (3.3 to 10.2)	
Sex (f/m)	7/8	5/7	
Target HtSDS	0.4 (–1.3 to 1.8)	–0.1 (–1.5 to 1.0)	
HtSDS	–1.6 (–4.0 to 0.5)	–1.7 (–5.3 to 0.4)	
BMI (SDS)	3.0 (–0.7 to 7.6)	2.1 (–1.3 to 5.1)	
GV (SDS) mean ± SD (range)	–1.9 ± 2.0 (–6.4 to 0.9)	–0.1 (–1.7 to 2.71)	
IGF-1 (SDS)	–1.6 (–3.0 to –0.6)	–1.4 (–2.4 to –0.1)	
Fat-free mass (kg) by DEXA: mean ± SD	14.9 ± 4.1	14.1 ± 3.0	
Fat-free mass (kg) by BIA: mean ± SD	14.6 ± 3.9	13.6 ± 3.3	
Body fat (%) by DEXA: mean ± SD	40.0 ± 10.5	34.8 ± 7.9	
Body fat (%) by BIA: mean ± SD	44.6 ± 9.2	41.3 ± 10.7	

Comments

BIA, bioelectrical impedance analyser; DEXA, dual-energy X-ray absorptiometry.

GV SDS was during 12 months before treatment commenced.

Results

Mean (range)	0.1 IU/kg/day GH (*n* = 15)	No treatment (*n* = 12)	*p*-value
BA (years)	8.0 (5.5 to 13.9)[a]	6.9 (3.9 to 11.4)	
BA (years) change from baseline	1.4 (0.0 to 2.8)	1.5 (0.4 to 2.6)	
HtSDS	–0.4 (–2.7 to 1.9)[a]	–1.8 (–5.1 to –0.2)	
BMI (SDS)	2.0 (–2.4 to 6.7)[a]	2.5 (0.1 to 6.1)	
GV (SDS) mean ± SD (range)	6.0 ± 3.2 (1.4 to 11.9)[a]	–1.4 (–3.2 to –0.3)	

IGF-1 (SDS)	1.8 (–0.1 to 4.1)[a]	–1.4 (–2.9 to –0.3)
Fat-free mass (kg) by DEXA: mean ± SD	19.8 ± 5.2[b]	15.2 ± 2.9
Fat-free mass (kg) by BIA: mean ± SD	21.7 ± 8.9[b]	14.8 ± 3.5
Body fat (%) by DEXA: mean ± SD	30.9 ± 11.4[b]	38.2 ± 9.1
Body fat (%) by BIA: mean ± SD	30.3 ± 10.5[b]	43.3 ± 12.9

a Change from baseline $p < 0.05$.

b Change from baseline $p < 0.001$.

Adverse effects

Intravenous glucose tolerance test was normal and unchanged in all children. Basal fasting insulin levels were significantly increased throughout the group in the GH group (from 10.4 mU/l ± 2.7 SD to 19.2 mU/l ± 10.5 SD, $p < 0.001$). No severe progression of scoliosis (angle ≥ 20°) in either group. Bone mineral density did not differ between groups. One child developed low levels of thyroxine without any change in TSH levels. He received substitution with L-thyroxine during the GH treatment. The increased levels of fasting insulin during the treatment may be regarded as laboratory AE. However, both levels of fasting glucose and HbA_{1c} were unchanged and, although increased compared with pretreatment, insulin levels were still within the normal range.

Methodological comments

Allocation to treatment groups: States children were randomised, but no further details given.

Blinding: Open label.

Comparability of treatment groups: Baseline age, height, BMI and HVs stated to be similar in both PWS groups.

Method of data analysis: Student's two-tailed paired and unpaired *t*-tests were used for normally distributed values, and non-parametric tests were used otherwise. Single regression analysis used for statistical comparisons. Not ITT. Data were analysed as change from baseline rather than between-group differences.

Sample size/power calculation: Not reported.

Attrition/dropout: One patient excluded at baseline evaluation because she had a severe scoliosis that required surgical intervention; one patient was excluded after 6 months in the control arm because she developed central precocious puberty.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Inadequate
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
Carrel *et al.* 2004,[22] Myers *et al.* 2007,[97] Whitman *et al.* 2004[98] *Country*: USA *Study design*: RCT *Number of centres*: two *Funding*: supported by Pharmacia Inc. (Pfizer)	1. 1 mg/m^2/day GH 2. No treatment *Duration of treatment*: 1 year *Other interventions used*: 0.1 g/kg of deuterium-labelled water was given on day 1 and 0.15 g/kg of oxygen-18 water	*Target population*: infants and toddlers with PWS *Number of participants*: Total: *n* = 32 (Whitman *et al.*); *n* = 29 (Carrel *et al.*); *n* = 25 (Myers *et al.*) 1. *n* = 15 2. *n* = 14 In Whitman paper – 30 patients completed first 6 months: *n* = 18, *n* = 12 *Sample attrition/dropout*: none in difference in *n* between Whitman paper and others suggests seven patients dropped out *Inclusion criteria for study entry*: confirmed diagnosis of PWS; age 4–37 months	*Primary outcomes*: not stated *Secondary outcomes*: % body fat, LBM, bone mineral density, GV SDS, change in height, IGF-1; mobility (not data extracted as not per protocol) *Method of assessing outcomes*: Harpenden stadiometer used for length/height for children >2, otherwise an infantometer was used; body composition measured by DEXA *Length of follow-up*: 1 year

Characteristics of participants

Mean ± SD	1 mg/m^2/day GH (*n* = 15)	No treatment (*n* = 14)	*p*-value
Age (months)	13 ± 8	15 ± 0	ns
Per cent female	50	42	ns
Length/HtSDS[a]	–1.6 ± 1.2	–1.3 ± 1.1	
GV SDS	1.4 ± 1.8	1.2 ± 1.4	
Body fat (%)[a]	28 ± 7	29 ± 12	
Lean mass (kg)[a]	5.8 ± 1.9	6.9 ± 2.0	
BMD (g/cm^2)[a]	0.60 ± 0.08	0.64 ± 0.09	
Total cholesterol (mg/dl)	163 ± 34	170 ± 30	
IGF-1 (ng/dl)[a]	34 ± 21	nr	
Fasting insulin (μIU/ml)	4.8 ± 3.7		

Comments

a From Myers paper, which had unclear patient numbers.
Baseline data are also given by Whitman *et al.* These have not been data extracted as they differ slightly from the group presented here. Whitman's results were for 6 months, so it is assumed that the Carrel data supersede these.

Results

Mean ± SD	1 mg/m^2/day GH (*n* = 15)	No treatment (*n* = 14)	*p*-value
Mean % body fat	23.2 ± 8.9	32.7 ± 8.8	0.03
Change in body fat	–4.8% ± 5.7%	4.1% ± 4.6%	0.001
Change in LBM (kg)	3.6 ± 0.5	1.8 ± 0.7	<0.001
Change in height (cm)	+15.4 ± 2.3	9.2 ± 3.2	<0.001
GV SDS	5.0 ± 1.8	1.2 ± 1.4	
IGF-1 (ng/ml)	231 ± 98	51 ± 28	<0.001
Fasting insulin (μIU/ml)	5.6 ± 7.1	5.7 ± 7.1	ns
Bone mineral density (%)	14.1 ± 10.4	9.0 ± 6.9	ns
Total cholesterol (mg/dl)	159 ± 40	183 ± 43	
Length/HtSDS[b]	–0.2 ± 1.5	–1.5 ± 0.7	

Comments

b From Myers paper, which had unclear patient numbers.
GVSDS in GH patients, $p < 0.001$ compared with baseline.

Length/HtSDS change from baseline in GH group, $p < 0.005$.

Adverse effects

No changes in the prevalence of scoliosis were seen between the treatment and control groups (Carrel *et al.*) although Myers *et al.* comment on progression of scoliosis in one patient. No other adverse effects were noted during this study, and no subject required thyroid hormone therapy. After the first 6 months, two children showed a 3.5 SD increase in head circumference. This was monitored, but the later papers do not mention it.

Methodological comments

Allocation to treatment groups: Randomisation following stratification by age (4–18 months and 19–37 months) and sex. No further details given. Myers and Whitman papers state that a 60:40 ratio was used, but this does not reflect numbers in the Carrel study, suggesting that attrition bias may have affected the results.

Blinding: None.

Comparability of treatment groups: Similar at baseline.

Method of data analysis: The *t*-test for between-group comparisons. Does not appear to be ITT. Data reported by Whitman *et al.* was for 25 patients who completed the first 6 months. All three papers appear to report data for a slightly different version of the patient group.

Sample size/power calculation: Not reported.

Attrition/dropout: Difference in *n* between Whitman paper and others suggests that seven patients dropped out.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Inadequate
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Inadequate

Reference and design	Intervention	Participants	Outcome measures
Carrel *et al.* 1999,[95] **Myers *et al.* 1999**[96] *Country*: USA *Study design*: open RCT *Number of centres*: not reported *Funding*: Genentech Foundation for Growth and Development	1. GH 1 mg/m^2/day 2. No treatment *Duration of treatment*: 1 year *Other interventions used*: standardised caloric intake	*Target population*: children with PWS without prior GH therapy *Number of participants*: Total: *n* = 54 1. *n* = 35 2. *n* = 19 *Sample attrition/dropout*: none *Inclusion criteria for study entry*: genetically confirmed patients with PWS were aged 4–16, with skeletal maturation < 13 for girls and < 15 for boys *Exclusion criteria for study entry*: prior GH therapy	*Primary outcomes*: not clearly stated *Secondary outcomes*: HtSDS; GV; GVSDS; body fat; lean mass; BM; IGF-1; IGFBP-3; insulin; cholesterol; HDL-C; strength and agility (not data extracted as not per protocol) *Method of assessing outcomes*: height measured by Harpenden stadiometer; Greulich and Pyle method of determining BA; body composition assessed using DEXA *Length of follow-up*: 1 year

HDL-C, high-density lipoprotein cholesterol.

Characteristics of participants

Mean ± SD	GH 1 mg/m^2/day (*n* = 35)	No treatment (*n* = 19)	*p*-value
Sex (% female)	42	58	
Mean age (years)	9.8	10.0	
Prepubertal (*n*)	34 (97%)	17 (90%)	
HtSDS	–1.1 ± 1.3	–1.5 ± 0.8	
Mean GV (cm/year)	4.72 ± 2.2	5.18 ± 1.5	
Mean GV SDS	–1.0 ± 2.5	–0.9 ± 1.7	
BA	9.1 ± 3.6	8.4 ± 3.1	
Body fat (%)	46.3± 8.4	42.6 ± 8.1	
Lean mass (kg)	20.5 ± 6.3	20.5 ± 5.0	
BMI (kg/m^2)	25.0 ± 6.7	24.2 ± 6.5	
IGF-1 (ng/ml)	127 ± 67	139 ± 64	
IGFBP-3 (ng/ml)	1.73 ± 0.49	1.84 ± 0.64	
Insulin-0 hour (mIU/l)	11.2 ± 9.9	9.3 ± 6.2	
Insulin-2 hour (mIU/l)	49.5 ± 40.7	41.6 ± 42.5	
Total cholesterol (mg/dl)	184 ± 36	190 ± 36	
HDL-C (mg/dl)	42 ± 8	44 ± 9	
Femoral neck BMD (g/cm^3)	0.656 ± 0.19	0.636 ± 0.9	
Spine BMD (g/cm^3)	0.744 ± 0.14	0.753 ± 0.12	
Scoliosis (°)	9.1 ± 6.0	14.7 ± 11.0	
Free fatty acids (mmol/l)	0.6 ± 0.4	0.6 ± 0.3	
Triglycerides (mg/dl)	91.6 ± 57.9	84.3 ± 39.6	

Results

Mean ± SD	GH 1 mg/m^2/day (*n* = 35)	No treatment (*n* = 19)	*p*-value
HtSDS	–0.6 ± 1.2	–1.6 ± 1.2	< 0.01
Mean GV (cm/year)	10.1 ± 2.5	5.0 ± 1.8	< 0.01
Mean GV SDS	4.6 ± 2.9	–0.7 ± 1.9	< 0.01
BA	10.6 ± 3.5	9.8 ± 3.0	ns
Body fat (%)	38.4 ± 10.7	45.8 ± 8.8	< 0.01
Lean mass (kg)	25.6 ± 4.3	21.7 ± 5.0	< 0.01

BMI (kg/m^2)	23.7 ± 6.3	25.2 ± 8.9	ns
IGF-1 (ng/ml)	522 ± 127	121 ± 52	<0.01
IGFBP-3 (ng/ml)	3.5 ± 0.73	2.07 ± 0.45	<0.01
Insulin-0 hour (mIU/l)	18.6 ± 14.6	8.8 ± 5.4	
Insulin-2 hour (mIU/l)	70.2 ± 44.2	47.1 ± 34.1	
Total cholesterol (mg/dl)	166 ± 34	193 ± 34	<0.01
HDL-C (mg/dl)	50 ± 10	44 ± 8	<0.01
Femoral neck BMD (g/cm^3)	0.797 ± 0.09	0.707 ± 0.09	<0.05
Spine BMD (g/cm^3)	0.834 ± 0.15	0.793± 0.13	
Scoliosis (°)	12.1 ± 7.0	16.6 ± 10.0	
Free fatty acids (mmol/l)	0.72 ± 0.40	0.64 ± 0.30	<0.01
Triglycerides (mg/dl)	86.0 ± 62.0	94.2 ± 49.0	

Comments

The *p*-values are for paired *t*-test before and after GH therapy, compared with either baseline values of treated patients or 12-month values of non-treated patients.

Adverse effects

Headaches in two patients treated with GH within first 3 weeks. Symptoms resolved with temporary cessation and gradual re-institution of GH. No pseudotumour cerebri.

Methodological comments

Allocation to treatment groups: reported as randomised 60:40. Method not stated.

Blinding: None.

Comparability of treatment groups: Similar at baseline.

Method of data analysis: ITT. Data were analysed using a Student's *t*-test for paired samples or two related samples.

Sample size/power calculation: Not reported.

Attrition/dropout: None.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Inadequate
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Adequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
de Lind van Wijngaarden *et al.* 2009,[93] Festen *et al.* 2008[94] *Country*: The Netherlands *Study design*: RCT *Number of centres*: 18 *Funding*: not stated	1. 1 mg/m^2 s.c. daily 2. No treatment *Duration of treatment*: 1 year for infants and 2 years for children After 1st year, infants were all offered a second year of GH treatment. Not discussed here as no control group *Other interventions used*: caloric intake and activity level standardised and monitored	*Target population*: infants and prepubertal children with PWS, who were not severely overweight, naive to GH treatment *Number of participants*: total *n* = 104 enrolled, *n* = 91 were available for follow-up: 42 infants (< 3.5 years) and 49 children over 3.5 years. Randomised groups not clear The following are the groups analysed at year 1: Infants:1. *n* = 19, 2. *n* = 19 Children:1. *n* = 23, 2. *n* = 21 *Sample attrition/dropout*: four infants and five children excluded from analysis *Inclusion criteria*: genetically confirmed diagnosis of PWS; age 6 months –14 years; BA < 14 (girls) or 16 (boys); prepubertal – Tanner breast stage ≤ 2 for girls and testicular volume < 4ml for boys *Exclusion criteria*: non-cooperative behaviour; on medication to reduce fat	*Primary outcomes*: not stated in Festen paper, scoliosis in Lind van Wijngaarden paper *Secondary outcomes*: HtSDS, BMI, BMI SDS, head circumference SDS, IGF-1, IGF-1 SDS, IGFBP-3, IGFBP-3 SDS, IGF-1/BP3 (SDS), LBM and scoliosis *Method of assessing outcomes*: Harpenden stadiometer used to measure height, using a mean of three values. Anthropometric measurements taken at baseline and every 3 months; DEXA used for fat measurements. FM, fat % and LBM were transformed into SDS, adjusting for age and sex. LBM is related to height, so LBM HtSDS were computed by comparing LBM of PWS with LBM of healthy children with the same height and sex. IGF-1 and IGFBP-3 were transformed to SDS using sex- and age-matched Dutch references *Length of follow-up*: 1 year (infants), 2 years (children)

Characteristics of participants from Festen et al. 2008[94] (other than scoliosis and trunk LBM/BSA), as this is the most complete

Baseline characteristics of infants (6 months to 3 years)

Median (IQR)	1 mg/m^2 s.c. daily rhGH (*n* = 20)	No treatment (*n* = 22)	*p*-value
Sex (m/f)	12/8	16/6	
Age (years)	2.0 (1.6 to 3.1)	1.3 (1.0 to 2.8)	
HtSDS	–2.3 (–2.8 to –0.7)	–2.1 (–3.2 to –1.0)	
BMI (kg/m^2)	16.4 (15.1 to 18.6)	16.1 (14.7 to 18.2)	
BMI (SDS)	0.5 (–0.9 to 1.9)	–0.8 (–1.7 to 1.6)	
Head circumference (SDS)	–0.8 (–1.6 to –0.3)	–1.1 (–1.8 to –0.5)	
IGF-1 (ng/ml)	27.0 (22.0 to 35.0) (*n* = 11)	47.0 (17.0 to 52.0)	
IGF-1 (SDS)	–1.9 (–2.8 to –1.3) (*n* = 11)	–1.6 (–2.6 to –0.4) (*n* = 11)	
IGFBP-3 (ng/ml)	0.8 (0.7 to 1.1) (*n* = 11)	1.1 (0.8 to 1.3) (*n* = 11)	
IGFBP-3 (SDS)	–2.6 (–3.3 to –2.0) (*n* = 11)	–1.5 (–2.6 to –0.7) (*n* = 11)	
IGF-1/BP3 (SDS)	–0.9 (–2.0 to –0.4) (*n* = 11)	–0.3 (–1.7 to 0.6) (*n* = 11)	
Scoliosis (%)	7 (37) (*n* = 19)	4 (21) (*n* = 19)	
Trunk LBM/BSA	7.4 (6.9 to 8.0) (*n* = 19)	7.3 (7.0 to 7.7)(*n* = 19)	

Baseline characteristics of children (3–14 years)

Median (IQR)	1 mg/m^2 s.c. daily rhGH (*n* = 25)	No treatment (*n* = 22)	*p*-value
Sex (m/f)	13/12	8/14	
Age (years)	6.8 (5.4 to 8.8)	5.9 (4.7 to 7.4)	
HtSDS	–2.0 (–3.1 to –1.7)	–2.5 (–3.3 to –1.9)	
BMI (kg/m^2)	17.7 (16.0 to 22.3)	18.1 (17.2 to 19.9)	
BMI (SDS)	1.2 (0.1 to 2.2)	1.3 (1.1 to 1.6)	

Head circumference (SDS)	–0.8 (–1.5 to –0.2)	–0.6 (–1.2 to –0.1)
IGF-1 (ng/ml)	60.0 (46.5 to 96.5) (*n* = 21)	56.0 (42.0 to 88.0) (*n* = 18)
IGF-1 (SDS)	–1.7 (–2.3 to –1.2) (*n* = 21)	–1.9 (–2.6 to –1.2) (*n* = 18)
IGFBP-3 (ng/ml)	1.3 (0.9 to 1.5) (*n* = 21)	1.2 (0.9 to 1.5) (*n* = 18)
IGFBP-3 (SDS)	–1.9 (–2.8 to –1.2) (*n* = 21)	–2.2 (–3.1 to –1.4) (*n* = 18)
IGF-1/BP3 (SDS)	–0.5 (–1.0 to 0.5) (*n* = 21)	–0.6 (–1.6 to 0.3) (*n* = 18)
Fat% (SDS)	2.1 (1.7 to 2.7) (*n* = ?)	2.3 (1.9 to 2.6) (*n* = ?)
Fat (SDS)	1.2 (0.8 to 2.0) (*n* = ?)	1.2 (0.7 to 1.6) (*n* = ?)
LBM age (SDS)	–1.7 (–3.0 to –1.0) (*n* = ?)	–1.9 (–3.4 to –1.2) (*n* = ?)
LBM HtSDS	–1.7 (–3.8 to –0.6) (*n* = ?)	–1.4 (–2.9 to 0.9) (*n* = ?)
Trunk fat (%)	36.0 (24.8 to 46.2) (*n* = ?)	36.0 (29.2 to 41.2) (*n* = ?)
Scoliosis (%)	7 (30) (*n* = 23)	9 (43) (*n* = 21)
Trunk LBM/BSA	8.0 (7.5 to 8.4)(*n* = 23)	7.6 (7.1 to 8.1) (*n* = 21)

Comments

n is unclear for body composition measures, as these were only available for children over the age of 4 at the start of the study. The *p*-values are for change in GH group vs control group.

Results: infants (6 months to 3 years), mostly from de Lind van Wijngaarden 2009 et al.[93] as this is the most complete data

Median (IQR)	**1 mg/m² s.c. daily rhGH 1 year (*n* = 19)**	**No treatment (*n* = 19)**	***p*-value**
HtSDS	–0.9 (–1.6 to –0.1)	–1.8 (–3.5 to –1.4)	0.003
ΔHtSDS	1.2 (1.0 to 1.6)	–0.2 (–0.6 to 0.3)	< 0.0001
BMI (kg/m²)	16.3 (15.7 to 18.2)	16.4 (15.4 to 19.8) (*n* = 15)	
BMI (SDS)	0.3 (–0.1 to 1.6)	0.3 (–0.6 to 1.6)	0.72
ΔTrunk LBM	1.7 (1.3 to 2.1)	0.7 (0.4 to 0.9)	< 0.0001
ΔTrunk LBM/BSA	1.2 (0.7 to 1.8)	0.3 (–0.3 to 0.6)	0.002
Head circumference (SDS)	0.0 (–0.9 to 0.7) (*n* = 16)	–0.8 (–1.6 to –0.3) (*n* = 15)	< 0.001
IGF-1 (ng/ml)	179.0 (119.5 to 241.0) (*n* = 12)	33.0 (22.5 to 47.8) (*n* = 15)	
IGF-1 (SDS)	2.5 (1.4 to 2.9)	–2.6 (–4.1 to –0.7)	< 0.0001
IGFBP-3 (ng/ml)	2.2 (1.6 to 2.4) (*n* = 12)	0.9 (0.7 to 1.3) (*n* = 12)	
IGFBP-3 (SDS)	0.5 (0.0 to 1.2) (*n* = 12)	–2.4 (–3.5 to –1.2) (*n* = 12)	
IGF-1/BP3 (SDS)	2.3 (1.7 to 3.4) (*n* = 12)	–1.1 (–2.1 to 0.0) (*n* = 12)	< 0.001
Onset scoliosis (%)	4 (21) (*n* = 19)	2 (11) (*n* = 19)	0.71
Progression of scoliosis	–6.0 (–12.5 to 12.8) (*n* = 19)	–7.5 (–7.5 to –5.0) (*n* = 19)	0.48

Results for children (3–14 years), mostly from de Lind van Wijngaarden 2009 et al.,[93] as this is the most complete data

Median (IQR)	**1 mg/m² s.c. daily rhGH**	**No treatment**	***p*-value**
Year 1 results			
	***N* = 23**	***N* = 21**	
HtSDS	–1.0 (–1.5 to –0.3)	–2.5 (–3.4 to –2.3)	< 0.0001
ΔHtSDS	0.9 (0.7 to 1.3)	–0.1 (–0.2 to 0.1)	< 0.0001
BMI (kg/m²)	17.5 (15.3 to 19.8) (*n* = 21)	18.6 (17.6 to 19.7) (*n* = 21)	
BMI (SDS)	0.8 (–0.1 to 2.1)	1.4 (1.0 to 1.6)	0.05
ΔTrunk LBM	1.8 (1.4 to 2.3)	0.7 (0.1 to 0.8)	< 0.0001
ΔTrunk LBM/BSA	1.3 (0.7 to 1.7)	0.0 (–0.4 to 0.3)	< 0.0001
Head circumference (SDS)	–0.2 (–1.2 to 0.2) (*n* = 21)	–0.6 (–0.9 to 0.3) (*n* = 21)	

IGF-1 (ng/ml)	337.0 (274.3 to 474.3) (*n* = 21)	55.0 (42.5 to 94.8) (*n* = 12)	
IGF-1 (SDS)	2.3 (1.5 to 2.8)	–2.5 (–3.1 to –1.5)	< 0.0001
IGFBP-3 (ng/ml)	2.5 (2.2 to 2.9) (*n* = 21)	1.3 (0.8 to 1.5) (*n* = 12)	
IGFBP-3 (SDS)	0.4 (–0.1 to 0.8) (*n* = 21)	–2.4 (–3.5 to –1.8) (*n* = 12)	< 0.001
IGF-1/BP3 (SDS)	2.5 (2.0 to 3.0) (*n* = 21)	–0.8 (–1.4 to –0.2) (*n* = 12)	< 0.001
Fat % (SDS)	1.5 (0.7 to 2.1) (*n* = ?)	2.3 (2.0 to 2.6) (*n* = ?)	< 0.001
Fat (SDS)	0.9 (0.2 to 1.4) (*n* = ?)	1.3 (0.7 to 1.9) (*n* = ?)	< 0.001
LBM age (SDS)	–0.5 (–1.3 to 0.7) (*n* = ?)	–2.1 (–4.1 to –1.3) (*n* = ?)	< 0.001
LBM HtSDS	–1.5 (–2.3 to –0.7) (*n* = ?)	–1.9 (–2.9 to 0.0) (*n* = ?)	< 0.05
Trunk fat (%)	28.0 (16.9 to 36.7) (*n* = ?)	37.2 (32.0 to 42.5) (*n* = ?)	< 0.001
Onset scoliosis (%)	5 (22) (*n* = 23)	6 (29) (*n* = 21)	0.52
Progression of scoliosis	–3.5 (–7.3 to 1.8) (*n* = 23)	0.0 (–1.0 to 1.0) (*n* = 21)	0.60
Year 2 results			
	***N* = 23**	***N* = 21**	
HtSDS	–0.5 (–0.8 to 0.0)	–2.6 (–3.4 to –2.3)	< 0.0001
ΔHtSDS	1.4 (1.3 to 1.8)	–0.1 (–0.4 to 0.1)	< 0.0001
BMI (kg/m^2)	17.5 (16.1 to 21.1) (*n* = 20)	19.1 (17.8 to 20.8) (*n* = 20)	
BMI (SDS)	1.1 (–0.2 to 1.7)	1.4 (1.1 to 1.6)	0.19
ΔTrunk LBM	2.8 (2.6 to 3.5)	0.8 (0.4 to 1.0)	< 0.0001
ΔTrunk LBM/BSA	1.4 (0.5 to 1.7)	–0.2 (–0.5 to –0.1)	< 0.0001
Head circumference (SDS)	–0.1 (–1.1 to 0.5) (*n* = 20)	–0.6 (–1.1 to 0.3) (*n* = 20)	< 0.05
IGF-1 (ng/ml)	424.0 (313.0 to 570.0) (*n* = 20)	92.0 (61.8 to 130.0) (*n* = 16)	
IGF-1 (SDS)	2.4 (2.1 to 2.8)	–1.6 (–2.5 to –1.0)	< 0.0001
IGFBP-3 (ng/ml)	2.8 (2.6 to 3.2) (*n* = 20)	1.5 (1.2 to 1.8) (*n* = 16)	
IGFBP-3 (SDS)	0.6 (0.3 to 1.1) (*n* = 20)	–1.7 (–2.3 to –1.2) (*n* = 16)	< 0.001
IGF-1/BP3 (SDS)	2.5 (1.8 to 2.9) (*n* = 20)	–0.6 (–1.2 to –0.1) (*n* = 16)	< 0.001
Fat % (SDS)	1.9 (0.7 to 2.3) (*n* = ?)	2.4 (2.1 to 2.7) (*n* = ?)	< 0.001
Fat (SDS)	1.1 (0.6 to 2.0) (*n* = ?)	4.5 (0.9 to 2.0) (*n* = ?)	< 0.01
LBM age (SDS)	–0.1 (–1.3 to 0.6) (*n* = ?)	–2.5 (–3.8 to –1.4) (*n* = ?)	< 0.001
LBM HtSDS	–1.9 (–2.4 to –1.4) (*n* = ?)	–2.3 (–2.7 to –1.3) (*n* = ?)	< 0.05
Trunk fat (%)	33.3 (17.3 to 40.9) (*n* = ?)	37.9 (35.0 to 45.7) (*n* = ?)	< 0.001
Onset scoliosis (%)	5 (22) (*n* = 23)	7 (33) (*n* = 21)	0.14
Progression of scoliosis	3.3 (–4.3 to 11.9) (*n* = 23)	–5.0 (–9.0 to –2.0) (*n* = 21)	0.27

Comments

n is unclear for body composition measures, as these were only available for children over the age of 4 at the start of the study. The *p*-values are for change in GH group vs control group.

Progression of scoliosis is change in Cobb angle during study

Adverse effects

Not reported – the reader is referred to three other papers by the same author, but two of these appear to be other smaller studies.

Methodological comments

Allocation to treatment groups: Prior to randomisation, infants were stratified for age and children (> 3.5 years) for BMI. All participants were randomised to GH treatment or no GH treatment.

Blinding: A double-blind placebo-controlled study was considered unethical.

Comparability of treatment groups: Anthropometric parameters were similar in the two groups, although no *p*-values are presented.

Method of data analysis: Reference data for the DEXA were not available for children under the age of 4, so only those > 4 years were included in the analysis. Data were expressed as median (IQR) as most were not Gaussian distributed. Differences from baseline between groups were calculated using Mann–Whitney *U*-tests. The *p*-values are for change in GH group vs control group.

Sample size/power calculation: De Lind van Wijngaarden reports that the power calculation estimated a total number of 40 patients (infants and prepubertal children) to yield a power of 0.80.

Attrition/dropout: Two excluded before treatment (one had a dose reduction due to high IGF-1 levels, another had spinal surgery for scoliosis and two other medical problems). In total, four infants and five children excluded from analysis – presumably due to incomplete study period for the other patients. Infants with repeated measures were older ($p = 0.025$), possibly reflecting early diagnosis of PWS during recent years.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Inadequate
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
Festen *et al.* 2007[91] *Country*: The Netherlands *Study design*: RCT *Number of centres*: not stated *Funding*: supported by Pfizer	1. 1 mg/m^2/day somatropin by s.c.i. (restricted to 0.5mg/m^2/day in the first 4 weeks to avoid fluid retention). 2. No treatment *Duration of treatment*: 2 years *Other interventions used*: caloric intake and activity levels standardised 3 months before study	*Target population*: prepubertal, generally not overweight children with PWS *Number of participants*: Total *n* = 20 1. *n* = 10 2. *n* = 10 *Sample attrition/dropout*: none *Inclusion criteria for study entry*: genetically confirmed diagnosis of PWS, age 4–9 years, prepubertal	*Primary outcomes*: adiponectin levels, body composition, carbohydrate metabolism and triglyceride levels *Secondary outcomes*: associations between adiponectin and body composition, carbohydrate metabolism and triglyceride levels; effect of GH on these parameters *Method of assessing outcomes*: anthropometric measurements at baseline, year 1 and year 2 (standing height, weight, BMI); body composition assessed using DEXA; biochemical marker assays performed in the same laboratory. HtSDS and BMI SDS calculated from age- and sex-specific Dutch reference data *Length of follow-up*: 2 years

Characteristics of participants: median (IQR)

Characteristic	1 mg/m^2/day GH (*n* = 10)	No treatment (*n* = 10)	*p*-value
N (male/female)	10 (5/5)	10 (3/7)	
Age (years)	6.2 (5.1 to 7.1)	5.8 (4.9 to 7.8)	
HtSDS	–2.2 (–3.1 to –1.8)	–2.8 (–3.4 to –2.0)	
BMI (kg/m^2)	16.9 (15.8 to 17.7)	17.3 (16.4 to 19.3)	
BMI SDS	0.8 (0.1 to 1.2)	1.1 (0.6 to 1.5)	
Adiponectin (mg/l)	15.9 (13.3 to 23.9)	17.1 (13.1 to 23.1)	
Glucose (mmol/l)	4.8 (4.6 to 5.0)	4.4 (4.3 to 4.7)	
Insulin (mU/l)	6.0 (3.8 to 10.0)	5.5 (4.8 to 7.3)	
Insulin–glucose ratio	1.3 (0.8 to 2.1)	1.3 (1.0 to 1.6)	
HOMA index	0.8 (0.5 to1.3)	0.7 (0.6 to 0.9)	
Triglycerides (mmol/l)	0.9 (0.7 to 1.7)	0.7 (0.6 to 1.0)	
IGF-1 SDS	–1.7 (–2.2 to –1.2)	–1.7 (–2.9 to –1.0)	
IGFBP-3 SDS	–2.0 (–3.0 to –1.3)	–2.5 (–3.2 to –1.5)	
LBM SDS	–2.2 (–2.7 to –2.0)	–2.3 (–2.8 to –1.8)	
FM SDS	0.8 (0.6 to 1.0)	0.8 (0.6 to 1.2)	
Per cent fat SDS	1.7 (1.6 to 2.0)	1.8 (1.5 to 2.4)	
Trunk fat/total fat	0.44 (0.34 to 0.47)	0.4 (0.35 to 0.46)	

Comments

HOMA, Homeostasis Model Assessment index.

Adiponectin levels were compared with healthy matched controls

Results (median, IQR)

	1 mg/m²/day GH (*n* = 10)		No treatment (*n* = 10)		*p*-value change from baseline group 1 vs group 2
Outcomes	**Year 1**	**Year 2**	**Year 1**	**Year 2**	
HtSDS	–1.3[a] (–1.7 to –0.8)	–0.6[a] (–0.9 to –0.3)	–2.8 (–3.5 to –2.0)	–3.0 (–3.5 to –1.8)	< 0.01[b]
BMI (kg/m²)	16.1[c] (15.2 to 17.6)	16.3 (15.8 to 19.0)	18.5 (17.6 to 19.3)	18.5 (17.5 to 20.6)	< 0.05[c]
BMI SDS	0.2[c] (–0.2 to 0.8)	0.4 (–0.3 to 1.1)	1.3 (1.0 to 1.6)	1.2 (0.9 to 1.5)	< 0.05[c]
Adiponectin (mg/l)	24.7 (15.0 to 25.9)[a,b]	24.6 (15.4 to 28.2)[a,b]	13.4 (11.6 to 21.4)	15.8 (12.5 to 19.2)	< 0.05[b]
Glucose (mmol/l)	4.4 (4.2 to 5.0)	4.6 (4.2 to 5.0)	4.6 (4.3 to 4.8)	4.7 (4.3 to 4.9)	
Insulin (mU/l)	9.0 (6.5 to 13.5)[a]	7.5 (6.0 to 11.5)	6.0 (3.3 to 8.3)	11.0 (6.0 to 24.0)[a]	
Insulin–glucose ratio	2.1 (1.5 to 2.6)[a]	1.6 (1.5 to 2.2)	1.3 (0.8 to 1.9)	2.3 (1.4 to 2.2)[a]	
HOMA index	1.2 (0.8 to 1.8)	1.0 (0.7 to 1.5)	0.8 (0.4 to 1.0)	1.4 (0.8 to 3.0)[a]	
Triglycerides (mmol/l)	0.8 (0.6 to 1.3)	0.7 (0.6 to 0.8)	0.6 (0.5 to 1.0)	1.0 (0.6 to 1.0)	
IGF-1 SDS	2.3 (1.6 to 3.0)[a,c]	2.3 (2.1 to 2.9)[a,c]	–2.5 (–3.2 to –0.8)	–2.0 (–2.7 to 1.0)	< 0.001[c]
IGFBP-3 SDS	0.5 (–0.1 to 1.0)[a,c]	0.6 (0.4 to 1.1)[a,c]	–2.4 (–3.8 to –1.9)	–1.8 (–2.7 to –1.5)	< 0.001[c]
LBM SDS	–1.6 (–1.9 to –1.4)[a]	–1.2 (–1.7 to –1.1)[a]	–2.5 (–3.0 to –1.8)	–2.8 (–3. to 1.9)[a]	
FM SDS	0.5 (0.2 to 1.0)	0.9 (0.4 to 1.4)	1.1 (0.9 to 1.2)[a]	1.2 (0.9 to 1.4)[a]	
Per cent fat SDS	1.4 (0.9 to 1.7)[a]	1.7 (0.9 to 1.9)[a]	2.1 (1.8 to 2.2)	2.1 (1.9 to 2.4)[a]	
Trunk fat/total fat	0.4 (0.33 to 0.42)	0.41 (0.34 to 0.46)	0.41 (0.40 to 0.44)	0.41 (0.38 to 0.45)	

Comments

Adiponectin levels were compared with healthy matched controls.

a $p < 0.05$ compared with baseline corrected for multiple testing.
b $p < 0.05$ change compared with baseline in GH group vs control group corrected for multiple testing.
c $p < 0.001$ change compared with baseline in GH group vs control group corrected for multiple testing.

Adverse effects

Not reported.

Methodological comments

Allocation to treatment groups: Stratified by age and BMI prior to randomisation. No further details given.

Blinding: Open-label trial.

Comparability of treatment groups: Similar at baseline. Note: adeponectin levels were compared against healthy controls, not the untreated PWS group.

Method of data analysis: Most data not Gaussian distributed, so data expressed as median (IQR) and non-parametric tests were used. Mann–Whitney *U*-tests used for differences between groups. Adiponectin levels of PWS children were compared with reference data of healthy sex- and age-matched controls ($n = 40$) with Wilcoxon signed-rank test.

Sample size/power calculation: Not reported.

Attrition/dropout: None.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	unknown
6. Was the care provider blinded?	Inadequate
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Adequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
Festen *et al.* 2007[92] *Countries*: The Netherlands and Sweden *Study design*: RCT *Number of centres*: multicentre *Funding*: Pfizer	1. GH 1 mg/m^2/day 2. No treatment *Duration of treatment*: 12 months *Other interventions used*: dietary advice given and compliance evaluated every 3 months	*Target population*: PWS infants and toddlers *Number of participants*: Total: 43 evaluated at baseline, then 29 entered treatment 1. *n* = 15 2. *n* = 14 *Sample attrition/dropout*: 14 were excluded from the study, and this appears to have taken place post-randomisation *Inclusion criteria for study entry*: Genetically confirmed diagnosis of PWS; aged 6 months to 3 years at start of protocol *Exclusion criteria for study entry*: severe scoliosis (> 20°); extremely low dietary intake	*Primary outcomes*: psychomotor development (BSID-II) (not data extracted as not per protocol) *Secondary outcomes*: body composition; IGF-1 and IGFBP-3 *Method of assessing outcomes*: height measured with a Harpenden stadiometer; Dutch references used to calculate age- and sex- specific SDS for median height, BMI and head circumference; body composition in Dutch participants measured using DEXA; IGF in Dutch children measured using an immunometric technique, and in Swedish infants using a semi-illuminescent technique *Length of follow-up*: 12 months

BSID-II, Bayley Scales of Infant Development II.

Characteristics of participants

Median (IQR)	GH 1 mg/m^2/day (*n* = 15)	No treatment (*n* = 14)	*p*-value
Sex (m/f)	7/8	8/6	
Age (years)	2.3 (1.7 to 3.0)	1.5 (1.2 to 2.7)	
HtSDS	–2.6 (–3.3 to –1.8)	–2.3 (–3.3 to –1.1)	
BMI (kg/m^2)	16.3 (14.5 to 17.8)	15.9 (14.7 to 16.8)	
BMI SDS	–0.3 (–1.1 to 1.3)	–0.9 (–1.8 to –0.8)	
Head circumference SDS	–1.0 (–1.7 to –0.3)	–1.1 (–1.8 to –0.9)	
Body fat (%)	26.2 (22.2 to 28.9)	25.8 (23.1 to 27.7)	
LBM (%)	72.1 (69.8 to 75.7)	73.3 (70.9 to 75.2)	
IGF-SDS	–2.1 (–2.7 to –1.7)	–2.0 (–2.6 to –0.3)	
IGFBP-3 SDS	–2.8 (–3.5 to –2.4)	–1.8 (–3.4 to –0.9)	

Results

Median (IQR)	GH 1 mg/m^2/day (*n* = 15)	No treatment (*n* = 14)	*p*-value
Age (years)	3.3 (2.7 to 4.0)	2.6 (2.3 to 3.8)	
HtSDS	–1.6[b] (–2.1 to –0.8)	–2.3 (–3.9 to –1.5)	
BMI (kg/m^2)	16.4 (15.2 to 18.5)	15.5 (14.9 to 17.6)	
BMI SDS	0.3 (–0.9 to 1.8)	–0.4[a] (–0.8 to 1.3)	
Head circumference SDS	–0.2[b,c] (–1.2 to 0.6)	–1.1[c] (–1.6 to –0.6)	
Body fat (%)	22.5 (11.3–33.2)	22.8 (19.5 to 32.9)	
LBM (%)	74.8 (63.7 to 82.3)	73.6 (61.6 to 75.9)	
IGF-SDS	1.7[b,d] (0.1 to 2.5)	–2.6[d] (–4.1 to –0.4)	
IGFBP-3SDS	0.4[a,c] (–0.3 to 1.1)	–3.1[c] (–4.0 to –2.2)	

a $p < 0.05$.
b $p < 0.005$: 12 vs 0 months.
c $p < 0.05$.
d $p < 0.001$: GH vs control.

Adverse effects

No results presented. Paper states that compared to randomised controls, GH did not induce disadvantageous effects on carbohydrate metabolism, sleep-related breathing disorders, and thyroid hormone levels.

Comments

Methodological comments

Allocation to treatment groups: Children were stratified for age before randomisation. No further details given.

Blinding: Open label.

Comparability of treatment groups: Similar at baseline, although GH group had slightly older median age.

Method of data analysis: For repeated measurement analysis, only children with 2 BSID-II scores were included. BSID-II can only be used if developmental age is maximally 3–5 years. Non-parametric statistics used as data not Gaussian distributed. Mann–Whitney *U*-tests used for two-tail differences at baseline, one-tailed ANCOVA used for data analysis.

Sample size/power calculation: Not reported.

Attrition/dropout: 14 of the original 43 were excluded from repeated BSID-II analysis, and therefore do not appear to have been randomised. However, the paper later states that results of 14 patients were excluded from analysis – not clear if this is the same 14, but assumed to be so, i.e. they were excluded post randomisation.

Reasons for exclusion: Five children had not reached 1 year of study, one infant was excluded due to thyroid hormone deficiency, eight had already passed the upper limit of BSID-II after 1 year of follow-up (divided equally between the GH group and the control group).

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Inadequate
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Inadequate

Reference and design	Intervention	Participants	Outcome measures
Haqq *et al.* 2003[102] *Country*: USA *Study design*: Double blind placebo-controlled crossover *Number of centres*: one *Funding*: grants from the General Clinical Research Center and Pharmacia Corp.	1. GH 0.043 mg/kg/day plus inactive ingredients, by daily s.c.i. 2. Placebo injection of inactive ingredients, by daily s.c.i. *Duration of treatment*: 6 months in each treatment arm, 12 months overall *Other interventions used*: none	*Target population*: children with PWS *Number of participants*: total *n* = 14 randomised, but data only given for *n* = 12 1. *n* = 6 2. *n* = 6 *Sample attrition/dropout*: *n* = 2 *Inclusion criteria for study entry*: PWS; naive to GH treatment *Exclusion criteria for study entry*: other chronic illnesses, taking medications that impact on long-term bone mineralisation or body composition	*Primary outcomes*: not stated *Secondary outcomes*: linear GV, body composition, pulmonary function, sleep, behaviour, cognition, resting energy expenditure (last five not data extracted as not per protocol) *Method of assessing outcomes*: assessed at 0.6 and 12 months; anthropometric measurements, side effects and compliance measured at 3 and 9 months; BA determined at 0 and 12 months using Greulich and Pyle analysis of wrist radiographs; height measured at 0.6 and 12 months using wall-mounted stadiometer; body composition measured using DEXA *Length of follow-up*: 6 months for outcomes, 12 months overall

Characteristics of participants

Mean ± SD	All patients (*n* = 12)	*p*-value
Age (years)	9.7 ± 3.3	
Sex (m/f)	6/6	
BA (years)	10.0 ± 4.2	
BMI SDS	2.5 ± 0.7	
IGF-1 (ng/ml)	169.3 ± 155.7	
IGF-1 SDS	−1.10 ± 1.15	
IGFBP-3 (ng/ml)	2169 ± 1010	
IGFBP-3 SDS	−1.67 ± 1.10	
Mean height (cm)	128.9 ± 19.7	
BMI (kg/m^2)	30.8 ± 8.3	
BMI (SDS)	2.5 ± 0.7	
HtSDS	−1.3 ± 1.2	
GV (cm/year)	4.2 ± 2.3	
Body fat (%)	54 ± 5.3	
FM (kg)	29.6 ± 16.7	
Lean mass (kg)	22.5 ± 10.9	
Lumbar spine BMD (SDS)	−0.51 ± 0.30	
Total BMC (g)	1263 ± 451	

Comments

Mean BA also reported as 10.2 ± 4.1 years later in the paper.

Results

Outcomes	GH 0.043 mg/kg/day (*n* = 12)	Placebo (*n* = 12)	*p*-value
BMI (kg/m^2)	31.2 ± 8.9	32.8 ± 9.7	< 0.05
BMI (SDS)	2.4 ± 0.5	2.5 ± 0.6	
HtSDS	–1.2 ± 1.1	–1.3 ± 1.3	
GV (cm/year)	7.5 ± 3.5	4.5 ± 2.7	< 0.05
Body fat (%)	49.7 ± 5.8	54.1 ± 5.6	< 0.05
FM (kg)	26.1 ± 12.8	29.1 ± 14.1	< 0.05
Lean mass (kg)	24.1 ± 8.8	22.4 ± 8.5	< 0.05
Lumbar spine BMD (SDS)	–0.33 ± 1.4	–0.4 ± 1.4	
Total BMC (g)	1337 ± 453	1342 ± 453	
IGF-1 (ng/ml)	720 ± 379	232 ± 182	< 0.001
IGFBP-3 (ng/ml)	6029 ± 1311	4247 ± 1209	< 0.01
Leptin (ng/ml)	49.7 ± 39.3	54.3 ± 46.2	0.06
Ghrelin (pmol/l)	272 ± 204	361 ± 309	0.11
FT4 (pmol/l)	12.9 ± 1.5	14.8 ± 1.4	< 0.05
TSH (mU/l)	1.81 ± 0.79	2.04 ± 1.13	
Insulin (pmol/l)	64.2 ± 42.6	64.2 ± 39	
Glucose (mmol/l)	5.0 ± 0.7	4.8 ± 0.5	
Osteocalcin (nmol/l)	10.5 ± 5.7	7.8 ± 5.9	0.06
Triglycerides (mmol/l)	0.80 ± 0.52	0.92 ± 0.42	
Total cholesterol (mmol/l)	4.7 ± 0.9	4.5 ± 1.7	

Comments

Mean BA (in all patients) increased to 11.3 ± 3.7 by the end of 12 months, compared with a chronological age of 9.7 ± 3.3 years. Mean height increased to 134.6 ± 19.3 cm. Only one patient required thyroid hormone replacement while receiving GH treatment.

Adverse effects

No patient developed a significant degree of scoliosis (> 20°). No evidence of impaired fasting glucose concentrations. GH treatment resulted in supranormal IGH-I and normal IGFBP-3 concentrations, but the consequences of this are unknown.

Methodological comments

Allocation to treatment groups: Reported to be randomised, but no further details given.

Blinding: Both GH and placebo injections were given using a Genotropin pen.

Comparability of treatment groups: Data only presented for whole group – crossover study design.

Method of data analysis: Not ITT. Differences between groups calculated using paired *t*-tests. For data not distributed normally, Wilcoxon signed-rank tests were used. $p < 0.05$ considered statistically significant. Weight, height and BMI SDS obtained using Epi Info 2000 (www.cdc.gov/epiinfo/).

Sample size/power calculation: Not reported.

Attrition/dropout: Two patients withdrew – one due to relocation, one due to non-compliance with daily injections. Not clear which group they belonged to.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	nr
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Unknown
7. Was the patient blinded?	Adequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Inadequate

Reference and design	Intervention	Participants	Outcome measures
Hauffa 1997[99] *Country*: Germany *Study design*: Open RCT *Number of centres*: one *Funding*: Pharmacia & Upjohn, Germany	1. GH 0.075IU/kg/day for first month, then continued at dose of 0.15IU/kg/day to a maximum of 8IU/day 2. No treatment *Duration of treatment*: 2-year study with control arm during 1st year *Other interventions used*: not stated	*Target population*: children aged 3–12 with PWS *Number of participants*: total *n* = 19 randomised, *n* = 17 included in study, *n* = 16 analysed 1. *n* = 8 2. *n* = 9 *Sample attrition/dropout*: two not entered following randomisation, one excluded from analysis due to AE-related dose reduction *Inclusion/exclusion criteria for study entry*: prepubertal, 3–12 years old, PWS (confirmed by molecular genetics), projected FH < 3rd centile for German population	*Primary outcomes*: not stated *Secondary outcomes*: changes in HtSDS, GV SDS, IGF-1, IGFBP-3 *Method of assessing outcomes*: nr *Length of follow-up*: 1 year

Characteristics of participants

Mean ± SD	GH 0.15IU/kg/day (*n* = 7)	No treatment (*n* = 9)	*p*-value
Age (years)	8.25 ± 2.4	7.56 ± 2.0	
Sex f/m	3/4	4/5	
BA (years)	7.91 ± 4.3	6.76 ± 2.4	
Height (cm)	120.9 ± 16.3	120.5 ± 11.2	
Weight (kg)	35.9 ± 18.2	32.5 ± 8.7	
Hip circumference (cm)	78.8 ± 19.6	77.6 ± 11.5	
Target height (cm)	172.9 ± 8.5	174.8 ± 8.2	
Results			
HV SDS	5.5	–2.3	0.0012
HtSDS	1.07	–0.25	
IGF-1	Increased significantly ($p < 0.008$), sometimes to above the upper limit of the reference range	'At or slightly below lower limit of reference range'	
IGFBP-3	Increased significantly ($p < 0.008$), mostly to above the upper limit of the reference range	'Within normal range'	

Comments

Height gain (1.02 SD) remained unchanged when analysed in relation to BA. No significant within- or between-group changes were detected for sitting height, BMI, skinfold thickness, waist or hip circumference or serum lipids.

Adverse effects

One patient in GH group developed pseudotumour cerebri after increasing the starting dose to the final dose. Symptoms resolved on discontinuation. No abnormalities of glucose regulation observed in either group.

Methodological comments

Allocation to treatment groups: Randomised (method not stated).

Blinding: open label.

Comparability of treatment groups: similar at baseline.

Method of data analysis: No details given.

Sample size/power calculation: Not reported.

Attrition/dropout: 19 randomised, two not entered (reasons not stated), one not included in analysis (discontinued after an AE then resumed at half of the dose).

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Inadequate
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Inadequate

CRI data extraction forms

Reference and design	Intervention	Participants	Outcome measures
Sanchez *et al.* 2002[103] *Country*: USA *Study design*: RCT *Number of centres*: one *Funding*: partly funded by Genentech Foundation for Growth and Development, and the Casey Lee Ball Foundation	1. 0.05 mg/kg rhGH, daily s.c.i 2. No treatment *Duration of treatment*: 12 months *Other interventions used*: All patients received either monoclonal or polyclonal anti-T cell therapy and were maintained on a 3-drug immunosuppressive regimen. None was given vitamin D sterols, oral calcium supplements or anticonvulsant medications	*Target population*: prepubertal paediatric kidney allograft recipients *Number of participants*: total 23 1. 12 2. 11 *Sample attrition/dropout*: group 1, one; group 2, one *Inclusion criteria for study entry*: pre-pubertal children, stable renal function for at least 1 year post operation, normal bone formation rates, patients with adynamic lesions who had not previously been treated with rhGH were also included *Exclusion criteria for study entry*: secondary hyperparathyroidism	*Primary outcomes*: appears to be skeletal changes, but not stated clearly *Secondary outcomes*: HtSDS, WtSDS, GV *Method of assessing outcomes*: height and weight measured at 3-month intervals; height measured using fixed wall-mounted stadiometer; bone biopsy and histomorphometry bone mass measured by DEXA; blood samples every 3 months; BA determined by Greulich and Pyle method from radiographs of left hand and wrist. WSDS and HSDS calculated using values for 50th percentile for children of same CA and sex *Length of follow-up*: 12 months

Characteristics of participants

Characteristic	0.05 mg/kg rhGH (*n* = 12)	No treatment (*n* = 11)	*p*-value
Mean age ± SD (years)	9.7 ± 4.5	11 ± 1.8	ns
Sex	18 boys, 5 girls	(Groups combined)	
Mean interval since transplantation (years)	3.4 ± 2.5	(Groups combined)	
HtSDS	–2.0 ± 1.1	Not given, but 'did not differ' stated	
Mean HtSDS 12 months before study	–2.2 ± 0.8	–2.6 ± 1.0	ns
Annual GV 12 months before study (cm/year)	5 ± 2.0	4 ± 2.0	ns
BA (years)	7.1 ± 3.6	8.8 ± 2.4	ns
Tanner score	1.9 ± 0.8	2.1 ± 1.1	ns
GFR (ml/min)	58 ± 15	58 ± 14	

Results (mean ± SE)

Outcomes	0.05 mg/kg rhGH (*n* = 12)	No treatment (*n* = 11)	*p*-value
HtSDS for height at end of study	–1.1 ± 1.0 (*p* < 0.02 compared with baseline)	No change from baseline	
Annual GV (cm/year)	8.0 ± 2.1	4.8 ± 1.7	< 0.01
Change in WtSDS	0.2 ± 0.3	–0.3 ± 0.3	< 0.01
BA (years)	8.5 ± 3.4	9.5 ± 2.8	ns
Tanner score	1.9 ± 0.7	2.2 ± 1.0	ns
GFR (ml/min)	61 ± 13 (change from baseline *p* = ns)	67 ± 19 (change from baseline *p* = ns)	

Biochemical markers	**Baseline**	**Final**	**Baseline**	**Final**
Serum calcium (mg/dl)	9.8 ± 0.7	10 ± 0.6	9.4 ± 0.5	9.6 ± 0.7
Serum phosphorous (mg/dl)	4.8 ± 0.8	4.8 ± 0.7	4.5 ± 0.8	4.2 ± 0.7
Serum osteocalcin (ng/ml)	24 ± 2.7	24 ± 0.3	20 ± 2.3	17 ± 1.7
Serum parathyroid hormone (pg/ml)	55 ± 5.0	55 ± 5.3	38 ± 4.0	34 ± 2.5
Serum alkaline phosphate (IU/l)	239 ± 9.0	255 ± 9.0	225 ± 9.0	198 ± 6.4
Serum 1,25-dihydroxyvitamin D (pg/ml)	43 ± 4.3	52 ± 4.7	39 ± 3.3	50 ± 3.1
Bone histomorphology	**Baseline**	**Final**	**Baseline**	**Final**
Bone area (%)	20 ± 2.6	21 ± 4.0	20 ± 4.8	22 ± 6.4
Osteoid area (%)	8.8 ± 4.0	7.9 ± 1.8	6.1 ± 2.5	8.2 ± 2.3
Eroded perimeter (%)	5.4 ± 4.8	4.0 ± 2.2	2.2 ± 1.7	3.0 ± 1.5
Bone formation rate ($\mu m^2/mm^2$/day)	266 ± 212	348 ± 304	262 ± 180	390 ± 232
SDS for bone mass at lumbar spine, based on CA	–0.1 ± 1.6	–0.1 ± 1.3 (p = ns)	–1.7 ± 0.9	–2.1 ± 1.0 (p < 0.5)
SDS for bone mass corrected for height age	1.1 ± 1.3	0.7 ± 0.8 (change from baseline p = ns)	0.01 ± 1.0	–0.3 ± 1.2 (p < 0.05 change from baseline)

Comments

Baseline serum levels of calcium, phosphorous, parathyroid hormone, alkaline phosphate, osteocalcin, and 1,25-dihydroxyvitamin D did not differ between patients given rhGH and untreated controls. Values remained unchanged after 12 months' follow-up in both groups. IGF-1 baseline values were similar between groups (actual values not given), and did not change from baseline in the untreated group. Change from baseline was significant for the treated group ($p < 0.001$), although subgroup analysis indicated that this was only in the subgroup of patients with normal rates of bone formation, who experienced an increase in serum IGF-1 levels of 54 ± 25% after 3 months and 98 ± 35% after 12 months of rhGH ($p < 0.05$). Serum IGF-1 levels remained unchanged in patients with adynamic bone, and values did not differ from those obtained in the untreated group. Cumulative dose of prednisone did not differ between groups. Two patients with normal rates of bone formation experienced acute rejection episodes after 3 and 12 months of rhGH therapy. One was associated with non-compliance to immunosuppressive medications. Both episodes reversed after treatment with methylprednisolone. No rejection episodes in untreated patients.

Methodological comments

Allocation to treatment groups: Statistician who had no information about patients' clinical or biochemical characteristics randomised to treatment groups depending on their initial bone histological finding. Details of randomization procedure not given. Not stratified by height, etc.

Blinding: Control group did not receive placebo injections.

Comparability of treatment groups: p = ns for difference in age at baseline.

Method of data analysis: Not ITT as two patients who withdrew were excluded from analysis. Unpaired *t*-tests were used to compare changes from baseline.

Sample size/power calculation: Sample size estimated with 80% power to detect differences in group means and a two group comparison that required 20 patients per group. Appears to have been based on bone formation rates in a previous study, and it is not clear what the primary outcome for the present study is.

Attrition/dropout: Two withdrawals: one in group 1 due to glucose intolerance after 3 months (which resolved in stopping treatment); one in group 2 due to being assigned to control group. Two group 1 patients also failed to undergo second bone biopsy.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Adequate
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Partial
6. Was the care provider blinded?	Inadequate
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
The Pharmacia and Upjohn Study Group 1996[107] *Country*: international *Study design*: open-label RCT *Number of centres*: multicentre *Funding*: Pharmacia & Upjohn	1. Daily s.c.i. of GH (1 IU/kg/week) 2. No treatment *Duration of treatment*:1 year of randomised treatment, followed by 1 year of GH treatment for both groups (only year 1 randomised data included here) *Other interventions used*: not reported	*Target population*: children who had received a kidney transplant *Number of participants*: Total: *n* = 203 1. *n* = 106 2. *n* = 97 *Sample attrition/dropout*: 23 excluded from analysis of renal function; 49 excluded from analysis of growth *Inclusion criteria for study entry*: ≥ 12 months since transplantation; 2 height measurements over last 6 months; height SDS <–2 or GV below the 25th centile; GFR ≥ 20ml/min/1.73m^2; normal serum thyroid hormone levels; testicular volume < 8 ml or breast development < B2 *Exclusion criteria for study entry*: HV ≥ 75th centile, dialysis therapy, any form of malignancy or treatment with GH during past 12 months	*Primary outcomes*: GFR *Secondary outcomes*: transplant rejections; GV; HtSDS Note: data extracted only where reported separately for prepubertal children *Method of assessing outcomes*: auxological and biochemical assessments every 3 months. GFR measured by insulin clearance, or creatinine clearance (Morris method) *Length of follow-up*: 1 year (later follow-up not data extracted as not randomised)

Characteristics of participants

Mean ± SD	1 IU/kg/week GH	No treatment	*p*-value
Boys/girls	71/35	72/25	
Age (years)	12.6 ± 3.4	12.1 ± 3.1	
Proportion prepubertal (%)	53	63	
Years since transplantation	3.6 ± 2.3	3.2 ± 2.4	
Proportion cadaver donors (%)	81	86	
HtSDS	–3.2 ± 1.4	–3.1 ± 1.1	
GV before treatment (cm/year)	3.6 ± 2.2	4.0 ± 2.1	
GFR (insulin)(ml/min/1.73 m^2)	48 ± 27	48 ± 26	
GF (Morris) (ml/min/1.73 m^2)	51 ± 21	51 ± 2.1	
Rejection episodes prior to study (n)			
0–1 episode	69	63	
2–4 episodes	30	32	
5–8 episodes	7	1	

Comments

N not clear for patient groups at baseline.

Results

Mean ± SD change from baseline	1 IU/kg/week GH (*n* = 28)	No treatment (*n* = 30)	*p*-value
Change in GV (cm/year)	3.7 ± 1.6	0.3 ± 1.6	< 0.0001
Change in HtSDS	+0.6 ± 0.3	+0.1 ± 0.3	< 0.0001

Comments

Primary outcome (GFR) and other outcomes not data extracted as not reportedly separately for prepubertal children.

Methodological comments

Allocation to treatment groups: Randomised centrally, but no further details given.

Blinding: Open label.

Comparability of treatment groups: No *p*-values given. Appear to be similar, although control group contained 10% more prepubertal patients than treatment group and no. of patients with a high no. of acute rejections was higher in the GH-treated patients (seven vs one).

Method of data analysis: No information given.

Sample size/power calculation: Not stated.

Attrition/dropout: 23 excluded from analysis of renal function (treatment occurred without randomisation, GFR < 20 ml/min/1.73 m^2; transplantation < 12 months before study entry; non-compliance); 49 excluded from analysis of growth [abnormal thyroid function, growing too well (or not being short enough) before the study, previous growth not documented].

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Inadequate
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
Fine *et al.* 1994[108] *Country*: USA *Study design*: RCT *Number of centres*: 17 *Funding*: Genentech	1. GH 0.05 mg/kg/day s.c. 2. Placebo in equivalent volume. Dose adjusted every 3 months for change in weight *Duration of treatment*: 2 years' treatment was discontinued at renal transplantation, significant adverse event, or when BA > 15 years for boys and > 14 years for girls and growth rate was < 2 cm/year. Treatment was paused if a patient's height percentile exceeded the Tanner target percentile for mid-parental height (4/82 group 1, 11/42 group 2) *Other interventions used*: dialysis was permitted as required; multivitamins, vitamin D analogue and various other therapies were permitted as required	*Target population*: prepubertal growth-retarded children with CRF *Number of participants*: Total: *n* = 125 1. *n* = 82 2. *n* = 43 *Sample attrition/dropout*: group 1 – 13 in year 1, 13 in year 2; group 2 – 12 in year 1, 3 in year *Inclusion criteria for study entry*: irreversible renal insufficiency, creatinine clearance > 5 and < 75 ml/min/1.73 m^2, height < 3rd percentile for CA, BA < 10 years for girls and < 11 years for boys, prepubertal status (Tanner stage 1) *Exclusion criteria for study entry*: evidence of a specific cause for growth failure other than CRF inability to obtain accurate height measurements, use of corticosteroids or other medications that influence growth, diabetes mellitus, active malignant disease or treatment of a malignant disease within past year, use of any other investigational drug therapy within 2 months of randomisation	*Primary outcomes*: not stated *Secondary outcomes*: GV, HtSDS height age, BA, Cumulative ΔHA–ΔBA, weight gain, triceps skinfold thickness, mid-arm muscle circumference *Method of assessing outcomes*: anthropometric measurements made by same observer every 3 months; radiological evaluation of BA every 6 months. HSDS calculated using age- and sex-specific norms from the NCHS *Length of follow-up*: 2 years

Characteristics of participants

Mean ± SD	GH 0.05 mg/kg/day (*n* = 82)	Placebo (*n* = 43)	*p*-value
Age (years)	6.0 ± 3.9	5.7 ± 3.6	
Sex (f/m)	21/61	14/28	
Height age	4.0 ± 2.9	3.8 ± 2.8	
BA	4.2 ± 3.0	4.2 ± 2.9	
HtSDS	–2.9 ± 0.9	–2.9 ± 1.0	
Standardised height	–2.94 ± 0.86 (*n* = 55)	–2.82 ± 0.97 (*n* = 27)	
IGF-1 (μg/ml)	121 ± 73 (*n* = 55)	141 ± 94 (*n* = 20)	
Fasting insulin (pmol/l)	70.3 ± 43.6 (*n* = 40)	87.8 ± 71.1 (*n* = 21)	
Postprandial insulin (pmol/l)	25.8 ± 26.8 (*n* = 43)	30.1 ± 14.6 (*n* = 19)	
Fasting glucose (mmol/l)	5.1 ± 1.1 (*n* = 49)	5.0 ± 0.7 (*n* = 24)	
Postprandial glucose (mmol/l)	5.3 ± 1.8 (*n* = 37)	6.0 ± 1.7 (*n* = 21)	
HbA_{1c} (%)	5.1 ± 0.9 (*n* = 48)	5.4 ± 1.0 (*n* = 24)	
Creatinine (μmol/l)	174 ± 111 (*n* = 48)	173 ± 97 (*n* = 24)	
Creatinine (mg/dl)	2.3 ± 1.5 (*n* = 48)	2.3 ± 1.3 (*n* = 24)	
Creatinine clearance (ml/sec/1.73 m^2)	0.55 ± 0.33 (*n* = 48)	0.52 ± 0.31 (*n* = 24)	
Creatinine clearance (ml/min/1.73 m^2)	32.8 ± 19.5 (*n* = 48)	31.1 ± 18.3 (*n* = 24)	
Blood urea nitrogen (mmol/l)	15.6 ± 6.6 (*n* = 48)	16.0 ± 7.3 (*n* = 24)	
Blood urea nitrogen (mg/dl)	43.6 ± 18.5 (*n* = 48)	44.9 ± 20.5 (*n* = 24)	

Results			
Mean ± SD	**GH 0.05 mg/kg/day (*n* = 82)**	**Placebo (*n* = 43)**	***p*-value**
GV year 1 (cm/year)	10.7 ± 3.1 (*n* = 55)	6.5 ± 2.6 (*n* = 27)	< 0.00005
GV year 2 (cm/year)	7.8 ± 2.1 (*n* = 55)	5.5 ± 1.9 (*n* = 27)	< 0.00005
HtSDS at year 2	–1.6, *p* < 0.00005 compared with baseline	–2.9, *p* = 0.52 compared with baseline	
Roche–Wainer–Thissen predicted AH at 2 years (cm)	5.4	–0.4	< 0.00005
Weight gain after 2 years (kg)	6.7 ± 2.2	4.6 ± 2.7	0.0004
Triceps skinfold thickness (mm)	–1.6 ± 2.6	0.6 ± 3.8	0.006
Mid-arm muscle circumference (cm)	2.1 ± 1.1	1.3 ± 1.2	0.007
Change in BA at 2 years (years)	2.3 ± 0.7	1.6 ± 0.5	0.0001
Standardised height (1 year)	–1.93 ± 1.01 (*n* = 55)	–2.90 ± 0.95 (*n* = 27)	
Cumulative change in HA – change in BA, year 1	0.28 ± 0.45 (*n* = 43)	–0.04 ± 0.36 (*n* = 21)	
Cumulative change in HA – change in BA, year 2)	0.15 ± 0.62 (*n* = 43)	–0.12 ± 0.43 (*n* = 21)	0.08
Standardised height (2 year)	–1.55 ± 1.16 (*n* = 55)	–2.91 ± 1.04 (*n* = 27)	< 0.00005
Height age (1 year)	4.5 ± 2.7 (*n* = 43)	5.0 ± 3.2 (*n* = 21)	
Height age (2 year)	5.6 ± 2.9 (*n* = 43)	5.7 ± 3.3 (*n* = 21)	< 0.00005
BA (1 year)	4.6 ± 2.6 (*n* = 43)	5.2 ± 3.1 (*n* = 21)	
BA (2 year)	5.8 ± 2.8 (*n* = 43)	6.0 ± 3.2 (*n* = 21)	0.0001
IGF-1 (μg/l), year 1	286 ± 158 (*n* = 47)	167 ± 97 (*n* = 20)	0.0004
IGF-1 (μg/l), year 2	244 ± 128 (*n* = 47)	135 ± 80 (*n* = 20)	0.0001
Fasting insulin (pmol/l) year 1	104.9 ± 54.5 (*n* = 40)	76.9 ± 28.4 (*n* = 21)	
Fasting insulin (pmol/l) year 2	80.9 ± 42.8 (*n* = 40)	59.1 ± 34.6 (*n* = 21)	0.03
Postprandial insulin (pmol/l), year 1	36.6 ± 29.0 (*n* = 43)	27.7 ± 17.2 (*n* = 19)	
Postprandial insulin (pmol/l), year 2	29.0± 20.7 (*n* = 43)	27.2 ± 16.9 (*n* = 19)	0.32
Fasting glucose (mmol/l), year 1	5.2 ± 0.6 (*n* = 49)	5.2 ± 1.0 (*n* = 24)	
Fasting glucose (mmol/l), year 2	5.0 ± 0.6 (*n* = 49)	5.1 ± 0.7 (*n* = 24)	0.70
Postprandial glucose (mmol/l), year 1	5.4 ± 1.1 (*n* = 37)	5.1 ± 1.2 (*n* = 21)	
Postprandial glucose (mmol/l), year 2	5.4 ± 1.1 (*n* = 37)	5.5 ± 1.1 (*n* = 21)	0.28
HbA_{1c} (%), year 1	5.0 ± 0.8 (*n* = 48)	5.0 ± 0.8 (*n* = 24)	
HbA_{1c} (%), year 2	4.9 ± 0.7 (*n* = 48)	5.0 ± 0.8 (*n* = 24)	0.33
Creatinine (μmol/l), year 1	218 ± 163 (*n* = 48)	192 ± 96 (*n* = 24)	
Creatinine (μmol/l), year 2	269 ± 205 (*n* = 48)	219 ± 114 (*n* = 24)	0.08

Creatinine (mg/dl), year 1	2.9 ± 2.1 (*n* = 48)	2.5 ± 1.3 (*n* = 24)	
Creatinine (mg/dl), year 2	3.5 ± 2.7 (*n* = 48)	2.9 ± 1.5 (*n* = 24)	0.08
Creatinine clearance (ml/sec/1.73 m^2), year 1	0.55 ± 0.42 (*n* = 48)	0.51 ± 0.33 (*n* = 24)	
Creatinine clearance (ml/sec/1.73 m^2), year 2	0.49 ± 0.35 (*n* = 48)	0.48 ± 0.34 (*n* = 24)	0.63
Creatinine clearance (ml/min/1.73 m^2), year 1	32.8 ± 25.2 (*n* = 48)	30.7 ± 19.9 (*n* = 24)	
Creatinine clearance (ml/min/1.73 m^2), year 2	29.3 ± 21.3 (*n* = 48)	28.9 ± 20.4 (*n* = 24)	0.63
Blood urea nitrogen (mmol/l), year 1	16.1 ± 8.8 (*n* = 48)	17.7 ± 8.7 (*n* = 24)	
Blood urea nitrogen (mmol/l), year 2	17.2 ± 8.7 (*n* = 48)	15.9 ± 7.1 (*n* = 24)	0.26
Blood urea nitrogen (mg/dl), year 1	45.0 ± 24.5 (*n* = 48)	49.7 ± 24.4 (*n* = 24)	
Blood urea nitrogen (mg/dl), year 2	48.2 ± 24.5 (*n* = 48)	44.5 ± 20.0 (*n* = 24)	0.26
Serum alkaline phosphatase level change from baseline (IU/l), year 1	120.1 ± 130.1 (*n* = 48)	45.6 ± 90.0 (*n* = 24)	0.014
Serum alkaline phosphatase level change from baseline (IU/l), year 2	nr		ns

Comments

Mean fasting insulin levels changed significantly in patients with GH between baseline and 12 months ($p = 0.0005$) but not between baseline and 24 months. Changes in placebo group were not significant. Postprandial insulin levels also significant for GH group between baseline and year 1 ($p = 0.0089$) but not significant between baseline and 24 months. Changes from baseline in placebo group were not significant. No significant change in HbA_{1c} or thyroxine or TSH in either group at either time period.

Biochemical measurements: There was no significant difference in the variation in the serum calcium, phosphorous, triglyceride or cholesterol levels between the two groups during the first 2 years of treatment.

Adverse effects

No differences between groups in year 1. Year 2 asthma or wheezing in 8 out f 55 GH patients and none of placebo. All episodes preceded by upper respiratory tract infections. 'No clinically significant side effects were associated with rhGH treatment.' During the 1st 12 months, 19 out of 82 patients had low titre GH antibodies (i.e. anti-GH antibody serum binding by radioimmunoassay at least twice background values after 10-fold dilution), but over 2 years there was no significant difference in growth rate between patients who acquired anti-GH antibodies and those who did not.

Methodological comments

Allocation to treatment groups: No information on randomisation except performed to place 2/3 in treatment and 1/3 in placebo and to maintain balance in age, sex, standardised height, degree of renal function and primary renal disease.

Blinding: Placebo used in equivalent volume, but no further detail given.

Comparability of treatment groups: IGF-1 and fasting insulin levels were higher in the placebo group, but were not reported to have been significantly different.

Method of data analysis: Between- and within-group comparisons were made with two-tailed *t*-tests; $p < 0.05$ was considered statistically significant. Many outcome measures are only presented for patients who completed both years of the study. Not ITT.

Sample size/power calculation: Not reported.

Attrition/dropout: GH: 13 in year 1, 13 in year 2; placebo: 12 in year 1, 3 in year 2. 41% of total withdrawals were due to renal transplant, 24% requested removal, 15% non-compliance.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Unknown
7. Was the patient blinded?	Adequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
Hokken-Koelega *et al.* 1991[104] *Country*: international *Study design*: crossover RCT *Number of centres*: multicentre *Funding*: Novo Nordisk A/S Denmark	1. 4 IU/m^2 biosynthetic human GH daily s.c.i., followed by crossover to placebo 2. Placebo followed by crossover to biosynthetic human GH daily s.c.i. *Duration of treatment*: 6 months in each arm of the study *Other interventions used*: phosphate-binding medication, calcium supplements and 1,25-dihydroxy vitamin D	*Target population*: prepubertal children with CRF and severe growth retardation *Number of participants*: total 20 1. 8 2. 8 Original assignment not stated *Sample attrition/dropout*: Four left due to kidney transplantation *Inclusion/exclusion criteria for study entry*: CRF ≥ 1 year, creatinine clearance below 20 ml/min/1.73 m^2, HtSDS for age <–1.88 and HV for age <25th percentile, prepubertal (Tanner stage I), BA < 10 years for girls and 12 years for boys, no evidence of growth retardation cause other than CRF, normal thyroid function, no osteodystrophy, no previous treatment with anabolic steroids, sex steroids or recombinant human erythropoietin	*Primary outcomes*: not stated *Secondary outcomes*: GV, GV SDS, BA (years), IGF-I and IFG-II plasma concentrations *Method of assessing outcomes*: height measured with a Harpenden stadiometer; BA calculated from radiographs at start of study and every 6 months. Baseline height expressed as SDS for CA compared with Dutch reference data. GV expressed as SDS for CA compared with references derived from Infant–Childhood–Puberty Model. *Length of follow-up*:12 months

Characteristics of participants (median, range)

Characteristic	4 IU/m^2 hGH/placebo (n = 8)	Placebo/4 IU/m^2 hGH (n = 8)	p-value
Age (years)	8.7 (4.4 to 11.3)	8.6 (4.4 to 16.0)	
Sex (m/f)	6/2	4/4	
BA (years)	7.4 (3.7 to 10.2)	7.5 (3.7 to 10.6)	
HtSDS	–2.3 (–3.9 to –1.8)	–2.7 (–5.6 to –2.0)	
GV (cm/6 months)	1.6 (0 to 3.0)	1.4 (0.2 to 2.6)	
Weight for height (%)	98.2 (86.7 to 113.5)	101.5 (90.3 to 116.5)	
Mean (SD) GV (cm/6 months) 6 months pre-study	1.5 (0.7)	1.5 (0.5)	
Mean (SD) HV SDS 6 months prestudy	–3.2 (1.4)	–2.9 (2.0)	
Mean (SD) BA (years) 6 months prestudy	6.9 (2.3)	7.7 (2.6)	
Mean (SD) IGF-I (ng/ml)	173 (135)	197 (94)	
SDS for BA	0.8 (2.7)	1.4 (1.6)	
Mean (SD) IGF-II (ng/ml)	1160 (485)	1178 (483)	
SDS for BA	2.5 (3.0)	3.4 (4.0)	
Mean (SD) IGFBP-3 (ng/ml)	5429 (1352)	6559 (2552)	
SDS for BA	3.2 (1.1)	4.2 (2.1)	
Mean (SD) IGFBP-1 (ng/ml)	195 (126)	190 (115)	
SDS for BA	30 (20)	29 (17)	

Results

Outcomes	4 IU/m² hGH/placebo (*n* = 8)		Placebo/4 IU/m² hGH (*n* = 8)		Overall mean effect of GH minus effect of placebo
	After 6 months' GH	After 6 months' placebo	After 6 months' placebo	After 6 months' GH	
Mean (SD) GV (cm/6 months)	5.2 (1.2)	1.5 (0.4)	2.4 (1.0)	4.4 (1.6)	2.9 (95% CI 2.3 to 3.5) ($p < 0.0001$)
Mean (SD) HV SDS	6.9 (2.4)	–3.0 (1.6)	–0.5 (3.2)	5.0 (4.5)	7.7 ($p < 0.0001$)
Mean (SD) BA (years)	7.0 (1.9)	7.6 (1.7)	8.0 (2.6)	8.4 (2.8)	–0.01
Mean (SD) IGF-1 (ng/ml) SDS for BA	264 (168) 2.6 (2.0)	160 (104) –0.2 (1.5)	160 (95) 0.3 (1.6)	268 (120) 2.9 (2.0)	106 2.7 ($p < 0.0001$)
Mean (SD) IGF-2 (ng/ml) SDS for BA	1174 (361) 2.8 (2.8)	983 (336) 0.9 (2.2)	1192 (340) 3.4 (2.4)	1346 (492) 4.6 (3.4)	172 1.6
Mean (SD) IGFBP-3 (ng/ml) SDS for BA	7708 (2323) 5.0 (1.3)	6102 (1892) 3.7 (1.3)	6501 (1988) 3.9 (1.4)	8706 (2275) 5.2 (1.4)	1906 1.3 ($p < 0.0001$)
Mean (SD) IGFBP-1 (ng/ml) SDS for BA	119 (95) 16.4 (16.8)	185 (119) 27.1 (22.4)	215 (106) 32 (19.5)	140 (90) 20 (16.6)	–70 ($p < 0.0001$) –11.2 ($p < 0.0001$)

Comments

For GV, there was no significant carry-over effect (–0.04 cm/6 months, $p = 0.94$). Period check was –0.9 cm/6 months ($p < 0.06$).

Adverse effects

Serum alkaline phosphate was significantly increased during GH treatment, but returned to pretreatment levels when GH therapy was replaced by placebo ($p < 0.0001$). There was no significant change in parathyroid hormone concentration during either treatment schedule. Thyroid function was normal.

Methodological comments

Allocation to treatment groups: States randomly and blindly assigned, but no further details given.

Blinding: Stated to be double blind.

Comparability of treatment groups: Similar at baseline, although IGF-1 and IGFBP-3 were higher in group 2 at baseline.

Method of data analysis: Not ITT. Paper states that statistical methods appropriate for crossover trials were used but no further details were given. Treatment effects were calculated and tested after taking into account any period effect.

Sample size/power calculation: No information in paper.

Attrition/dropout: Four children left the study to have kidney transplants; 3 at 6 months and 1 at 7 months.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Unknown
7. Was the patient blinded?	Unknown
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
Hokken-Koelega *et al.* 1996[105] *Country*: international *Study design*: crossover RCT *Number of centres*: multicentre *Funding*: Novo Nordisk A/S	1. 4 IU/m^2 GH/placebo daily s.c.i. 2. Placebo/4 IU/m^2 GH daily s.c.i. *Duration of treatment*: 6 months in each arm *Other interventions used*: immunosuppressive therapy	*Target population*: prepubertal children after renal transplant *Number of participants*: total $n = 11$ 1. $n = 6$ 2. $n = 5$ *Sample attrition/dropout*: none *Inclusion criteria for study entry*: postrenal transplant (≥ 12 months), stable condition without rejection episodes (≥ 12 months), HtSDS for age < –1.88 and HV for age < 50th percentile OR HtSDS above –1.88 with HV < 25th percentile, prepubertal (Tanner stage I), BA < 10 years for girls and 12 years for boys, prednisone dose ≤ 0.25 mg/kg/day ≥ 6 months, no evidence of growth retardation cause other than following renal transplant, normal thyroid function and acid–base balance, no previous treatment with sex steroids	*Primary outcomes*: not stated *Secondary outcomes*: HV, GVSDS, BA, GFR, ERPF, IGF-1 measures, insulin and other biochemical markers *Method of assessing outcomes*: same investigator examined children at enrolment and every 3 months; height measured with a Harpenden stadiometer until three consecutive readings within 0.2 cm; GV references derived from Infant–Childhood–Puberty Model; Dutch reference data used for baseline HtSDS; BA determined from wrist radiographs *Length of follow-up*: 12 months

Characteristics of participants

Median, range	4 IU/m^2 GH/placebo ($n = 6$)	Placebo/4 IU/m^2 GH ($n = 5$)	*p*-value
Age (years)	12.1 (9.1 to 18.7)	11.1 (8.3 to 14.9)	
Sex (m/f)	5/1	4/1	
HtSDS	–3.0 (–7.6 to –1.2)	–2.6 (–3.6 to –2.1)	
GV (6 months)	1.4 (0.5 to 2.6)	0.8 (0.6 to 1.8)	
BMI SDS	3.1 (–1.1 to 4.2)	1.3 (–0.2 to 3.7)	
GFR (ml/min/1.73 m^2)	62 (56 to 81)	38 (19 to 74)	
BA (years)	9.5 (7.9 to 11.5)	7.5 (5.2 to 10.5)	

Results (mean, SD)

	4 IU/m^2 GH/placebo ($n = 6$)			Placebo/4 IU/m^2 GH ($n = 5$)			
Outcomes	Prestudy	After 6 months' GH	After 6 months' placebo	Prestudy	After 6 months' placebo	After 6 months' GH	Overall mean effect of GH minus effect of placebo
HV (cm/6 months)	1.5 (0.7)	5.3 (1.0)	1.5 (0.9)	1.0 (0.5)	1.9 (0.7)	3.9 (1.3)	2.9 (95% CI 1.9 to 3.9) ($p < 0.0001$)
GVSDS	–1.7 (1.8)	9.1 (2.9)	–1.3 (2.9)	–3.3 (0.9)	–0.4 (1.7)	5.3 (4.0)	8.0 ($p < 0.0001$)
BA (years)	9.5 (1.7)	9.7 (1.4)	10.5 (2.2)	7.7 (2.2)	8.0 (2.1)	8.1 (1.2)	–0.5
GFR (ml/min/1.73 m^2)	66 (13)	80 (30)	64 (1)	44 (22)	49 (22)	47 (38)	5.5
ERPF (ml/min/1.73 m^2)	261 (75)	254 (87)	264 (77)	173 (79)	191 (62)	184 (86)	–15.6
IGF-1 (ng/ml) SDSBA	280 (121) 0.9 (1.6)	594 (180) 5.4 (2.8)	240 (143) 1.0 (2.5)	274 (89) 2.8 (1.8)	321 (94) 3.4 (0.5)	488 (237) 6.4 (1.9)	228 3.7 ($p < 0.0001$)
IGF-2 (ng/ml) SDSBA	759 (114) 0.5 (0.9)	799 (186) 1.1 (1.7)	689 (31) 0.0 (0.4)	728 (349) 0.9 (3.2)	898 (56) 2.2 (1.2)	900 (63) 2.3 (1.0)	73 0.5
IGFBP-3 (ng/ml) SDSBA	4902 (1099) 2.8 (1.8)	7457 (2088) 4.5 (1.5)	5681 (1588) 3.7 (2.9)	5787 (1037) 3.8 (0.7)	6228 (2193) 3.9 (1.5)	8495 (2921) 5.3 (1.5)	1698 0.9
IGFBP-1 (ng/ml) SDSBA	52 (32) 4.7 (4.6)	52 (23) 4.6 (3.5)	71 (43) 7.5 (6.3)	83 (40) 9.7 (6.8)	62 (28) 6.7 (4.9)	43 (35) 5.1 (5.2)	–19 –2.1

Cholesterol (mM/l)	6.4 (1.1)[a]	6.0 (1.0)[a]	6.5 (1.8)[a]	6.3 (0.7)[a]	6.5 (0.7)[a]	6.2 (0.6)[a]	–0.3
LDL mM/l	4.0 (1.4)	3.2 (0.6)	4.0 (2.3)	3.7 (1.0)	4.1 (0.9)	3.7 (0.7)	–0.5
Apolipoprotein A1 (mg/dl)	155 (22)	163 (29)	130 (45)	171 (52)	151 (18)	141 (25)	10
Apolipoprotein B (mg/dl)	110 (33)	91 (18)	113 (40)	111 (28)	112 (20)	115 (27)	–9
Fructosamine (mM/l)	282 (40)	296 (16)	277 (36)	338 (59)	313 (62)	312 (37)	8
OGTT – glucose (mM/l)							
Fasting	4.7 (1.2)	5.3 (0.9)	5.1 (1.1)	5.2 (0.3)	4.5 (0.5)	4.8 (0.3)	0.3
Integrated	738 (163)	784 (165)	691 (79)	943 (249)	846 (143)	854 (168)	55
OGTT – insulin (μU/ml)							
Fasting	20 (14)	38 (12)	22 (14)	12 (5)	19 (15)	17 (8)	7
Integrated	2481 (1006)	4582 (3042)	3648 (1643)	2319 (1019)	2349 (444)	4267 (1092)	1532 ($p<0.05$ GH vs placebo)

Comments

ERPF, effective renal plasma flow; GVSDS, chronological age; SDSBA, SDS for BA.

a $p<0.05$ GH vs placebo.
For HV, there was no significant carry-over effect (0.5 cm/6 months, $p=0.30$). Period effect was 0.9 cm/6 months ($p=0.06$). Cholesterol and other outcomes above were compared against controls. Not data extracted as not part of randomised study.

Adverse effects

None of the patients had an acute rejection episode during the study. No SAEs.

Methodological comments

Allocation to treatment groups: States randomly and blindly assigned to groups, but no further details given.

Blinding: No details provided.

Comparability of treatment groups: Similar at baseline (although BA 2 years higher in group 1).

Method of data analysis: Paper states that statistical methods appropriate for crossover trials were used. Reference cited, but no further details given. Treatment effects were calculated and tested after taking into account any period effect. ANOVA used to test influence of baseline variables. Correlations were tested by Spearman non-parametric test. ITT analysis performed.

Sample size/power calculation: Not stated.

Attrition/dropout: All children completed the study.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Unknown
7. Was the patient blinded?	Adequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Adequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
Powell *et al.* 1997[106] *Country*: USA *Study design*: multicentre, open-label RCT *Number of centres*: 26 *Funding*: Genentech Inc.; government grants	1. 0.05 mg/kg/day s.c. rhGH 2. No treatment *Duration of treatment*: 1 year *Other interventions used*:	*Target population*: prepubertal children with chronic renal failure *Number of participants*: total 69 entered, 44 analysed 1. *n* = 30 2. *n* = 14 *Sample attrition/dropout*: 20 left (12 ESRF, six entered puberty, one allergic to rhGH, one drowned); four group 1 and one group 2 completed study but were excluded as they had insufficient serum for the 0- and 12-month protein assays *Inclusion criteria for study entry*: irreversible renal insufficiency (GFR > 10 and < 40 ml/min/1.73 m^2), height < fifth percentile for age, age > 2.5 years, ability to stand for height measurement, BA < 10 for girls and 11 for boys, Tanner stage 1 *Exclusion criteria for study entry*: serum albumin < 2.5 g/dl, receiving medications that influence growth, presence of illness affecting growth, diabetes mellitus, presence or past history of malignancy	*Primary outcomes*: not specified *Secondary outcomes*: height gain; HtSDS; BA; mid-arm muscle circumference; triceps skinfold thickness; weight gain; various IGF measures; insulin; ALS; GHBP *Method of assessing outcomes*: anthropometric measurements taken at 0, 3 and 12 months; height measured using wall-mounted stadiometer; BA determined by a left hand and wrist radiograph at 0 and 12 months *Length of follow-up*: 1 year

Characteristics of participants (mean ± SD)

Characteristic	0.05 mg/kg/day rhGH (*n* = 30)	No treatment (*n* = 14)	*p*-value
Sex (% male)	83	86	
GFR (ml/min/1.73 m^2)	27.5 ± 8.9	27.6 ± 8.8	
Age (years)	5.6 ± 2.0	5.7 ± 2.6	
BA (years)	4.0 ± 1.5 (*n* = 27)	4.2 ± 1.8	
HtSDS	–2.7 ± 0.7	–2.7 ± 0.8	
Weight for HtSDS	0.0 ± 1.3	–0.2 ± 1.5	
MAMC (cm)	14.1 ± 1.6 (*n* = 29)	14.4 ± 2.8	
TSF (mm)	7.9 ± 3.2 (*n* = 29)	8.5 ± 3.2	
IGF-1 (nM)	15 ± 10	10 ± 5	
IGF-1 SDS	–0.7 ± 1.3	–1.2 ± 1.0	
Free IGF-1 (pM)	71 ± 41 (*n* = 17)	141 ± 94 (*n* = 9)	0.029
IGF-2 (nM)	100 ± 29	101 ± 41	
IGF-2 SDS	1.2 ± 1.2	1.1 ± 1.3	
Insulin pM [b]	19 ± 14	52 ± 66	0.021
Total IGF (nM)	115 ± 34	111 ± 45	
IGFBP-1 (nM)	18 ± 9	17 ± 21	
IGFBP-1 SDS	2.4 ± 0.6	2.1 ± 1.4	
IGFBP-2 (nM)[a]	50 ± 17	51 ± 26	
IGFBP-3 (nM)[b]	130 ± 50	109 ± 25	
IGFBP-3 SDS[c]	1.7 ± 2.0	0.7 ± 1.1	
ALS (nM)	207 ± 81	179 ± 40	
GHBP (pM)	183 ± 104	144 ± 104 (*n* = 12)	
GHBP SDS	0.4 ± 1.7	0.0 ± 1.3 (*n* = 12)	

a Values > normal range (22 ± 11), $p < 0.001$.
b Values not different from normal range (98 ± 17).
c Values > normal range (–0.2 ± 0.7), $p = 0.013$.

Results (mean ± SD change from 0–12 months)

Outcome	0.05 mg/kg/day rhGH (*n* = 30)	No treatment (*n* = 14)	*p*-value
BA (years)	1.0 ± 0.3 (*n* = 27)	0.9 ± 0.4 (*n* = 13)	0.5282
Height gain (cm)	9.1 ± 2.8	5.5 ± 1.9	< .0001
Weight gain (kg)	3.5 ± 1.5	2.2 ± 1.0	0.007
HtSDS	0.8 ± 0.5	0.0 ± 0.3	< 0.0001
Weight for HtSDS	0.4 ± 0.7	0.4 ± 0.5	0.8703
MAMC (cm)	1.2 ± 0.9 (*n* = 29)	–0.2 ± 1.7 (*n* = 13)	0.0015
TSF (mm)	–1.9 ± 2.5 (*n* = 29)	0.9 ± 1.2 (*n* = 13)	0.0003
IGF-1 (nM)	No actual values presented – only small diagram, which is hard to read accurately. Not data extracted		< 0.006
IGF-1 (SDS)	0.2 ± 1.0	No change from baseline – no values reported	< 0.006
Free IGF-1 (pM)	No actual values presented – only small diagram, which is hard to read accurately. Not data extracted		< 0.0464
IGF-2 (nM)			< 0.006
IGF-2 SDS	2.1 ± 1.3	No change from baseline – no values reported	< 0.006
Insulin (pM)	No actual values presented – only small diagram which is hard to read accurately. Not data extracted		< 0.017
Total IGF (nM)			< 0.011
IGFBP-1 (nM)			< 0.017
IGFBP-1 SDS			< 0.017
IGFBP-2 (nM)			ns
IGFBP-3 (nM)			< 0.011
IGFBP-3 SDS	4.0 ± 3.2	No change from baseline – no values reported	< 0.011
ALS (nM)	No actual values presented – only small diagram, which is hard to read accurately. Not data extracted		< 0.011
GHBP (pM)			ns
GHBP SDS			ns

Comments

10 healthy children (80% male; mean age 7.4 ± 2.7 years) provided serum samples for control values for IGFBP-2 and IGFBP-3 measurements.

Adverse effects

Not reported.

Methodological comments

Allocation to treatment groups: Randomised 1 : 2, no information on method of randomisation. Groups balanced for age, gender, height, GFR at baseline and nature of primary renal disease

Blinding: Open label.

Comparability of treatment groups: Free IGF-1 and insulin were statistically significantly higher in control group, otherwise groups were similar. 10 healthy children (80% male; mean age 7.4 ± 2.7 years) provided serum samples for control values for IGFBP-2 and IGFBP-3 measurements. Mean age for control children was approximately 2 years older than for the randomised children.

Method of data analysis: Not ITT. Data presented as mean ± SD but converted to log10 values for statistical analysis. ANCOVA used to test differences between groups; $p \leq 0.05$ considered significant. Multiple regression analysis used to analyse effect of multiple variables on change in HtSDS, but not data extracted here.

Sample size/power calculation: Not reported, and primary outcome not clearly defined.

Attrition/dropout: 20 left (12 ESRF; six entered puberty; one allergic to rhGH; one drowned); four group 1 and one group 2 completed study but were excluded as they had insufficient serum for the 0- and 12-month protein assays.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Inadequate
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Adequate

SGA data extraction forms

Reference and design	Intervention	Participants	Outcome measures
Lagrou *et al.* 2008[110] *Countries*: Belgium and Luxembourg *Study design*: RCT *Number of centres*: 11 *Funding*: Belgian Study Group for Paediatric Endocrinology/ GH provided by Pfizer	1. GH 0.066 mg/kg/day 2. Untreated (did not receive placebo injections) *Duration of treatment*: 2 years *Other interventions used*: none stated	*Target population*: prepubertal children born SGA *Number of participants*: total: 40 1. 20 2. 20 *Sample attrition/dropout*: One treated patient dropped out due to family problems *Inclusion/exclusion criteria for study entry*: birth weight and or length below –2 SD for gestational age, CA between 3 and 8 years, current height below –2.5 SD, GV SDS below +1.0 SD during the last 6–18 months *Exclusion criteria for study entry*: gestational age < 34 weeks; endocrine disease, including GH deficiency; severe chronic disease; Turner, Noonan or Down Syndrome or other genetically confirmed syndromes; chromosomal abnormalities, bone disease, current or previous irradiation therapy, current or previous (up to 18 months before inclusion) treatment with glucocorticoids, severe mental retardation (IQ ≤ 50)	*Primary outcomes*: GV *Secondary outcomes*: HtSDS, WtSDS, BMI SDS, head circumference SDS, perception of short stature (not data extracted), perception of changes in height and physical appearance (not data extracted), perceptions of changes in psychosocial functioning (not data extracted) *Method of assessing outcomes*: standard auxological assessment of height, weight and head circumference measurements every 6 months, SDS calculated using British references, psychological assessments performed at start of study and after 2 years of follow-up (not data extracted) *Length of follow-up*: 2 years

Characteristics of participants

Characteristic	GH 0.066 mg/kg/day (*n* = 20)	Untreated (*n* = 20)	*p*-value
Birth WtSDS	–2.7 ± 0.9	–2.6 ± 0.8	ns
Gestational age	37.3 ± 2.1	38.2 ± 1.6	ns
Age (years)	5.5 ± 1.6	5.1 ± 1.3	ns
HtSDS	–3.3 ± 0.6	–3.2 ± 0.9	ns
WtSDS	–3.8 ± 1.3	–3.9 ± 1.4	ns
BMI (SDS)	–1.7 ± 1.1	–2.0 ± 1.5	ns
Head circumference (SDS)	–2.7 ± 1.4	–2.8 ± 1.6	ns

Results (mean ± SD)

Outcomes	GH 0.066 mg/kg/day (*n* = 20)	Untreated (*n* = 19)	*p*-value
HtSDS	–1.9 ± 0.7	–3.1 ± 0.9	< 0.001
WtSDS	–2.3 ± 1.2	–3.7 ± 1.5	< 0.01
BMI (SDS)	–1.5 ± 1.1	–2.0 ± 1.5	ns
Head circumference (SDS)	–2.0 ± 1.4	–2.8 ± 1.5	< 0.05

Adverse effects

Tolerance only discussed in terms of perceptions of the injection by parents and children. No AEs reported or discussed.

Methodological comments

Allocation to treatment groups: States randomised taking into account: gender, chronological age, WtSDS and study centre, no further details.

Blinding: No details given, untreated participants not given placebo injections.

Comparability of treatment groups: Authors report no differences in the auxological parameters between groups at baseline.

Method of data analysis: Differences of continuous variables between subgroups were evaluated by Students unpaired *t*-test or by the Mann–Whitney *U*-test as appropriate. The level of significance of difference was set at $p < 0.05$.

Sample size/power calculation: Based on 0.8 power to detect a significant difference ($p = 0.05$). 20 subjects in each group were required, assuming a difference of 2 cm/year in GV and a SD of 2.2 cm/year.

Attrition/dropout: One treated patient dropped out due to family problems. Data for untreated group is for 19 after 2 years, no explanation of this.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Unknown
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Inadequate

Reference and design	Intervention	Participants	Outcome measures
Carel *et al.* 2003[111] *Country*: France *Study design*: RCT *Number of centres*: not stated *Funding*: Sanofi–Synthélabo	1. Daily GH injections: 0.21U/kg/day (0.067 mg/kg/day) 2. No treatment *Duration of treatment*: Until reached AH. The mean duration of treatment was 2.7 ± 0.6 years *Other interventions used*: none stated	*Target population*: children born SGA *Number of participants*: total 168 1. 112 2. 56 *Sample attrition/dropout*: For treatment: group 1, *n* = 21; group 2, *n* = 23 For analysis: group 1, *n* = 10; group 2, *n* = 9 *Inclusion criteria for study entry*: birth length < –2 SDS for gestational age and term > 30 weeks; at study inclusion, height ≤ –2.5 for age or less; CA > 10.5 years for girls and > 12.5 years for boys; BA ≥ 9 years for girls and ≥ 10 years for boys; peak plasma GH concentration after pharmacological stimulation at least 10 µg/l to exclude GH deficiency; Tanner stage I or II, with testicular volume < 8 ml or uterus length < 50 mm *Exclusion criteria for study entry*: chromosomal abnormalities in girls; constitutional bone diseases, any chronic disease interfering with growth; steroid or sex steroid treatment; dysmorphic syndromes other than Russell–Silver; no catch-up growth criteria were specified	*Primary outcomes*: AH SDS *Secondary outcomes*: gain in SD units between height at inclusion and AH *Method of assessing outcomes*: follow-up visits were every 3 months for the treated group, and every 6 months for the control group and the following data recorded: height, weight, CA, pubertal stage, dose and tolerance. BA analysed yearly. SDS calculation appears to be based on French registry study *Length of follow-up*: criteria for stopping treatment/follow-up were < 1 cm growth over the last 6 months, and a BA of ≥ 15 years for girls, and ≥ 16 years for boys. Only 4% of patients met this criteria when treatment was stopped, so authors considered treatments to be almost complete for analytical purposes if GV was 2 cm or less over the last 6 months, or BA was ≥ 13 years for girls, and ≥ 15 years for boys. Patients who had discontinued follow-up before reaching AH were contacted later for a final AH measurement. Those who had not reached AH were maintained in the analysis without correction

Characteristics of participants

Characteristic	Daily GH injections: 0.21U/kg/day (0.067 mg/kg/day) (*n* = 102)	Untreated (*n* = 47)	*p*-value
Target height	–1.2 ± 0.9	–0.9 ± 1.0	
Duration of pregnancy (weeks)	39 ± 2	39 ± 2	
Birth length (SDS)	–2.8 ± 0.8	–3.1 ± 1.0	< 0.05
Birth WtSDS	–1.8 ± 0.8	–1.9 ± 0.8	
Age (years)	12.7 ± 1.4	12.8 ± 1.6	
Height (cm)			
HtSDS	–3.2 ± 0.7	–3.2 ± 0.6	
WtSDS	–1.9 ± 0.7	–2.2 ± 0.6	
GV (cm/year)			
BA (years)	10.6 ± 1.4	10.8 ± 1.6	
Pubertal (Tanner stage II) (%)	22	21	

Comments

Four patients had Russell–Silver syndrome. GV and height (cm) were not detailed for the groups as a whole, but for boys and girls within the group separately.

Results

Outcomes	Daily GH injections: 0.21IU/kg/day (0.067 mg/kg/day) (*n* = 91)	Untreated (*n* = 33)	*p*-value
At inclusion: age (years)	12.6 ± 1.5	12.9 ± 1.4	
At inclusion: HtSDS	–3.2 ± 0.6	–3.2 ± 0.6	
At inclusion: height (cm)	nr for whole group	nr for whole group	
At end of treatment: age (years)	15.7 ± 1.5	nr	
At end of treatment: HtSDS	–2.1 ± 1.0	nr	
At end of treatment: height (cm)	nr for whole group	nr	
At AH measurement: age (years)	nr	nr	
At AH measurement: HtSDS	–2.1 ± 1.0	–2.7 ± 1.0	0.005
At AH measurement: height (cm)	nr for whole group	nr for whole group	
At AH measurement: total height gain (cm)	26 ± 7	22 ± 6	0.005
At AH measurement: total height gain (SDS)	1.1 ± 0.9	0.5 ± 0.8	0.002
At AH measurement: difference from target HtSDS	–0.9 ± 1.2	–1.7 ± 1.2	0.005

Comments

A difference of 0.6 SDS was observed in FH between the control and treated groups (95% CI 0.2 to 0.9). (A difference of 0.4 was observed at baseline, unclear if this is accounted for in finding the 0.6 result significant.) The measurements above that have not been reported for the whole group are reported in the paper separately for boys and girls.

Adverse effects

Overall, 44% of treated patients reported AEs, 10% having 4 or more events. The most frequently reported events involved the respiratory system (19%), osteomuscular system (14%), central nervous system (9%), and digestive tract (8%). Authors state that all of these were mild, reversible, benign conditions that were unlikely to be related to GH treatment. 16 AEs recorded in 14 treated patients were considered severe: trauma, psychiatric symptoms, abdominal symptoms, otitis, asthma, varicocele, striae, and migraine. Again, authors state that these are unlikely to be related to GH treatment – two were causally related to treatment: one slipped capital epiphysis after 1.5 years of treatment and had one single seizure episode 10 minutes after first injection.

Methodological comments

Allocation to treatment groups: Allocation sequence generated centrally and faxed to participants.

Blinding: Group assignment was not masked, and the treated group was twice as large as the control group.

Comparability of treatment groups: There is a significant difference in birth length between the treated and untreated groups, with the treated group being longer than the untreated group ($p = 0.04$). On other characteristics the groups appear to be broadly similar.

Method of data analysis: Means and SD values are presented. Mann–Whitney *U*-test to compare groups. An α risk of 5% was set as the significance threshold. Not ITT.

Sample size/power calculation: Not reported.

Attrition/dropout: Four patients in the treatment group were excluded from analysis due to severe diseases interfering with growth (sickle cell anaemia, pulmonary hypertension, type 1 neurofibromatosis and severe prematurity). Five patients assigned to the treatment group refused GH treatment but remained in the study and were analysed as part of the control group; 15 patients left the study early (14 in control and one in the treated group). Treatment was completed in 4/102 patients and almost complete in 64/102. The reasons for interrupting treatment early were: growth rates considered insufficient by patient/physician (*n* = 12), weariness with the treatment (*n* = 10), loss to follow-up (*n* = 5), satisfaction with height (*n* = 2), local intolerance (*n* = 1), and striae attributed to the treatment by the patient (*n* = 1). In addition, some of the investigators wrongly considered that the treatment duration was limited to 3 years and stopped the treatment early (*n* = unclear). 102 treated and 47 control patients are included in the analysis. Authors state that group reassignments or protocol deviations concerned 12 and 5 patients followed to AH in the treated and control groups respectively. Appear to have been significant problems with attrition for various reasons, appears to be fully described. Group assignment was not blinded and, despite the study being randomised and centrally allocated, the treatment group is twice as large as the control: either this was 2:1 randomisation (this is not reported) or large numbers of the control group dropped out after randomisation, or possibly swapped to the treatment group: this is unclear.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Inadequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Inadequate
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
De Schepper *et al.* 2007[109] *Country*: Belgium *Study design*: RCT *Number of centres*: eight *Funding*: Belgian Study Group for Paediatric Endocrinology/ Pfizer	1. High-dose GH: 66 ± 3 μg/kg s.c. once daily, adjusted every 6 months to body weight 2. Untreated (did not receive placebo injections) *Duration of treatment*: 2 years *Other interventions used*: none stated	*Target population*: children born SGA *Number of participants*: total: 40 (25) 1. 11 2. 14 *Sample attrition/dropout*: The trial cohort was reduced from 40 to 25 based on the availability of the same absorptiometry apparatus to assess body composition in a homogeneous fashion across eight centres. No anthropometric differences were detectable between the study population and the non-included subcohort (authors state, no data reported) *Inclusion criteria for study entry*: birth weight, length or both <–2 SD for gestational age, current height <–2.5 SDGV <+1 SD in the last 6–18 months, age between 3 and 8 years at study start *Exclusion criteria for study entry*: premature birth (gestational age <34 weeks); evidence for endocrine or bone disease; severe chronic disease; Turner, Noonan, Down or other genetic syndrome; irradiation treatment; current or previous glucocorticoid treatment; severe cognitive dysfunction (est. IQ <50)	*Primary outcomes*: none clearly stated *Secondary outcomes*: HtSDS and WtSDS, anthropometric and absorptiometric characteristics *Method of assessing outcomes*: study participants seen every 3 months, height measured with Harpenden stadiometer, and weight with electronic scale. Mid-upper arm circumference and four skinfolds were measured at study start and after 1 and 2 years *Length of follow-up*: 2 years

Characteristics of participants

Characteristic	High-dose GH (GH) (*n* = 11)[a]	Untreated (*n* = 14)	*p*-value
Age (years)	5.1 ± 1.6	5.1 ± 1.4	
Gestational age (weeks)	37 ± 3	38 ± 2	
Birth WtSDS	–2.4 ± 0.8	–2.5 ± 0.8	
Birth length (SDS)	–3.1 ± 0.6	–2.9 ± 0.7	
Mid-parental height[b]	–0.9 ± 0.8	–0.8 ± 0.7	
HtSDS	–3.3 ± 0.7	–3.2 ± 1	
WtSDS	–3.5 ± 1.2	–3.6 ± 1.5	
Subscapular skinfold (mm)	5.4 ± 1.1	6.4 ± 2.1	
Triceps skinfold (mm)	7.9 ± 1.4	8.3 ± 2.1	
Subscapular/triceps	0.7 ± 0.2	0.8 ± 0.2	
Sum skinfolds (mm)	22.1 ± 3	24.3 ± 6	
Body fat fraction (%)	12.9 ± 2.1	14.1 ± 3.6	
MUAMA (cm)	12.8 ± 2.5	14.1 ± 3.5	
MUAFA (cm)	5.5 ± 1.1	5.7 ± 1.7	
Lean mass (kg)	10 ± 3	9.9 ± 2.2	
FM (kg)	2.3 ± 0.5	2.5 ± 0.9	
Lean mass (%)	78 ± 4	77 ± 5	
FM (%)	15 ± 3	20 ± 5	
Trunk fat (kg)	0.7 ± 0.3	0.8 ± 0.4	

Limb fat (kg)	1.1 ± 0.3	1.2 ± 0.5
Trunk fat/limb fat	0.6 ± 0.2	0.6 ± 0.2
Trunk fat/leg fat	0.8 ± 0.3	0.8 ± 0.3

MUAFA, mid upper arm fat area; MUAMA, mid upper arm muscle area.

a Not significant for baseline comparisons between groups.
b [Father's HtSDS + mother's HtSDS]/2.

Results

	High-dose GH (GH) (*n* = 11)[a]		**Untreated (*n* = 14)**		
Outcomes	**1 year**	**2 years**	**1 year**	**2 years**	***p*-value[a]**
HtSDS	–2.1 ± 0.7[b]	–1.7 ± 0.7[b,e]	–3.1 ± 1[c]	–3 ± 1[c]	< 0.0001
WtSDS	–2.4 ± 1.3[b]	–1.8 ± 1[b,e]	–3.5 ± 1.4	–3.4 ± 1.6[c]	< 0.0001
Subscapular skinfold (mm)	4.7 ± 0.8[c]	5.1 ± 1	5.7 ± 1.8[c]	6 ± 2.1	ns
Triceps skinfold (mm)	4.9 ± 1.5[b]	5.5 ± 2.1[b]	8.2 ± 2.3	7.9 ± 2.4	< 0.001
Subscapular/triceps	1 ± 0.3[d]	1 ± 0.3[b,f]	0.7 ± 0.2	0.8 ± 0.2[i]	0.001
Sum skinfolds (mm)	16.6 ± 3.4[b]	18.1 ± 5[d]	22.4 ± 5.8[c]	22.9 ± 6.8	< 0.005
Body fat fraction (%)	9.1 ± 2.1[b]	10.1 ± 3[d]	13.3 ± 3.5	13.4 ± 3.5	< 0.005
MUAMA (cm)	15.2 ± 2.9[b]	17 ± 2.7[b,g]	13.3 ± 2.3[d]	14.1 ± 2.9[b,h]	< 0.005
MUAFA (cm)	3.6 ± 1.2[b]	4.3 ± 1.9[d,h]	5.8 ± 2	5.7 ± 1.9	0.001
Lean mass (kg)	13.2 ± 3.4[b]	15.5 ± 3.4[b,e]	10.9 ± 2.4[b]	12.2 ± 2.5[b,e]	< 0.0001
FM (kg)	2.4 ± 0.7	2.9 ± 1[c,g]	2.8 ± 1.1[c]	3.1 ± 1.1[b,h]	ns
Lean mass (%)	82 ± 3[d]	82 ± 3[c]	77 ± 6	77 ± 5	< 0.05
FM (%)	15 ± 3[d]	15 ± 2[c]	20 ± 6	20 ± 5	< 0.05
Trunk fat (kg)	0.9 ± 0.3	1 ± 0.3[c]	0.9 ± 0.5	1 ± 0.6[b]	ns
Limb fat (kg)	0.9 ± 0.5	1.3 ± 0.7[g]	1.4 ± 0.6[c]	1.5 ± 0.6	< 0.05
Trunk fat/limb fat	1 ± 0.5[d]	0.9 ± 0.3[d,f]	0.6 ± 0.2	0.7 ± 0.2[i]	< 0.0001
Trunk fat/leg fat	1.5 ± 0.7[d]	1.3 ± 0.4[d,f]	0.8 ± 0.3	0.9 ± 0.3[i]	< 0.0001

Comments

a Difference between untreated and treated group (analysis of variance) unclear if this is totals over the 2 years of the study, including baseline measurements.
b $p < 0.0005$ paired *t*-test or Wilcoxon rank test@ baseline – year 1, baseline – year 2.
c $p < 0.05$.
d $p < 0.005$.
e $p < 0.0005$ paired *t*-test or Wilcoxon rank test: year 1 – year 2.
f Elevated for age.
g $p < 0.005$.
h $p < 0.5$.
i Normal for age.

GH treatment was accompanied by a gain of lean mass ($p < 0.0001$) and by a centripetal redistribution of FM ($p < 0.0001$) but not by an overall gain or loss of FM. The effects of high dose GH on adiposity are not readily detectable in the trunk and are essentially limited to the limbs.

Adverse effects

Authors state that 'none had a noteworthy adverse event during the 2 years of study'.

Methodological comments

Allocation to treatment groups: States randomised, no information reported on allocation to groups. Original trial cohort was 40, this was reduced to 25 due to availability of equipment.

Blinding: No information on blinding reported, untreated group did not receive placebo injections.

Comparability of treatment groups: Groups appear comparable at baseline – authors state there were no detectable baseline differences in the subgroups.

Method of data analysis: Results are expressed as mean ± SD. Repeated measures analysis of variance was used to test for differences between subgroups. The level of statistical significance was set at $p < 0.05$.

Sample size/power calculation: None reported.

Attrition/dropout: 15 children from the original cohort were withdrawn due to issues with availability of measuring equipment – unclear at what stage this happened. No dropouts are reported from the 25 included in the study, apart from this.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Unknown
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
de Zegher *et al.* 2002[113] *Countries*: UK and Belgium *Study design*: RCT *Number of centres*: two *Funding*: Pharmacia Ltd	1. High-dose GH (100 μg/kg/day) 2. No treatment *Duration of treatment*: 2 years *Other interventions used*: None stated	*Target population*: short children born SGA *Number of participants*: total 13 1. 9 2. 4 *Sample attrition/dropout*: nr *Inclusion criteria for study entry*: birth weight/length <–2 SD for gestational age, current height <–3.0 SD, GV below 0.0 SD, age between 2 and 8 years *Exclusion criteria for study entry*: identified syndrome other than Silver–Russell	*Primary outcomes*: not clearly stated *Secondary outcomes*: growth response and its relationship to pretreatment GH secretion (not data extracted) HtSDS, WtSDS, BMI SDS, GV (cm/year) *Method of assessing outcomes*: Overnight GH profiles and GH stimulation tests at baseline (not data extracted), intravenous glucose tolerance tests were performed at baseline, yearly on GH treatment and 3 months post GH treatment. Height, weights and BMI converted to age- and sex- adjusted SDS using current UK reference data *Length of follow-up*: 2 years

Characteristics of participants

Characteristic	High-dose GH (100 μg/kg/day) (*n* = 9)	No treatment (*n* = 4)	*p*-value
Age (years)	6.3 (4.0 to 8.0)	4.7 (2.3 to 6.3)	
HtSDS	–3.6 (–5.5 to –2.8)	–3.1 (–3.4 to –2.8)	
WtSDS	–4.5 (–7.2 to –2.6)	–3.8 (–5.5 to –2.7)	
BMI SDS	–2.3 (–5.0 to –0.7)	–2.0 (–4.2 to –0.1)	
GV (cm/year)	5.1 (4.0 to 6.8)	6.4 (5.3 to 7.5)	

Results (means and ranges)

Outcomes	High-dose GH (100 μg/kg/day) (*n* = 9)	No treatment (*n* = 4)	*p*-value
Age (years) (year 1)	7.2 (5.0 to 8.8)	5.7 (3.3 to 7.3)	
Age (years) (year 2)	8.2 (6.0 to 9.9)	6.5 (4.3 to 8.3)	
HtSDS (year 1)	–2.4 (–4.6 to –1.4)[a]	–3.0 (–3.3 to –2.7)	
HtSDS (year 2)	–1.8 (–3.9 to –0.5)[a]	–3.0 (–3.3 to –2.5)	
WtSDS (year 1)	–2.9 (–4.7 to –1.7)[a]	–4.0 (–5.4 to –3.2)	
WtSDS (year 2)	–2.1 (–3.6 to –0.9)[a]	–3.8 (–4.8 to –3.2)	
BMI SDS (year 1)	–1.6 (–3.8 to –0.8)[a]	–2.3 (–3.9 to –1.3)	
BMI SDS (year 2)	–1.2 (–3.4 to –0.4)[a]	–2.1 (–2.9 to –1.4)	
GV (cm/year) (year 1)	11.0 (7.4 to 13.3)	nr	
GV (cm/year) (year 2)	8.5 (6.3 to 10.2)	5.6 (4.4 to 6.8)	

Comments

a $p < 0.0001$ from baseline.

Authors state that GH-treated children showed significant increments in HtSDS, WtSDS and BMI SDS over 2 years (all $p < 0.0001$). Untreated SGA children remained on their height, weight and BMI SD levels.

Glucose and insulin metabolism markers not data extracted as reported for the treated group, no results reported for controls. Authors state that compared to baseline levels, children in the treated group showed significant increases in fasting levels of insulin (year 1, $p = 0.003$; year 2, $p = 0.0002$) and decreases in insulin sensitivity (year 1, $p = 0.003$; year 2, $p = 0.0002$).

Adverse effects

Not reported/discussed. No child showed impaired glucose tolerance.

Methodological comments

Allocation to treatment groups: Randomised on a 2:1 basis, no further details.

Blinding: No details given. No placebo used.

Comparability of treatment groups: Groups appear similar.

Method of data analysis: Means and ranges are presented. Changes in height/weight, glucose and insulin parameters analysed using paired *t*-tests. ITT.

Sample size/power calculation: Not reported.

Attrition/dropout: Not reported.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the care provider blinded?	Unknown
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Adequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
de Zegher *et al.* 1996[112] *Country*: Belgium *Study design*: open-label RCT *Number of centres*: multicentre *Funding*: support from Pharmacia Peptide Hormones	1. GH 0.2IU/kg/day s.c. 2. GH 0.3IU/kg/day s.c. 3. Untreated *Duration of treatment*: 2 years *Other interventions used*: None stated	*Target population*: children born SGA *Number of participants*: total 54 1. 20 2. 21 3. 13 *Sample attrition/dropout*: group 1, $n=2$; group 2, $n=1$; group 3, $n=1$ *Inclusion/exclusion criteria for study entry*: birth weight/length <–2 SD for gestational age, HtSDS for age <–2.5, GV SDS for age <+1, CA between 2 and 8 years, serum GH concentration >10 μg/l after exercise, glucagon or insulin tolerance test, available growth data concerning the period preceding the start of the study *Exclusion criteria for study entry*: endocrine disorders, Turner or Downs syndrome, previous or concomitant irradiation or anabolic steroid therapy, severe chronic disease, severe mental retardation	*Primary outcomes*: not clearly stated *Secondary outcomes*: height, HtSDS, GV, GV SDS, WtSDS, weight gain, BMI and BMI SDS, serum IGF-1, IGF-II, IGFBP-3, osteocalcin *Method of assessing outcomes*: study visits including history, auxological evaluation, BA determination, and dose adjustment were scheduled every 6 months. Biochemical examinations were performed yearly. All BAs were read according to Tanner–Whitehouse II method, HtSDS for BA was used as an index of FH prognosis *Length of follow-up*: 2 years

Characteristics of participants

Characteristic	GH 0.2IU/kg/day ($n=20$)	GH 0.3IU/kg/day ($n=19$)	Untreated ($n=13$)	*p*-value
Birth weight (g)	2082.0 ± 139.0	1842.0 ± 115.0	1996.0 ± 136.0	ns
Birth length (cm)	42.3 ± 1.1	42.5 ± 0.9	42.1 ± 1.1	ns
Chronological age (years)	5.4 ± 0.5	5.1 ± 0.4	4.9 ± 0.5	ns
BA (years)	4.5 ± 0.5	3.7 ± 0.5	3.7 ± 0.5	ns
HtSDS	–3.5 ± 0.2	–3.7 ± 0.2	–3.4 ± 0.3	ns
GV (cm/year)	6.6 ± 0.4	7.0 ± 0.5	6.7 ± 0.7	ns
GV SDS	–0.9 ± 0.2	–0.7 ± 0.3	–0.6 ± 0.3	ns
Weight (kg)	13.2 ± 0.9	12.3 ± 0.7	12.0 ± 0.8	ns
WtSDS	–2.5 ± 0.2	–2.9 ± 0.2	–2.8 ± 0.2	ns
BMI	14.0 ± 0.4	13.8 ± 0.4	13.5 ± 0.4	ns
BMI SDS	–1.8 ± 0.4	–1.8 ± 0.3	–2.0 ± 0.4	ns
Serum IGF-1 (μg/l)	107.0 ± 15.0	108.0 ± 14.0	108.0 ± 21.0	ns
Serum IGF-2 (μg/l)	557.0 ± 44.0	748.0 ± 60.0	699.0 ± 103.0	ns
Serum IGFBP-3 (mg/l)	3.34 ± 0.33	3.36 ± 0.38	3.35 ± 0.38	ns
Serum osteocalcin (μg/l)	69.0 ± 3.0	69.0 ± 2.0	63.0 ± 3.0	ns

Results are mean ± SEM. The 52 participating children were considered to have no specific syndrome ($n=33$), Silver–Russell syndrome ($n=10$), fetal alcohol syndrome ($n=4$), Dubowitz syndrome ($n=3$), 4p- syndrome ($n=1$) or lacrimo-auriculo-dento-digital syndrome ($n=1$).

Results

Outcomes at 2 years, unless otherwise stated	**GH 0.2 IU/kg/day (*n* = 20)**	**GH 0.3 IU/kg/day (*n* = 19)**	**Untreated (*n* = 13)**	***p*-value**
Gain in BA (years)	1.35 ± 0.16	1.33 ± 0.24	0.84 ± 0.07	< 0.001 treated vs untreated
GV (cm/year) (year 1)	11.5 ± 0.4	12.0 ± 0.4	nr	
GV (cm/year)	10.2 ± 0.2	11.0 ± 0.4	5.7 ± 0.3	< 0.001 untreated vs treated; < 0.05 group 1 vs group 2
GV SDS (year 1)	5.3 ± 0.3	5.8 ± 0.4.	nr	
GV SDS	4.3 ± 0.3	5.2 ± 0.4	–0.9 ± 0.3	< 0.001 untreated vs treated
Gain in HtSDS	2.1 ± 0.1	2.5 ± 0.1	0.2 ± 0.1	< 0.001 untreated vs treated
Gain in HtSDS for BA	1.0 ± 0.2	1.2 ± 0.4	0.0 ± 0.3	< 0.05 untreated vs treated
Weight gain (kg)	6.9 ± 0.6	7.8 ± 0.5	3.6 ± 0.4	< 0.001 untreated vs treated
Gain in WtSDS	1.3 ± 0.1	1.8 ± 0.1	0.4 ± 0.1	< 0.001 untreated vs group 1; < 0.01 group 1 vs group 2
Serum IGF-I (μg/l) (year 1)	274 ± 30	392 ± 43	145 ± 23	< 0.01 group 1 vs untreated; < 0.05 group 1 vs group 2
Serum IGF-I (μg/l)	332 ± 29	655 ± 69	168 ± 46	< 0.0001 group 1 vs group 2; < 0.01 group 1 vs untreated
Serum IGF-II (μg/l) (year 1)	745 ± 72	944 ± 101	756 ± 108	
Serum IGF-II (μg/l)	834 ± 53	966 ± 56	881 ± 125	ns
Serum IGFBP-3 (mg/l) (year 1)	5.37 ± 0.42	6.35 ± 0.44	3.88 ± 0.48	
Serum IGFBP-3 (mg/l)	6.10 ± 0.35	6.50 ± 0.52	4.00 ± 0.58	ns for group 1 vs 2; < 0.001 untreated vs group 1
Serum osteocalcin (μg/l) (year 1)	89.4 ± 5.9	93.6 ± 9.9	59.9 ± 1.9	
Serum osteocalcin (μg/l)	100.0 ± 8.6	102.7 ± 9.8	72.5 ± 7.3	< 0.05 untreated vs group 1, ns group 1 vs group 2

Comments

Results are mean ± SEM. Compliance: Over 2 years less than 10 injections were said to be missed in 36/38 children. In two children, respectively, 3% and 8% of the injections were reportedly omitted. Children with and without specified syndromes appeared to present similar growth responses. The GV during the first year was higher than during the second year, both in group 1 (11.5 ± 0.4 vs 8.8 ± 0.2 cm/year) and group 2 (12.0 ± 0.4 vs 10.0 ± 0.3 cm/year). After 2 years all untreated children still had a HtSDS < –2.2, whereas this was no longer the case for 35/38 treated children. BMI and BMI SDS remained similar in the three groups after 1 and 2 years. BMI of the study population is reported, not separately for the groups, or treated vs untreated. Fasting serum insulin concentrations were twice as high ($p = 0.01$) in treated children compared with untreated children both after 1 year (20.3 ± 2.2 mU/l vs 10.6 ± 2.4 mU/l) and 2 years (18.9 ± 3.0 mU/l vs 9.4 ± 1.3 mU/l) with no difference between the treated groups.

Adverse effects

Four SAEs, which authors state conceivably not related to GH. One treated child received antibiotics for possible osteomyelitis of the distal tibia. Three children hospitalised in relation to viral diseases: one untreated and two treated. Treatment was not interrupted. Cutaneous eczema was aggravated in one child in group 1, no treatment interruption. Three treated children reported a possible increase in size or number of pigmented naevi, treatment was not interrupted. After 2 years, all HbA_{1c} values were normal.

Methodological comments

Allocation to treatment groups: Stated to be weighted randomisation, no further details.

Blinding: Open label. Assessor for BA blinded to chronological age and treatment randomisation.

Comparability of treatment groups: No significant differences at baseline.

Method of data analysis: Wilcoxon rank-sum test used for differences between groups for growth variables, and Student's *t*-test for biochemical markers. Statistically significant differences were considered to be obtained at $p < 0.05$. Results are mean ± SEM. Not ITT. Paper does not mention if there were any adjustments for multiple comparisons.

Sample size/power calculation: None reported.

Attrition/dropout: Two children allocated to 0.31U/kg did not start. Two children dropped out of the study for psychosocial reasons, one control after the start visit and one child from group 1 after 19 months.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Partial
6. Was the care provider blinded?	Unknown
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Adequate

Data extraction form for primary studies

Reference and design	Intervention	Participants	Outcome measures
Phillip *et al.* 2009[114] *Country*: multinational Study design: RCT *Number of centres*: multicentre *Funding*: Novo Nordisk	1. rhGH 0.033 mg/kg/day 2. rhGH 0.1 mg/kg/day 3. Untreated *Duration of treatment*: 2 years, but data only extracted for year 1 as control group received rhGH in year 2 *Other interventions used*: none	*Target population*: 3- to 8-year-olds with persistent short stature, born SGA *Number of participants*: total *n* = 15 1. *n* = 51 2. *n* = 51 3. *n* = 47 *Sample attrition/dropout*: *n* = 2 *Inclusion/exclusion criteria for study entry*: birth weight/length ≤ –2 SDS; HtSDS ≤ –2.5 SDS; GV SDS ≤ 0 during last 3 months; parental height ≥ –2 SDS; normal response to GH test	*Primary outcomes*: measurement of height during 2 years. Treatment effect was additional height gain compared with untreated children *Secondary outcomes*: HtSDS, IGF-1, IGFBP-3, glucose, insulin *Method of assessing outcomes*: Harpenden stadiometer; sex-adjusted target height calculated based on national references; BA assessed using radiograph; HtSDS calculated using appropriate population references by country *Length of follow-up*: 1 year

Characteristics of participants

Mean ± SD	rhGH 0.033 mg/kg/day (*n* = 51)	rhGH 0.1 mg/kg/day (*n* = 51)	No treatment (*n* = 47)	*p*-value
Sex (m/f) (%)	55/45	47/53	51/49	nr
Birth length (cm)	44.3 ± 5.3	44.6 ± 4.3	43.9 ± 5.0	nr
Birth weight (kg)	1.9 ± 0.6	2.0 ± 0.6	2.0 ± 0.6	nr
Gestational age (weeks)	36.9 ± 3.6	37.6 ± 3.3	37.5 ± 3.2	nr
Target HtSDS	–0.9 ± 0.6	–0.8 ± 0.6	–0.9 ± 0.8	nr
Height (cm)	99.0 ± 9.3	98.9 ± 9.0	99.2 ± 7.9	nr
HtSDS	–3.1 ± 0.5	–3.2 ± 0.7	–3.1 ± 0.5	nr
Age (years)	5.5 ± 1.5	5.5 ± 1.4	5.6 ± 1.4	nr
BA (years)	4.7 ± 1.8	4.9 ± 1.8	5.0 ± 1.9	nr
BA–CA	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	nr
IGF-1 (ng/ml)	116.7 ± 59.4	145.9 ± 92.3	130.0 ± 84.1	nr
IGFBP-3 (μg/l)	3.2 ± 0.9	3.5 ± 0.9	3.4 ± 1.1	nr
IGF-1 SDS	–1.4 ± 0.6	–1.1 ± 0.9	–1.2 ± 1.0	nr
Fasting glucose (mmol/l)	4.6 ± 0.6	4.7 ± 0.6	4.6 ± 0.4	nr
Fasting insulin (μIU/ml)	3.1 ± 2.8	2.7 ± 1.9	2.8 ± 3.3	nr
HbA_{1c} (%)	5.2 ± 0.4	5.2 ± 0.3	5.1 ± 0.4	nr

Results at year 1 (mean ± SD)

	rhGH 0.033 mg/kg/day (*n* = 51)	rhGH 0.1 mg/kg/day (*n* = 51)	No treatment (*n* = 45)	*p*-value
HtSDS	–2.3 ± 0.6	–1.8 ± 0.8	–3.0 ± 0.6	nr
Change in HtSDS	0.8 ± 0.3	1.4 ± 0.4	0.1 ± 0.3	nr
Additional height gain (cm)	3.3 ± 0.2 (95% CI 2.9 to 3.7)	6.5 ± 0.2 (95% CI 6.0 to 6.9)	n/a	nr
IGF-1 (ng/ml)	345.6 ± 177	594.3 ± 221	176.3 ± 107	nr
IGFBP-3 (μg/l)	4.8 ± 1.1	6.1 ± 1.4	3.9 ± 1.1	nr
IGF-1 SDS	0.9 ± 1.9	3.3 ± 2.1	–0.9 ± 1.2	nr
Fasting glucose (mmol/l)	4.8 ± 0.5	5.0 ± 0.5	4.8 ± 0.6	nr
Fasting insulin (μIU/ml)	5.3 ± 3.5	8.9 ± 5.0	4.1 ± 6.3	nr
HbA_{1c} (%)	5.3 ± 0.4	5.3 ± 0.2	5.2 ± 0.4	nr

Adverse events

Only reported for overall 2-year study, so treatment arms are different (no control arm). The majority (349/358, 73.5%) of AEs were mild to moderate in severity, and the most common events (57%) were childhood infections. 16 SAEs were reported, three of which were likely to be related to rhGH (convulsions, epilepsy, papilloedema – all stabilised/resolved after rhGH discontinued).

Methodological comments

Allocation to treatment groups: Randomised 1 : 1 to double-blind treatment in the two rhGH groups or to a control group that was untreated in the first year and received rhGH in the second. A computer-controlled, centralised system was used to assign treatment.

Blinding: BA assessed centrally by clinicians blinded to subject's characteristics (other than gender) and treatment.

Comparability of treatment groups: Similar at baseline, but no *p*-values reported.

Method of data analysis: Mixed-effects model (ANCOVA) used where effects of age, sex and treatment duration were included. Tests were two-sided *F*-tests, performed at the 5% significance level.

Sample size/power calculation: At least 50 patients per group were required to detect a difference in height gain of 0.75 cm between the two rhGH groups with a power of 90% and a significance level of 0.05. To allow for comparison with the third group, and allowing for a dropout rate of 20%, 180 patients were required to be enrolled.

Attrition/dropout: Two randomised patients missing from analysis. Reasons not given.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Unclear
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Partial
6. Was the care provider blinded?	Inadequate
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Inadequate

SHOX deficiency data extraction forms

Reference and design	Intervention	Participants	Outcome measures
Blum *et al.* 2007[49] *Countries*: international (14) *Study design*: RCT *Number of centres*: 33 *Funding*: Eli Lilly & Co.	1. Daily s.c.i. of 50 μg GH 2. No treatment 3. Daily s.c.i. of 50 μg GH *Duration of treatment*: 2 years *Other interventions used*:	*Target population*: prepubertal children with SHOX-D *Number of participants*: total 68 patients had SHOX gene deletions or mutations, of which 52 with SHOX-D enrolled. A further 26 (group 3) with TS were enrolled as an additional GH arm 1. $n = 27$ 2. $n = 25$ 3. $n = 26$ (not data extracted as not per protocol) *Sample attrition/dropout*: one *Inclusion criteria for study entry*: confirmed SHOX-D; age ≥ 3 years; prepubertal (Tanner stage 1); height < 3rd percentile or < 10th percentile with HV < 25th percentile; BA < 10 years (boys) or < 8 years (girls); < 9 years (TS girls); no GH deficiency or resistance; no chronic disease; no growth-influencing medications	*Primary outcomes*: First year GV *Secondary outcomes*: comparison between treatment effects in SHOX-D and patients with TS (not data extracted as not per protocol); AEs *Method of assessing outcomes*: height, IGF-1 and IGFBP-3 measured at baseline, 3 months, 6 months, then at 6-month intervals for remainder of the 2 years; left hand and wrist radiographs for BA performed at baseline, 1 year and 2 year – assessed centrally using Greulich and Pyle method; glucose and routine blood analysis at baseline and first year. HtSDS calculated using a central European reference *Length of follow-up*: 2 years

Characteristics of participants (mean ± SD, unless otherwise stated)

Characteristic	SHOX-D		*p*-value, group 1 vs group 2
	Group 1: 50 μg GH ($n = 27$)	**Group 2: no treatment ($n = 25$)**	
Complete deletion of SHOX gene (*n*)	18	16	
Partial gene deletions (*n*)	2	2	
Point mutations (*n*)	7	7	
Female/male (%)	52/48	56/44	
LWS/ISS phenotype (%)	56/40	44/56	0.689
Chronological age (years)	7.5 ± 2.7	7.3 ± 2.1	0.914
BA (years)	6.6 ± 2.8	6.5 ± 2.0	0.928
BA–CA	–1.0 ± 0.9	–0.8 ± 0.8	0.809
BA SDS	–1.2 ± 1.1	–1.0 ± 1.0	0.641
HtSDS	–3.3 ± 1.0	–3.3 ± 0.8	0.111
Target HtSDS	–1.3 ± 1.0	–1.5 ± 0.9	0.013
BMI SDS	0.2 ± 0.9	0.6 ± 0.9	0.147
IGF-1 SDS	–0.8 ± 1.0	–0.9 ± 1.0	0.521
IGFBP-3 SDS	0.6 ± 1.3	0.1 ± 1.1	0.058

ISS, idiopathic short stature; LWS, Léri–Weill syndrome.

Results (mean ± SD, unless otherwise stated)

Outcome	SHOX-D Group 1: 50 µg GH	SHOX-D Group 2: no treatment	*p*-value group 1 vs group 2
Baseline HV (cm/year)	4.8 ± 0.3 (*n* = 18)	5.0 ± 0.5 (*n* = 14)	0.721
Baseline HV SDS	–1.2 ± 0.3 (*n* = 12)	–1.0 ± 0.6 (*n* = 10)	0.605
Baseline HtSDS	–3.3 ± 0.2 (*n* = 27)	–3.2 ± 0.2 (*n* = 24)	0.822
1st-year HV (cm/year)	8.7 ± 0.3 (*n* = 27)	5.2 ± 0.2 (*n* = 24)	< 0.001
1st-year HV SDS	3.0 ± 0.3 (*n* = 25)	–0.7 ± 0.2 (*n* = 22)	< 0.001
1st-year HtSDS	–2.6 ± 0.2 (*n* = 27)	–3.1 ± 0.2 (*n* = 24)	< 0.001
2nd-year HV (cm/year)	7.3 ± 0.2 (*n* = 27)	5.4 ± 0.2 (*n* = 24)	< 0.001
2nd-year HV SDS	2.3 ± 0.3 (*n* = 27)	–0.4 ± 0.1 (*n* = 22)	< 0.001
2nd-year HtSDS	–2.1 ± 0.2 (*n* = 27)	–3.0 ± 0.2 (*n* = 24)	< 0.001
2nd-year height gain (cm)	16.4 ± 0.4 (*n* = 27)	10.5 ± 0.4 (*n* = 24)	< 0.001
Catch-up of BA	1.34 ± 0.07	1.1 ± 0.09	0.161

AEs

	SHOX-D Group 1: 50 µg GH (*n* = 27)	SHOX-D Group 2: no treatment (*n* = 25)	*p*-value group 1 vs group 2
At least 1 treatment-emergent AE (mostly common childhood illnesses) (%)	85	68	
Arthralgia	3	2	
Gynecomastia (males)	1 (*n* = 12 males)	0 (*n* = 12 males)	
Increased number of cutaneous naevi	2	0	
Recurrent otitis media	1	1	
Scoliosis	1	0	
Diabetes	0	0	

Comments

Overall, 41% of GH-treated patients with SHOX-D reached a height within the normal range for age and gender (> –2.0 SDS), compared with only one patient in the control group. For the GH-treated patients with SHOX-D, 1st year GV was somewhat greater for males (9.3 ± 0.5 cm/year) than for females (8.4 ± 0.5 cm/year), the baseline to second-year change in GV was very similar. Subgroup analysis for ISS phenotype vs LWS phenotype presented but not data extracted as not per protocol. IGF-1 SDS were in the low-normal range in each of the study groups at baseline and remained there for the untreated group. In the GH-treated group, values increased to the upper-normal range. IGF-1 concentrations exceeded two SDS at least once during GH treatment in 10 (37%) of patients and no untreated patients. IGFBP-3 SDS at baseline were closer to the normal mean than the corresponding IGF-1 SDS in both study groups and increased to the upper-normal range in the treated group. There was a strong relationship between IGF-1 SDS and IGFBP-3 SDS values during GH treatment, such that no subject had an IGF-1 SDS in the upper tertile with an IGFBP-3 SDS in the lower tertile. No significant changes in thyroid function. No SAEs were reported for subjects with SHOX-D.

Methodological comments

Allocation to treatment groups: After stratification by sex and according to presence or absence of LWS, patients were randomised on a 1 : 1 basis. No further details given.

Blinding: Blood analyses were carried out in a central facility. Open label.

Comparability of treatment groups: Similar at baseline, although target HtSDS is statistically significantly lower in the rhGH group.

Method of data analysis: HtSDS calculated using a central European reference.

Sample size/power calculation: Not reported.

Attrition/dropout: One subject who discontinued with no postbaseline height data was excluded from the efficacy analyses; all patients were included in the safety analyses. ANOVA used for between-group differences.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Partial
6. Was the care provider blinded?	Inadequate
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Inadequate

Appendix 5
List of excluded studies

Excluded due to wrong patient group (*n* = 40)

Arends NJ, Boonstra VH, Mulder PG, Odink RJ, Stokvis-Brantsma WH, Rongen-Westerlaken C, *et al*. GH treatment and its effect on bone mineral density, bone maturation and growth in short children born small for gestational age: 3-year results of a randomised, controlled GH trial. *Clin Endocrinol* 2003;**59**:779–87.

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Excluded due to study design (*n* = 27)

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Excluded due to wrong intervention (*n* = 4)

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Excluded due to wrong outcomes (*n* = 4)

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Reason for exclusion – repeat publication with no new randomised data

Lindgren AC, Ritzen EM. Five years of growth hormone treatment in children with Prader-Willi syndrome. Swedish National Growth Hormone Advisory Group. *Acta Paediatr* 1999;**88**(Suppl. 433):109–11.

Reason for exclusion – conference paper pre-2006

Fine RN, Kohaut EC, Frane JW, Perlman AJ. Multicenter randomized double-blind placebo-controlled study of recombinant human growth-hormone (r-hGH) in children with chronic-renal-failure (CRF). *Clin Res* 1993;**41**:A283.

Reason for exclusion – previous HTA report

Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, *et al*. Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation. *Health Technol Assess* 2002;**6**(18).

Reason for exclusion – conference paper abstract

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born small for gestational age (SGA). *Value Health* 2008;**11**:A223.

Reason for exclusion – children of short stature, not part of scope

Lee JM, Davis MM, Clark SJ, Hofer TP, Kemper AR. Estimated cost-effectiveness of growth hormone therapy for idiopathic short stature. *Arch Pediatr Adolesc Med* 2006;**160**:263–9.

Reason for exclusion – disease-specific QoL measure used

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Sheppard L, Eiser C, Davies HA, Carney S, Clarke SA, Urquhart T, *et al*. The effects of growth hormone treatment on health-related quality of life in children. *Horm Res* 2006;**65**:243–9.

Reason for exclusion – mixed patient group of adults and children

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Reason for exclusion – review article

Petrou S, McIntosh E. Measuring the benefits of growth hormone therapy in children: a role for preference-based approaches? *Arch Dis Child* 2008;**93**:95–7.

Reason for exclusion – unclear whether adult or child onset

Suzukamo Y, Noguchi H, Takahashi N, Shimatsu A, Chihara K, Green J, *et al*. Validation of the Japanese version of the Quality of Life-Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA). *Growth Horm IGF Res* 2006;**16**:340–7.

Appendix 6

List of eligible abstracts

The following conference abstracts were identified in searches and were of relevance to the review, but did not contain sufficient information to be included.

Gardner M, Boshart M, Carron L, Sandberg D. Effects of growth hormone in childhood on quality of life end points: a systematic review. Paediatric Acadamic Societies' (PES) Conference, Baltimore, May 2009.

Phillip M, Lebl J, Steensberg A, Kappelgaard A-M, Ibanez L. Metabolic parameters during growth hormone treatment in short children born small for gestational age. *Hormone Research* 2008;**70**(Suppl.1);100.

Salgin B. Effect of growth hormone treatment on insulin secretion and sensitivity in relation to growth of children born small for gestational age. *Hormone Research* 2008;**70**(Suppl.1);76.

Appendix 7

List of ongoing studies

Searches identified two relevant RCTs, which are ongoing

Study NCT00190658 aims to compare the mean first-year GV of somatropin-treated prepubertal patients with SHOX-D with the GV of a control group of untreated prepubertal patients with SHOX-D. Both groups will be compared to a somatropin-treated group of girls with TS.

- Sponsor: Eli Lilly & Co.
- Estimated end date: December 2010.

Study NCT00625872 focuses on the effect of a 1-year somatropin treatment (0.035 mg/kg/day or 0.067 mg/kg/day) on neuromuscular function and cognitive performance in short children born SGA. Height gain and GV are included as secondary outcome measures. Inclusion criteria are birth length- and/or birth weight-SDS adjusted to gestational age < –2.0, current HtSDS < –2.5 and parental adjusted HtSDS below –1, GV SDS < 0 during the last year before inclusion.

- Sponsor: Pfizer.
- End date: not reported.

Appendix 8

Critique of industry submissions (clinical effectiveness)

Six of the seven manufacturers submitted reports to NICE, and these are briefly appraised below. Please see Chapter 4 (Review of the manufacturers' submissions) for a discussion of the economic models and results included in the MSs.

SHTAC review of clinical effectiveness in Eli Lilly's submission

Comprehensiveness of ascertainment of published studies

- The MS uses the Novo Nordisk systematic review, which did not include SHOX. The MS states (p. 13) that the evidence for SHOX came from Lilly's databases, i.e. there was no systematic review for this. The conditions listed as inclusion criteria for SGA include IUGR, which was not in the NICE scope. The comparator was clearly stated to be 'no treatment'. However, the inclusion criteria also state that active-controlled RCTs were included. This is then contradicted by the exclusion criteria, which state that studies comparing somatropin with other treatments known or presumed to affect growth would be excluded.
- The MS clearly reports search dates, search strategies and databases searched.
- Enough detail was provided for the searches to be reproducible.
- The MS does not present information on searches for ongoing studies.
- Conference proceedings were excluded from the review.
- The MS includes a separate search for QoL data in adolescents and adults.

Searches identified

The MS contains a summary of the included trials, but there is no tabulation of details such as study type, treatment arms, etc. The review included the following RCTs:

- *GHD* Five placebo/no treatment-controlled RCTs (mostly during transition phase): Jorgensen 2002 (excluded by SHTAC as mean age = 20), Underwood 2003 (excluded by SHTAC as mean age = 23.8), Drake 2003, Shalet 2003 and Mauras 2005 (all excluded by SHTAC as patients had completed linear growth). The manufacturer included six other studies that were either dosing studies or compared two different versions of somatropin.
- *TS* Nine RCTs (three placebo controlled: Gravholt 2002, 2005; Quigley 2002; all included by SHTAC) and six other studies [Bannick 2006, van Pareren 2003, Sas 2001 (all excluded by SHTAC as dose studies), Davenport 2007, Johnston 2001, CGHAC 2005 (all included by SHTAC)].
- *CRI* Four CTs: de Graaf 2003 (SHTAC excluded as this is analysis of body proportions in an RCT that we have already included for height and body composition outcomes – Hokken Koelega 1991), Hertel 2002 (SHTAC excluded as compares two doses, no placebo arm), Sanchez 2002 (included by SHTAC), Fine 2002 (SHTAC excluded as includes pubertal children, with no separate data analysis).
- *SGA* Twenty RCTs identified, of which six had placebo or no treatment as control arm [Boguszweski 1998, Butenadt 1997, Arends 2003 2004, Boonstra 2006 (SHTAC excluded these as patient group did not meet our criteria), van Pareren 2003 (SHTAC excluded as this is a follow-up of a dose–response study)].
- *PWS* not relevant for this drug.
- *SHOX* not included in systematic review. Reported data comes from the GDFN study ($n = 78$), Blum *et al.* 2007 (SHTAC included this).
- None of the additional studies met SHTAC's inclusion criteria.

Clinical analysis

- The MS also reports observational studies, in particular data from the KIGS database.
- Given that the manufacturer included a range of studies that did not meet SHTAC's inclusion criteria, it is not possible to compare their conclusions with those of SHTAC.
- The MS did not include a meta-analysis or indirect comparison.

- The MS includes a short narrative summary of the included trials for each disease, but there is no overall tabulation of the included studies' characteristics or results and no quality assessment of the trials.
- The MS uses the same outcome measures as the SHTAC review.
- The MS reports more detail on AEs from observational studies in addition to the limited information available in the RCTs.

Interpretation

- The MS does not present any tabulated data from the studies included in the systematic review; there is simply a short narrative summary of each disease. It is therefore not possible to assess whether or not the manufacturer's analysis is supported by data in the included trials.

Key issues

- The manufacturer's systematic review included a broad range of studies, for example dosage studies, which did not meet their own inclusion criteria.
- Very little detail is presented for the included studies (e.g. patient characteristics, treatment arms, length of study) and there is no tabulation of data. The manufacturer's conclusions seem to be based on both trials that met their inclusion criteria and those that clearly did not (e.g. dosage studies).

SHTAC review of clinical effectiveness in Novo Nordisk's submission

Comprehensiveness of ascertainment of published studies

- Databases searched and the dates of searches are specified. Searches were conducted from the date of the original NICE appraisal – w/c 28 August 2008, and from 1996 to w/c 28 August 2008 for SGA (not included in the last review).
- Search strategies are supplied in the appendices.
- Search strategies are detailed and appear reproducible.
- Novo Nordisk does not appear to have searched for other ongoing studies, but do report on two ongoing studies, specifically of Norditropin – NESGAS and NordiNet IOS.
- Conference proceedings were not searched for and are listed in the exclusion criteria.

Clinical analysis

- Novo Nordisk did not include PWS or SHOX. Uncontrolled trials were included. For long-term effects of rhGH treatment, i.e. FH/AH/near adult height, open-label extension studies were 'deemed to be appropriate as the length of the RCTs was likely to be too short to capture the long term treatment effect'. Dose–response trials have been included. In the case of SGA, these form the majority of the submission.
- *SGA* Novo Nordisk have included 21 studies. None of these was included in SHTAC's MTA. Exclusions in the SHTAC MTA were on the basis of patient group not meeting the inclusion criteria or on design, as 14 of the 21 were dose–response studies. The five studies included in our MTA were not included in the Novo Nordisk submission. Novo Nordisk also included open-label extension studies.
- *GHD* Novo Nordisk have included 13 studies. One of these is the GHD study included in SHTAC's MTA. Eight are transition-phase studies – these are not included in SHTAC's systematic review. Four are dose–response studies and therefore are excluded from the MTA. Two are biosimilars compared with their reference product.
- *TS* Novo Nordisk discuss the Turner Cochrane Review. A total of 23 studies were included, including the six included in SHTAC's MTA. The remaining studies were dose response, with the exception of one, which compared once-daily versus twice-daily injections.
- *CRI* Novo Nordisk have included nine studies, five of which were included in SHTAC's MTA. Of the four excluded from the MTA, two were dose–response studies, one was excluded on patient group.
- Nothing in the excluded reasons indicates why all of SHTAC's included SGA papers are excluded.

Conclusions

- *SGA* It is not possible to compare the conclusions as the studies included in the two reviews are so different.
- *GHD* Again the conclusions are difficult to compare as Novo Nordisk include transition phase studies, which SHTAC excluded from the main systematic review as patients had completed linear growth; dose–response studies; and studies comparing biosimilars to their reference drug. Novo Nordisk's conclusions tend to be based on dose–response

studies, and how far an outcome/result is dose dependent.
- *TS* Novo Nordisk concludes that height is improved in a 'dose-dependent' manner: The SHTAC MTA does not include dose–response studies or consider dose issues. SHTAC has concluded that there is evidence of improved body composition and height outcomes in girls with TS; this needs to be weighed against issues of quality of reporting and size of trials.
- *CRI* Height conclusions are dose related, and body composition 'does not appear to be negatively influenced by rhGH therapy'.
- Outcome measures are broadly similar.
- Additional AE rates from KIGS and NCGS databases are included in an appendix.

Interpretation
- *SGA* Conclusions do not appear to fully reflect Novo Nordisk's analyses, although the analysis contains few results and is a broad summary in itself. Very few of the points discussed in the analyses compare treated and untreated groups, predominantly focusing on dose–response or differences in the treated group from baseline.
- *TS* Apart from height outcomes, few results are reported and, again, the focus is often on dose-related effects. The summary somewhat overstates the evidence presented.
- *CRI* Conclusions do appear to match analyses, although again few detailed results are presented. Novo Nordisk does not comment on the quantity/quality of research available to support their conclusions.
- *GHD* Novo Nordisk considered transition-phase studies alongside non-transition phase studies for height and other outcomes, but separately for biochemical/body composition markers. The authors then summarise that the transition phase studies may lead to an underestimation of growth in children with GHD. Other conclusions appear to match the analyses.
- Quality is discussed to a degree in the results sections – it is mentioned, for example, if trials are short, or low in patient numbers. However, this, or its possible effects on conclusions/findings, is not referred to in the summary.

Key issues
- The submission does not include the SGA papers included in SHTAC's review, but does include studies whose patients do not meet the birth length/WtSDS criteria and/or current HtSDS criteria included.
- Dose–response studies are included for all conditions.

SHTAC review of clinical effectiveness in Pfizer's submission

Comprehensiveness of ascertainment of published studies
- The manufacturer supplied full details of the systematic review, specifying dates and databases searched.
- Search strategies were supplied.
- Enough detail was provided for the searches to be reproducible.
- Inclusion criteria differed from that used by SHTAC in that cohort, observational, and retrospective studies were included. The manufacturer's inclusion criteria defined children as being < 16 years old, whereas SHTAC included those up to 18 since they may still be growing and thus able to benefit from rhGH treatment. The manufacturer did not specify what the comparator should be (NICE's final scope indicates that this should be treatment without somatropin).
- The manufacturer restricted the review to only those studies which used Genotropin, or were sponsored by Pfizer. They excluded studies which used a competitor's brand of somatropin. However, they also report the results of the Novo Nordisk full systematic review – see SHTAC assessment of the Novo Nordisk MS for more details.
- The MS does not report ongoing studies.
- The MS does not state whether or not they searched for conference proceedings.

Searches identified (studies for Genotropin)
- *GHD* Three RCTs and 17 observational studies. None of the three RCTs met our inclusion criteria. Coelho *et al*. (2008) compared two doses of Genotropin; Romer *et al*. (2007) compared omnitrope with Genotropin; Dorr *et al*. (2003) compared Genotropin delivered via two different devices.
- *TS* One RCT and eight observational studies: the single RCT by Johnston (2001) was also included in the SHTAC review.
- *PWS* Twelve RCTs (three from previous appraisal) and six observational studies. One of these (Festen 2007) is not included

in our review as it is not a fully randomised study (children were stratified by age, and only the under-12s were randomized – older children were all given rhGH, but results were not reported separately for the randomised patients). Two of the studies included by the manufacturer have been combined by SHTAC, as they report data from the same RCT [Festen *et al*. 2008 and de Lind van Wijngaarden 2009 (cited as Roderick *et al.* 2009 in the MS)].
- *CRI* No new RCTs, three observational studies. The submission discusses only the Broyer study from the previous review, and not the others that SHTAC included as these were not observing Genotropin.
- *SGA* Thirteen RCTs, 10 observational studies. Of the 13 RCTs, only five reported treatment versus no treatment/placebo. SHTAC excluded the review by Lagrou (2007) as its outcomes did not meet our inclusion criteria. We also excluded the reviews by Bundak (2001) and Carracosa (2006) as their patient groups did not match our criteria. We included the De Schepper (2008) study and the de Zegher (2002) studies.
- None of the manufacturer's included studies reported QoL as an outcome measure.
- The MS also includes a summary of the Novo Nordisk systematic review. Please see SHTAC's appraisal of that submission for further details.

Clinical analysis
- The manufacturer has only included RCTs of its own brand of somatropin, so it is not possible to compare their findings directly with those of SHTAC.
- *GH and SGA RCTs* The MS and SHTAC reviews included different RCTs, so it is not possible to compare the evidence reported. The RCTs included for GHD were not placebo/no treatment controlled.
- *PWS* The MS includes two studies (Roderick *et al.* 2009 and Festen *et al.* 2008), which appear to be the same RCT – SHTAC has treated these as one RCT to avoid double-counting.
- Given that the manufacturer included a range of studies that did not meet SHTAC's inclusion criteria, and focused only on studies of their own product, it is not possible to compare their conclusions directly with those of SHTAC.
- The MS did not include a meta-analysis or indirect comparison. Results are presented in tables and there is a narrative synthesis for each disease area.
- The MS uses the same outcome measures as the SHTAC review.
- The MS includes data from the KIGS database, which is not included in the SHTAC review of clinical effectiveness as it is observational data. Additional adverse event data from the KIGS database is presented on p. 97 of the MS.

Interpretation
- The manufacturer's interpretation of the clinical data in the RCTs matches their analyses.
- There are separate sections discussing the results of RCTs and of observational studies.
- Data from observational studies have not been checked by SHTAC.

Key issues
- The manufacturer's systematic review included dose comparison studies for GHD, which SHTAC excluded.
- Many of the studies included for the manufacturer's review of SGA studies were excluded by SHTAC, as their patients did not meet our inclusion criteria.

SHTAC review of clinical effectiveness in Merck Serono's submission

Comprehensiveness of ascertainment of published studies
- The MS uses the SHTAC review conducted in 2002[6] and the systematic review conducted by Novo Nordisk for studies published since then (see Novo Nordisk critique) for the licensed indications for Saizen (GHD, TS, CRI and SGA).

Searches identified
- Studies identified and reported are all those from the previous SHTAC report (RCTs and non-RCTs reporting FH) plus RCTs published since then identified by the Novo Nordisk review.
- *GHD* No additional RCTs were reported for GHD although an additional one is included in the SHTAC MTA (Mauras 2005).
- *TS* 4 RCTs (Johnston 2001; CGHAC 2005; Quigley 2002; Davenport 2007). However, the MS did not identify two RCTs included in the SHTAC MTA (both Gravholt 2005).
- *CRI* Three RCTs (de Graaf 2003; Fine 2002; Sanchez 2002). Two of these (de Graaf and Fine) are not included in the SHTAC MTA review because they do not meet our inclusion criteria. One RCT (Fine 2004) is not included

in the MS but meets the SHTAC MTA inclusion criteria and is therefore included in that.
- *SGA* Four RCTs (Buttenandt 1997; Boguszewski 1998; Arends 2004; Van Pareren 2003). These do not match the studies identified in the SHTAC MTA (from which they are excluded on the basis of patient group and study design).
- The MS does not identify any RCTs that meet the inclusion criteria of the SHTAC MTA that are not already included.

Clinical analysis
- Evidence reported is broadly similar to the SHTAC MTA in that it uses RCTs in the original SHTAC report; there are some discrepancies on RCTs since that time and on the extra indication SGA.
- Narrative synthesis is somewhat selective. All included studies are tabulated, but only height results are reported.
- Manufacturer's submission also includes some non-systematic review data on psychological outcomes and body composition, and long-term data from the KIGS observational database.
- Conclusions are generally similar to the SHTAC MTA.
- *GHD* The MS has used the previous SHTAC review so conclusions on growth are similar but no data on LBM/biochemical markers.
- *TS* Conclusions are broadly similar to the SHTAC MTA in terms of growth and LBM.
- *CRI* Conclusions broadly similar to the SHTAC MTA in terms of growth; no statement on other outcomes.
- *SGA* Conclusions broadly similar to the SHTAC MTA in terms of growth; no statement on other outcomes.
- Growth outcomes measures are same as the SHTAC MTA.

Interpretation
- Overall MS interpretation of the clinical data matches the MS analyses, although the MS relies heavily on the previous SHTAC report. The new evidence is not really synthesised except for SGA, which includes studies that are not in the SHTAC MTA. Conclusions are based on selective statements and focus on height outcomes.
- Manufacturer's submission states that new data has 'not materially changed the understanding of the efficacy of GH in children'.

Questions
- The major areas of discrepancy compared with the SHTAC MTA relate to studies omitted from the MS (GHD 1, TS 2, CRI 1 and SGA 5).

SHTAC review of clinical effectiveness in Ipsen Ltd's submission

Comprehensiveness of ascertainment of published studies
- The databases and dates searched are specified.
- Search strategies were supplied and appear comprehensive enough to be reproducible.
- Ongoing studies were not searched for or reported in this submission.
- Conference proceedings were excluded.
- This review includes CRI, GHD and TS, and 'somatropin' as intervention, including products from other manufacturers, and published and available in full studies in the English language. Exclusion criteria given but reasons for individual studies' exclusions not stated.
- Assessment of article quality looks at allocation concealment, patient blinding, investigator blinding, baseline differences of the experimental groups and 'completeness of follow-up'. The MS did not appear to assess if there was an ITT analysis, or care-provider blinding.

Clinical analysis
- For the results of the systematic review, we are referred to the submission prepared by Novo Nordisk. Studies are not referenced in the text. No conclusions in this submission, apart from on the limitations of RCTs for FH data, and the subsequent need to rely on observational studies (i.e. KIGS database) for this. The number of studies for each condition reporting certain outcomes is given, but the results are in the Novo Nordisk submission and not detailed in the Ipsen submission.
- Manufacturer has included 11 GHD studies; most appear to be transition-phase studies.
- MS states that nine TS studies were found.
- MS states that four CRI studies were found.
- Limited new data on FH from RCTs, so appear to have included observational studies for this outcome. However, no references are given in the text so cannot check.
- The MS states that 'there are limited data available on the effect of GH on height in

RCTs [therefore] use of observational data from … KIGS was appropriate.' This appears to have been used to inform the economic model.
- A 'rapid appraisal of the literature' was undertaken by Eli Lilly for QoL 'impact of short stature in adults' due to lack of data on children and QoL.
- No conclusions stated here: referred to Novo Nordisk submission.
- There are no indirect comparisons included here.
- No outcome results are reported here, but those outcomes reported in the included studies reflect those in the SHTAC review.
- *GHD* Four out of eight studies reporting AE 'found that a higher dose was associated with a greater incidence of AEs and/or serious AEs'. The remaining studies reported no differences between groups. Only one study in the SHTAC review reported AEs, with a slightly higher percentage in the GH group experiencing these. Only one event in each group was thought to be study drug related: oedema in GH and sluggishness in placebo. MS reports AEs that are thought to be related to study drug.
- *CRI* Three studies in the MS report AEs: one study reported a higher number of SAEs related to GH therapy compared with no treatment; another study reported SAEs that were 'therapy-related'. SAEs related to therapy reported here include diabetes mellitus, hypertension and injection pain. This is not reflected in the studies included in SHTAC review. Difficulty with comparisons as there are no references in the text.
- *TS* A greater incidence of AE in the GH group was reported in two out of four studies reporting AEs in the SHTAC review. In the MS, one study showed GH to be associated with 'greater incidence of treatment emergent AEs'. No major differences between the groups were found in the other studies in the MS.
- No references are given for these studies and AEs, and no proportions/means are reported – just these general results.

Interpretation
- No interpretation included here – referred to the Novo Nordisk submission.

Key issues
- Inclusion of observational data to inform FH differs from SHTAC review.
- Studies not referenced here – cannot cross-check with SHTAC review. See Novo Nordisk submission for further details.

SHTAC review of clinical effectiveness in Sandoz's submission

Comprehensiveness of ascertainment of published studies
- The submission did not include a systematic review, so there were no details of search strategies, databases or dates searched.

Searches identified
- The MS includes details of two phase III studies: AQ-study and LYO-study. Neither meets SHTAC's inclusion criteria; AQ-study compares different doses of omnitrope with a reference product and LYO-study is a non-comparative trial.

Clinical analysis
- The evidence reported in the Sandoz submission is from trials specific to their biosimilar product. The submission does not include any trials of rhGH versus no treatment. It is therefore not possible to compare their submission with the evidence presented in the SHTAC systematic review.
- The submission uses the same outcome measures as the SHTAC review.
- The submission includes a summary of AEs from the AQ-study and the LYO-study, neither of which was included in the SHTAC review. The manufacturer stated that the safety profiles of omnitrope and Genotropin were comparable.

Interpretation
- The manufacturer's interpretation of the clinical data matches their analyses.

Key issues
- The manufacturer presents evidence for the use of omnitrope compared with other somatropin formulations, but does not present any information for its effectiveness compared with no treatment. The included studies did not meet SHTAC's inclusion criteria.

Appendix 9

Critical appraisal of manufacturers' economic evaluation

TABLE 61 *Critical appraisal checklist of economic evaluation (questions in this checklist based on Drummond and Jefferson, the NICE reference case, and the ISPOR checklist)*

	Item	MS[a]
1	Is there a well-defined question?	Yes
2	Is the patient group in the study similar to those of interest in UK NHS?	Yes
3	Is the correct comparator used that is routinely used in NHS?	Yes
4	Is the study type and modelling methodology reasonable?	Yes
5	Is an appropriate perspective used for the analysis?	Yes
6	Is the health-care system or setting comparable to UK?	Yes
7	Is the effectiveness of the intervention established based on a systematic review?	No
8	Is the model structure appropriate and does it fit with the clinical theory of the disease process?	Yes
9	Are assumptions reasonable and appropriate?	Yes
10	Are health benefits measured in QALYs using a standardised and validated generic instrument from a representative sample of the public?	Yes
11	Are the resource costs used reasonable and appropriate for the NHS?	Yes
12	Are the health states and parameters used in the model described clearly and are they reasonable and appropriate for the NHS?	?
13	Is an appropriate discount rate used?	Yes
14	Has the model been validated appropriately?	?
15	Is sensitivity analysis undertaken and presented clearly?	Yes

a Yes/no/? (unclear or partially true).

Appendix 10

Critical appraisal of Sandoz MS (cost-effectiveness)

This appendix describes a critical appraisal of the cost-effectiveness section of the Sandoz MS. The submission attempts a cost-minimisation analysis comparing omnitrope with Genotropin (which was defined as the reference product) in patients with GHD and TS, rather than a cost-effectiveness analysis. There is no indication that a systematic review of clinical evidence has been undertaken. The cost-effectiveness analysis according to NICE guidance[138] was not presented.

Appraisal of the manufacturer cost-effectiveness analysis

A summary of the MS compared with the NICE reference case requirements is given in *Table 62*.

Summary of general concerns

The MS did not comply with NICE's recommended structure[138] and did not estimate QALYs or present cost-effectiveness analysis. The MS attempted a cost-minimisation analysis, implicitly suggesting that treatment with omnitrope is equally effective as treatment with Genotropin (in terms of additional height in children with GHD and TS), but is associated with less cost to the NHS. Due to the number of uncertainties it is not clear whether this assertion is justified. In particular, there was limited clinical efficacy data to support the non-inferiority of omnitrope compared with Genotropin. The only head-to-head RCT comparing omnitrope with Genotropin was of insufficient duration and might not have been designed as a non-inferiority trial.

TABLE 62 *Assessment of Sandoz submission against NICE reference case requirements*

NICE reference case requirements	Included in submission
Decision problem: as per the scope developed by NICE	×[a]
Comparator: no treatment alternative	×[a]
Perspective on costs: NHS and PSS	✓[b]
Perspective on outcomes: all health effects on individuals	×[c]
Type of economic evaluation: cost-effectiveness analysis	×
Synthesis of evidence on outcomes: based on a systematic review	No evidence synthesis
Measure of health benefits: QALYs	×
Description of health states for QALY calculations: use of a standardised and validated generic instrument	×
Method of preference elicitation for health state values: choice based method (e.g. TTO, SG, not rating scale)	×
Source of preference data: representative sample of the public	×
Discount rate: 3.5% p.a. for costs and health effects	×

✓, yes; ×, no.
a Scope states that rhGH (somatropin) be compared with no treatment alternative. The cost comparison includes only omnitrope and Genotropin.
b Only costs of pharmaceuticals omnitrope and Genotropin are included in cost comparison.
c The MS does not include an economic evaluation according to the NICE guidance. Patient outcomes (either observed or the final outcomes) are not included in the health economics part of the MS.

The MS did not include any clinical evidence in relation to licensed indications other than GHD. Without clinical evidence that unequivocally demonstrated the non-inferiority of omnitrope in comparison with Genotropin, the results of a cost-minimisation analysis cannot be confirmed.

The results of the cost comparison reported in the MS were not comparable with the results of cost-effectiveness analysis reported in the submissions by Pfizer, Eli Lilly, Ipsen, Novo Nordisk and Merck Serono because Sandoz have not presented results either as an estimated incremental cost per QALY or as an incremental cost per extra centimetre gained, and the reported cost was neither a lifetime cost nor the cost per duration of treatment (until near-adult height is achieved).

Appendix 11
Quality of life from HSE 2003

The Health Survey for England database was reanalysed in a similar way to Christensen and colleagues for adults aged older than 18 years. The HSE 2003 contains variables for height (estht) and EQ-5D (eqmean). Incomplete records were omitted. For those with complete records (n = 13,321), the HSE 2003 data had mean AH for males of 175 cm (SD 7.2) and mean AH for females of 161 cm (6.8). There were 50 observations less than –3 SDS or greater than 3 SDS (i.e. 0.4%) and 617 observations less than –2 SDS or greater than 2 SDS (4.6%).

An analysis was completed to see the effect of different ages on QoL scores using a subset of people of age 18–49 years and over 50 years old. QoL score for all ages was 0.86; age 18–49 years QoL had mean 0.91 (SD = 0.18); and age 50+ years QoL had mean 0.8 (SD = 0.26). The QoL in the younger category was significantly better than for the older category and so it is logical to estimate the EQ-5D for each of these age groups.

There were few individuals in the SDS < –3 group and the estimates are highly variable. In addition, the majority of these individuals are in the older age group (mean age 72 years). It is therefore more logical to fit the distribution to all data and use this in the model.

TABLE 63 *Frequency of individuals at different ages and HtSDS in HSE 2003*

	Age 18–49 years		Age 50+ years	
SDS	***n***	**Eqmean**	***n***	**Eqmean**
<–3.0	5	0.85	24	0.63
–3 to < –2.5	6	0.75	62	0.70
–2.5 to < –2.0	42	0.88	161	0.73
–2 to < –1.5	140	0.85	397	0.78
–1.5 to < –1.0	475	0.91	798	0.79
–1.0 to <–0.5	845	0.90	1133	0.78
–0.5 to <0	1331	0.90	1288	0.82
0 to <0.5	1485	0.91	1029	0.81
0.5 to < 1.0	1288	0.91	707	0.83
1.0 to < 1.5	837	0.91	368	0.84
1.5 to <2.0	431	0.91	152	0.85
2.0 to <2.5	201	0.92	41	0.84
2.5 to <3.0	42	0.89	12	0.83
>3.0	20	0.98	1	0.90

TABLE 64 *Quality of life from fitted values*

Age	Fitted QoL score
18–49 years	$-0.0024x^2 + 0.0177x + 0.9017$
> 50 years	$-0.0054x^2 + 0.0297x + 0.817$

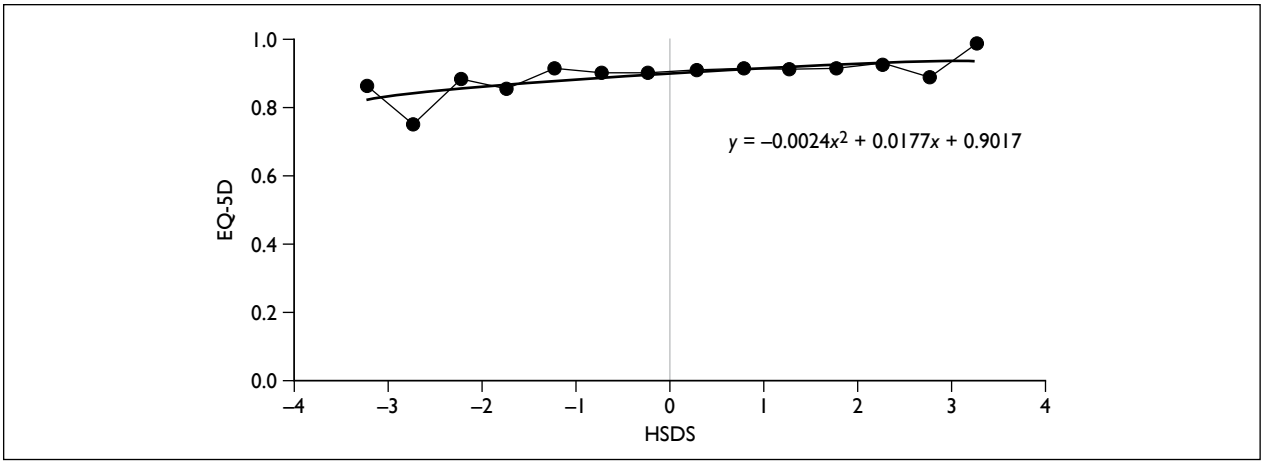

FIGURE 9 *Relationship between height (HtSDS) and EQ-5D score for adults aged 18 –50 years in HSE 2003.*

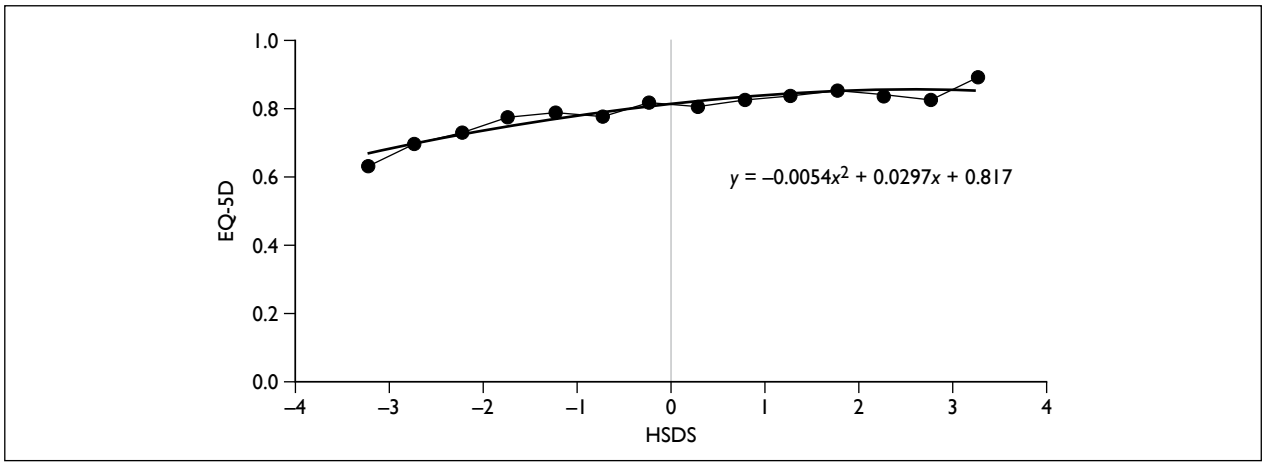

FIGURE 10 *Relationship between height (HtSDS) and EQ-5D score for adults aged older than 50 years in HSE 2003.*

Appendix 12

Input parameters for probabilistic sensitivity analysis

The distribution assigned to each variable included in the PSA and the parameters of the distribution are reported in this appendix.

Health-state utility

The utility increments for HtSDS below –2.0, between –2.0 and 0, and above 0 were sampled using estimated standard errors. These were derived from an assumption that a variation of plus or minus 20% was an appropriate CI for the average utility gain. No other summary statistic was available. These were sampled using a normal distribution.

Compliance

The compliance of the model was based on the range of 69% to 95% compliance estimated in the compliance review conducted by Merck Serono. The estimated 'standard errors' for compliance was derived from this range, as this was thought to provide the best estimate of variability due to lack of other summary data.

Height standard deviations

The reported mean HtSDSs were taken from the applicable RCTs and KIGS data for both the treated and untreated groups consistent with the base-case analysis. The standard errors were calculated for each mean HtSDS, except for PWS, for which there was no mean reported; in this case a median value was assumed to adequately represent the mean. A SD of 1 was used to estimate the standard error for PWS. This is consistent with the level of dispersion reported for the other conditions. The HtSDS were simulated using the normal distributions. See *Table 67* for mean and standard errors for each condition:

Starting age and treatment length

The starting age and treatment length were sampled using estimated 'standard errors'. These were derived from CIs placed 2 years either side of the mean starting age and treatment length. This method was used instead of calculating the standard errors from the KIGS database. It was felt that the very small standard errors from KIGS did not reflect the possible variability in starting age and treatment length. These were sampled using normal distributions.

Childhood drug dose

The means for the childhood drug dose for all the conditions were the same as used in the base-case analysis. The estimated 'standard errors' attempted

TABLE 65 *Health-state utility parameters and distribution*

			95% CI		
Health-state utility	**Mean**	**'Standard error'**	**Lower**	**Upper**	**Distribution**
Below –2 HtSDS	0.061	0.0061	0.049	0.730	Normal
Between –2 and 0 HtSDS	0.010	0.0010	0.008	0.120	
Above 0 HtSDS	0.002	0.0002	0.0016	0.0024	

TABLE 66 *Compliance parameters and distribution*

	Mean	**'Standard error'**	**Alpha**	**Beta**	**Distribution**
Compliance	0.85	0.085	14.150	2.497	Beta

TABLE 67 *HtSDS parameters and distribution*

Condition	HtSDS	Mean	Standard error	Distribution
GHD	Treated baseline	–2.99	0.0134	Normal
	Treated end	–1.17	0.0216	
	Untreated baseline	–2.99	0.0134	
	Untreated end	–2.99	0.0216	
TS	Treated baseline	–3.40	0.1152	
	Treated end	–1.80	0.0206	
	Untreated baseline	–3.40	0.1220	
	Untreated end	–3.10	0.2294	
PWS	Treated baseline	–2.00	0.2000	
	Treated end	–0.50	0.2085	
	Untreated baseline	–2.50	0.2132	
	Untreated end	–2.60	0.2182	
CRI	Treated baseline	–2.90	0.1214	
	Treated end	–1.60	0.1925	
	Untreated baseline	–2.90	0.0994	
	Untreated end	–2.90	0.1525	
SGA	Treated baseline	–3.10	0.0700	
	Treated end	–2.30	0.0840	
	Untreated baseline	–3.10	0.0729	
	Untreated end	–3.00	0.0894	
SHOX-D	Treated baseline	–3.30	0.1925	
	Treated end	–2.10	0.0385	
	Untreated baseline	–3.30	0.1600	
	Untreated end	–3.00	0.0408	

TABLE 68 *Starting age and treatment length parameters and distribution*

			95% CI		
	Mean	'Standard error'	Lower	Upper	Distribution
Starting age					
GHD	9.0	1.020	7.0	11.0	Normal
TS	10.0	1.020	8.0	12.0	
PWS	7.0	1.020	5.0	9.0	
CRI	9.0	1.020	7.0	11.0	
SGA	8.0	1.020	6.0	10.0	
SHOX-D	8.0	1.020	6.0	10.0	
Treatment length					
GHD	7.0	1.0200	5.0	9.0	Normal
TS	6.0	1.0200	4.0	8.0	
PWS	8.0	1.0200	6.0	10.0	
CRI	5.0	1.0200	3.0	7.0	
SGA	6.0	1.0200	4.0	8.0	
SHOX-D	7.0	1.0200	5.0	9.0	

TABLE 69 *Childhood drug dose parameters and distribution*

Childhood dose	Mean	'Standard error'	95% CI		Distribution
			Lower	Upper	
GHD	0.025	0.00255	0.020	0.030	Normal
TS	0.045	0.00255	0.040	0.050	
PWS	0.035	0.00255	0.030	0.040	
CRI	0.045	0.00255	0.040	0.050	
SGA	0.035	0.00255	0.030	0.040	
SHOX-D	0.040	0.00255	0.040	0.050	

to express the appropriate variability of doses used in the KIGS database and also the maximum doses suggested in the BNF. These were sampled using normal distributions.

Proportion of males

The reported mean proportion of males for each condition was taken from the KIGS database for both the treated and untreated groups. This was consistent with the base-case analysis. The standard errors were calculated for each mean proportion of males and sampled using a normal distribution.

Costs

Costs included in the PSA were those related to outpatient visits, nurse visits and monitoring tests. Drug costs were not varied in the PSA, but were included at values quoted in the BNF. Costs derived from *NHS Reference Costs* were sampled using estimated 'standard errors'. These assumed that a variation of plus or minus 25% was an appropriate CI for the average reference costs. The estimated standard errors are shown in column 3 of the *Table 71*. Parameters for gamma distributions (shown in columns 4 and 5) were derived using the means and estimated 'standard errors'. The simulated values were inflated to 2008–9 prices using appropriate inflation indices, as for the base-case and deterministic sensitivity analyses.

TABLE 70 *Proportion of males parameters and distribution*

Proportion of males	Mean	Standard error	Distribution
GHD	0.70	0.0100	Normal
TS	0.00	0.0000	
PWS	0.50	0.0045	
CRI	0.71	0.0040	
SGA	0.596	0.0032	
SHOX-D	0.48	0.0019	

TABLE 71 *Costs parameters and distribution*

Item	Mean	'Standard error'	Alpha	Beta	Distribution
Outpatient (first)	206.28	24.57	126.07	1.64	Gamma
Outpatient (subsequent)	127.97	11.40	126.07	1.02	
Specialist nurse	73.00	6.50	126.07	0.58	
District nurse	64.00	5.70	126.07	0.51	
Blood test	51.00	4.54	126.07	0.40	
X-ray	28.64	2.55	126.07	0.23	
Pituitary function test	246.50	21.95	126.07	1.96	

Appendix 13

Weight tables for males and females by age (Western Europe KIGS)

Age (years)	Weight (kg)								
	SGA		GHD		PWS		CRI		TS
	Male	Female	Male	Female	Male	Female	Male	Female	Female
0	4.00	3.0	6.01	5.63	4.00	3.00	4.00	3.00	3.00
1	6.00	5.7	8.40	7.96	9.41	8.37	8.14	6.60	7.03
2	8.07	8.48	10.18	9.81	10.96	10.15	10.42	9.60	10.19
3	10.10	10.04	12.18	11.98	14.48	12.08	12.39	11.77	11.91
4	11.13	11.39	13.97	13.63	17.67	15.92	14.26	13.13	13.80
5	13.63	13.62	15.72	15.41	20.55	20.00	16.24	15.22	15.56
6	15.58	15.79	17.79	17.49	23.37	23.18	17.98	18.15	17.67
7	17.96	17.86	20.15	19.76	26.96	26.64	20.14	19.33	20.20
8	20.06	19.86	22.76	22.41	31.48	29.42	22.42	21.47	23.14
9	22.27	22.45	25.4	25.42	35.82	33.94	24.92	23.41	26.57
10	24.93	24.83	28.5	28.79	40.95	41.24	27.49	26.42	30.04
11	27.73	28.52	31.74	32.02	44.46	44.29	30.49	30.17	34.05
12	31.08	31.71	35.00	35.99	51.70	47.49	34.08	34.78	38.47
13	34.53	35.36	39.28	40.26	57.96	52.80	37.43	37.27	42.33
14	38.89	38.22	44.40	44.19	63.80	56.84	41.15	39.80	46.00
15	44.33	40.27	49.91	47.72	69.02	59.07	44.84	41.03	49.05
16	49.04	43.05	54.47	49.97	74.43	56.32	48.70	41.15	51.47
17	53.50	47.03	58.5	53.38	74.14	61.15	50.4	42.66	52.53

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We look forward to hearing from you.

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