NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Somatrogon for treating growth disturbance in children and young people aged 3 and over [ID5086]

Committee Papers

The following documents are made available:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission summary** from Pfizer

2. **Patient group, professional group and NHS organisation submissions** from:
   a. Child Growth Foundation

3. **NICE Medicines Optimisation Team briefing**

4. **External Assessment Report** prepared by CRD and CHE Technology Assessment Group, University of York

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Somatrogon for treating growth disturbance in children and young people aged 3 and over [ID5086]

Document B

Company evidence submission

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Contents

Tables and figures

Table of Abbreviations

Abbreviation	Definition
ADA	Anti-drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
BIA	Budget Impact Analysis
BM	Bone Maturation
BMI	Body Mass Index
BNF	British National Formulary
BSPED	British Society for Paediatric Endocrinology and Diabetes
CADTH	Canadian Agency for Drugs and Technologies
CI	Confidence Interval
CTP	C-terminal Peptide
DCOA	Dyad Clinical Outcome Assessment
dGH	Daily Growth Hormone
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
EMA	European Medicines Agency
EQ	EuroQoL
EU	European Union
FAS	Full Analysis Subset
GH	Growth Hormone
GH-1	Growth Hormone-1 Gene
GHD	Growth Hormone Deficiency
hCG	Human Chorionic Gonadotropin
hGH	Human Growth Hormone
HRQoL	Health-related Quality of Life
HT	Height
HTA	Health Technology Assessment
HTSDS	Height SDS
HV	Height Velocity
HSUV	Health State Utility Value
ICER	Incremental Cost Effectiveness Ratio
IGF	Insulin-like Growth Factor
IMRD	IQVIA Medical Research Database
KIGS	Pfizer International Growth Database
LAGH	Long-acting Growth Hormone
LOCF	Last Observation Carried Forward
LS	Least Square
LT-OLE	Long Term Open Label Extension
MHRA	Medicines and Healthcare products Regulatory Agency

mITT	Modified Intention to Treat
MPHDS	Multiple Pituitary Hormone Deficiencies
MTA	Multiple Technology Appraisal
NA	Not Applicable
NCT	Trial Name
NHS	National Health Service
NHSE	National Health Service England
NICE	The National Institute for Health and Care Excellence
OLE	Open-label Extension
PAS	Patient Access Schemes
ppGH	Peak Plasma Growth Hormone
pGHD	Paediatric Growth Hormone Deficiency
PH3	Phase 3
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per Protocol
Q4	Quarter 4
QoL	Quality of Life
QoLISSY	Quality of Life in Short Stature Youth
RCT	Randomised Controlled Trial
rhGH	Recombinant Human Growth Hormone
SAE	Serious Adverse Event
SD	Standard Deviation
SDS	Standard Deviation Score
SE	Standard Error
SHOX	Short Stature Homeobox-containing Gene
SLR	Systematic Literature Review
SmPC	Summary of Product Characteristics
STAT	Signal Transducer and Activator of Transcription
TA	Technology Appraisal
UK	United Kingdom

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

B.1.1.1 Population

The submission covers the technology, somatrogon's full anticipated marketing authorisation for this indication, which is: children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone. Therefore, the CP-4-006 Phase 3 pivotal study, which assessed the efficacy and safety of weekly somatrogon compared to daily Genotropin® (somatropin) in pre-pubertal children with growth hormone deficiency is the main focus of the current submission. The Phase 2 dose finding study and the open label extension phase as well as the C0311002 Phase 3 treatment burden study, all included children and adolescent patients with growth hormone deficiency (GHD), are also presented for supportive purposes.

The decision problem addressed by the submission is shown in Table 1.

B.1.1.2 Comparators

The National Institute for Health and Cate Excellence (NICE) scope outlines daily recombinant human growth hormone (rhGH) (somatropin), and management strategies without human growth hormone as the relevant comparators.

In the United Kingdom (UK) there are seven preparations of daily rhGH treatment (somatropin) are available: Genotropin®, Pfizer; Humatrope®, Lilly; Norditropin®, Novo Nordisk; NutropinAq®, Ipsen; Omnitrope®, Sandoz; Saizen®, Merck Serono; Zomacton®, Ferring. All seven preparations are relevant comparators, [redacted]% of the market value given their wide usage in clinical practice.[1]

These comparators have several licence indications, TA188. However, all are indicated for the use of treatment in children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone. This is the population in scope and relevant for this submission and thus no subgroup

comparator analysis is required. The evidence base provided is direct head-to-head evidence versus the comparator (daily rhGH) with only a simple cost acquisition model.

Table 1: ***The decision problem***

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale if different from the final NICE scope**
Population	Children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone	Children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone	In line with Medicines and Healthcare products Agency (MHRA) marketing authorisation granted 25th March 2022: Ngenla® (somatrogon) is indicated for the treatment of children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone.
Intervention	Somatrogon (Ngenla®)	Somatrogon (Ngenla®)	-
Comparator(s)	• Recombinant human growth hormone (somatropin) • Management strategies without human growth hormone	The position of somatrogon in the treatment pathway is expected to displace existing daily growth hormone therapies (dGH), recombinant human growth hormone, somatropin (rhGH).	In the UK there are seven preparations of daily GH treatment (somatropin) are available: Genotropin®, Pfizer; Humatrope®, Lilly; Norditropin®, Novo Nordisk; NutropinAq®, Ipsen; Omnitrope®,

			Sandoz; Saizen®, Merck Serono; Zomacton®, Ferring. All seven preparations were selected as the most appropriate comparators, [redacted]% of the market value given their wide usage in clinical practice.
Outcomes	• Annual height velocity • 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-growth velocity relative to the distribution of growth in children of the same chronological age (or bone age)	• Annual height velocity • Height standard deviation score-height relative to the distribution of height in children of the same chronological age • Body composition, and biochemical and metabolic markers • Change in bone maturation • Adverse effects of treatment • Treatment burden assessed as difference between mean overall Life Interference total	Some of the outcomes were not captured in the clinical trial, and also not captured in TA188, thus there is limited availability of sufficient evidence to assess the outcomes beyond those captured directly in the trials. The company submission proposes to focus on those outcomes captured as part of the clinical trial programmes.

	• Body composition, and biochemical and metabolic markers. • Change in bone maturation • Adverse effects of treatment • Health-related quality of life	scores after each 12-week treatment period	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out.	Somatrogon provides similar health benefits at similar cost to the comparator, recombinant daily human growth hormone (somatropin), as demonstrated by direct head-to-head evidence. Only acquisition costs are considered as other NHS and Personal Social Services perspective costs are considered equal across all available treatment options.	This is expected to be the most efficient and effective way to assess the intervention (somatrogon) vs. the stated comparator (daily somatropin). There is evidence to suggest that reduced frequency of injections leads to increased utility, a key driver of the prior economic model. This suggests that a cost-comparison analysis where somatrogon is within the existing costs of daily growth hormones could provide additional benefit to the NHS.

	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an National Health Service (NHS) and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	The model considered the costs of all available somatropin treatment preparations. A patient access scheme for somatrogon will not be included as part of the analysis, there are no patient access schemes for any of the comparators.	Of note; somatropin products have different device options which appeal to different patient segments together with variable patient support offerings. Somatrogon will provide comparable device option(s) and patient support to demonstrate competitive value. The value of these offerings are subjective and as such are not included in the economic analysis.
Subgroups to be considered	None identified		

Special considerations including issues related to equity or equality	None identified		

B.1.2 Description of the technology being evaluated

The technology being evaluated is described in the table below.

Table 2: ***Technology being evaluated***

UK approved name and brand name	Non-proprietary name: Somatrogon Brand name: Ngenla®
Mechanism of action	Somatrogon is a glycoprotein comprised of the amino acid sequence of human growth hormone (hGH) with one copy of the of C-terminal peptide (CTP) from the beta chain of human chorionic gonadotropin (hCG) at the N-terminus and two copies of CTP (in tandem) at the C-terminus. The glycosylation and CTP domains account for the half-life of somatrogon, which allows for weekly dosing. Somatrogon binds to the Growth Hormone (GH) receptor and initiates a signal transduction cascade culminating in changes in growth and metabolism. Consistent with GH signalling, somatrogon binding leads to activation of the signal transducer and activator of transcription (STAT) signalling pathway and increases the serum concentration of Insulin-like Growth Factor (IGF-1). IGF-1 was found to increase in a dose-dependent manner during treatment with somatrogon partially mediating the clinical effect. As a result, GH and IGF-1 stimulate metabolic changes, linear growth and enhance growth velocity in paediatric patients with growth hormone deficiency (GHD).[2]
Marketing authorisation/CE mark status	MHRA marketing authorisation was granted 25th March 2022 European Medicines Agency (EMA) marketing authorisation was granted 14th February 2022
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Ngenla® (somatrogon) is indicated for the treatment of children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone. Treatment should be initiated and monitored by physicians who are qualified and experienced in the diagnosis and management of paediatric patients with growth hormone deficiency (GHD).

Method of administration and dosage	Subcutaneous injection The recommended dose is 0.66mg/kg body weight administered once weekly. Somatrogon dose may be adjusted as necessary, based on growth velocity, adverse reactions, body weight and serum insulin-like growth factor 1 (IGF-1) concentrations. Dose adjustments should be targeted to achieve average IGF-1 standard deviation score (SDS) levels in the normal range, i.e. between -2 and +2 (preferably close to 0 SDS). In patients whose serum IGF-1 concentrations exceed the mean reference value for their age and sex by more than 2 SDS, the dose of somatrogon should be reduced by 15%. More than one dose reduction may be required in some patients. Evaluation of efficacy and safety should be considered at approximately 6 to 12 month intervals and may be assessed by evaluating auxological parameters, biochemistry (IGF-1, hormones, glucose levels) and pubertal status. Routine monitoring of serum IGF-1 SDS levels throughout the course of treatment is recommended. More frequent evaluations should be considered during puberty. Treatment should be discontinued in patients having achieved a final height or near final height i.e., an annualised height velocity <2 cm/year or a bone age > 14 years in girls, or > 16 years in boys.
Additional tests or investigations	N/A
List price and average cost of a course of treatment	24mg/1.2ml, 1=£189.60 60mg/1.2ml, 1=£474.00 This is equivalent to £7.90 per mg. At the recommended dose of 0.66mg/kg/week the estimated annual treatment cost for a 40kg patient is £10,845.
Patient access scheme/commercial arrangement (if applicable)	Not applicable

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Paediatric growth hormone deficiency overview

Paediatric growth hormone deficiency (pGHD) is a rare disease, causing short stature, poor growth velocity, impaired bone development, altered body composition and increased risk of cardiovascular diseases[3]. GHD results from the disruption of the growth hormone (GH) secretion due to abnormalities in pituitary gland or hypothalamus.[4]

GH is a peptide produced by and released from the anterior pituitary gland in pulses in response to stimulation by GH-releasing hormone produced by the hypothalamus.[5] Upon release, GH triggers the production of IGF-1 in liver and cartilage.[5] Both GH and IGF-1 play a key role in stimulating bone growth during childhood.[5, 6] GH is also involved in the regulation of lipid metabolism and muscle and bone development.[4, 7, 8]

GHD may be classified based on its cause:[4, 5, 9]

- Idiopathic: No known or diagnosable cause of the disease, most commonly diagnosed (Proportion of all diagnosed GHD cases 82.8% in the US, 77.1% in Europe, 92% in Japan based on the Pfizer International Growth Database [KIGS] database of paediatric GHD cases reported between 1987 and 2012)

- Acquired: develops during childhood and can be due to many different cases (e.g., trauma, radiation therapy, brain tumour, inflammation); (proportion of all diagnosed GHD cases 7.8% in the US, 12.2% in Europe, 6.5% in Japan, as per KIGS database study)

- Congenital: present from birth, either due to genetic abnormalities (e.g., mutations in the growth hormone-1 gene [GH-1], pituitary-specific positive transcription factor 1 gene [Pit-1], GH releasing hormone receptor gene) or all congenital malformation of the pituitary gland or hypothalamus (proportion of all diagnosed GHD cases: 9.4% in the US, 10.8% in Europe, 1.7% in Japan, as per KIGS database study)

GHD also may be defined as isolated (i.e., presenting in the absence of deficiencies in other pituitary gland hormones) or combined with multiple pituitary hormone deficiencies (MPHDS) that may present simultaneously or develop later in the course of disease .[10]

B.1.3.2 Epidemiology

In the UK, the prevalence of GHD is estimated to be between 1 in 3500 and 1 in 4000 children. In approximately half of the children with GHD (50%), the cause is unknown (idiopathic growth hormone deficiency).[11] According to a survey of endocrine clinics published in 2006 by the British Society for Paediatric Endocrinology and Diabetes (BSPED), 4758 patients have been receiving recombinant human growth hormone (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.[12, 13]

B.1.3.3 Clinical pathway of care

Recombinant human growth hormone (rhGH), somatropin, remains the main treatment option in GHD, through once daily subcutaneous injections, and is currently the only active option for growth failure in children with GHD.[11, 14] The primary goals of rhGH treatment for children with GHD are: to normalise height during childhood, for the treated child to reach a ‘normal’ adult height as defined by the parental target and for mature somatic development to be reached around age 25.[11]

The place of somatropin in the treatment pathway depends on the child's particular condition and his or her age at diagnosis. For children with congenital GHD, rhGH therapy is not generally started before the child is four years old. However, if there is profound growth failure or evidence of recurrent hypoglycaemia, which may occur in infants under the age of one, treatment may be started earlier. For children who acquire GHD at an older age, treatment can start at a time appropriate to their condition and stage of growth.

The growth response to rhGH treatment is typically maximal in the first year of treatment and then gradually decreases over the subsequent years of treatment. It

has been suggested that a significant improvement in height velocity (HV) is seen when rhGH dose is adjusted based on IGF-1 concentrations. It is critically important to maximise height with GH therapy before the onset of puberty. Growth velocity decreases and may even be zero after epiphyseal fusion, that is, after growth plate closure in late puberty.[15] The earlier the GH is commenced, the more likely is the child to achieve a height that is appropriate for the target height.[16]

Treatment is discontinued after the first year if there is a poor response despite optimal rhGH dose, i.e. growth velocity increases <50% from baseline, or if there are insurmountable problems with adherence. Otherwise, treatment can continue until final height is attained or approached, i.e. growth velocity is <2 cm/year.[16] The decision to stop treatment should be made in consultation with the patient and/or carers either by paediatricians with specialist expertise in managing growth disorders in children, or an adult endocrinologist, if care of the patient has been transferred from paediatric to adult services.

B.1.3.4 Disease burden and unmet need

The currently available rhGH formulations are administered via daily subcutaneous injections, with studies showing high rates of treatment cessation.[17, 18] Poor adherence is associated with suboptimal response to treatment, with reduced linear growth and nonattainment of genetic height potential.[17, 19] Non-compliance has been shown to increase over time and is a significant issue for long-term treatment.[20, 21]

Recent research to understand the burden associated with daily somatropin compared with weekly somatrogon injections found the primary endpoint of ‘life interference’ to have significantly lower scores for weekly compared to daily GH (dGH) injections.[22] In addition to experiencing life interference, the majority of caregivers worry about administering daily injections to children, which is expected to impact adherence and compliance.[23] The treatment burden of daily injections on children and their caregivers commonly leads to poor compliance. A UK-based study of 75 pGHD patients who attended regional paediatric endocrinology clinics and found that almost 1 in 4 (23%) missed >2 injections per week and this was associated with lower predicted height velocities.[24] Reducing treatment burden is a key unmet need as the cumulative impact of missed doses prevents children from realising key growth outcomes and optimal health-related quality of life (HRQoL).[25-27]

Given the patient complaints surrounding the burden of dGH treatments, such as unhappiness with frequent injections, disruption of overnight travel plans, and nightly interruption of activities to administer medication, it is thought that these will be mitigated by less frequent injections.[28, 29] A recently conducted discrete choice experience also demonstrated that patients prefer a less frequent injection regimen for treatment GHD.[30]

B.1.3.5 Comparators

In the UK, seven preparations of daily GH treatment (somatropin) are available: Genotropin®, Pfizer; Humatrope®, Lilly; Norditropin®, Novo Nordisk; NutropinAq®, Ipsen; Omnitrope®, Sandoz; Saizen®, Merck Serono; Zomacton®, Ferring (Table 3). Each product is produced by recombinant Deoxyribonucleic Acid (DNA) technology and has a sequence identical to that of human growth hormone produced by the pituitary gland. The summary of product characteristics for somatropin states that the dosage and administration should be tailored to the needs of each individual child. All daily growth hormone medicines currently on the market in the UK are considered.

Table 3: **Comparators**

Proprietary name	Formulation	Company
Humatrope®	Once daily injection	Lilly
Zomacton®	Once daily injection	Ferring
NutropinAq®	Once daily injection	Ipsen
Norditropin®	Once daily injection	Novo Nordisk
Genotropin®	Once daily injection	Pfizer
Omnitrope®	Once daily injection	Sandoz
Saizen®	Once daily injection	Merck Serono

The clinical evaluation of somatrogon was conducted globally. Genotropin® was chosen as a comparator in these global studies since it is one of the most well studied and prescribed rGH formulations globally. It was introduced on the market in 1987, and its safety and efficacy is supported by real-world evidence, with

approximately 83,803 children (277,264 patient-years) in 52 countries who participated in the international KIGS registry.[9] As such, other manufacturers evaluating different approaches to manage GHD have also selected Genotropin® as the comparator in their studies also. In the UK, Genotropin® remains a relevant comparator as it is one of the seven GH products currently marked in the UK market. As with all the other GH available in UK, Genotropin® contains the same active ingredient, i.e. somatropin (rDNA origin) for injection. These products have also been assessed by NICE through an MTA (TA188) and were considered to offer equivalent clinical benefits.[11]

The long-acting growth hormone lonapegsomatropin (TransCon, Ascendis Pharma) (European Union (EU) marketing authorisation in January 2022) and Somapacitan (Sogroya, Novo Nordisk; anticipated licence in Q4 2022) are currently not used in clinical practice for treatment of paediatric growth hormone deficiency in the UK therefore not considered relevant comparators in this appraisal.

B.1.4 Equality considerations

Among children treated with rhGH for GHD, a higher frequency of boys than girls has been noted[31], and this is consistent throughout the world as well as over the period since rhGH became available in 1985.[9, 32] Boys are over-represented among referrals for short stature to general and specialist hospitals. A global appreciation of gender biases is required for the proper care of short girls.

With regard to GH treatments, several studies have evaluated the effects of socioeconomic status on adherence to prescribed GH therapy with mixed findings.[33, 34] In a 2011 literature review, key drivers of poor GH adherence identified both psychological/emotional and social problems and stressed the interconnected nature of these factors to socioeconomic issues such as poverty, low education levels, and lack of social support.[35] Since poor adherence to prescribed GH regimens is associated with decreased final height, children with pGHD who are socioeconomically disadvantaged may be less likely to achieve maximum adult height potential, possibly impacting quality of life (QoL) in the longer term. GH regimens with fewer doses and more convenient dosing requirements, such as long-acting growth hormone (LAGH), could potentially help to improve adherence and outcomes among socioeconomically disadvantaged children.[36]

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

The relevant NICE guidance for pGHD) is TA188 Human growth hormone (somatropin) for the treatment of growth failure in children.[11] A multiple technology appraisal (MTA) assessed the clinical and cost effectiveness of seven preparations of somatropin (Genotropin®, Pfizer; Humatrope®, Lilly; Norditropin®, Novo Nordisk; NutropinAq®, Ipsen; Omnitrope®, Sandoz; Saizen®, Merck Serono; Zomacton®, Ferring) for treating GHD, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, born small for gestational age with subsequent growth failure at 4 years of age or later and short stature homeobox-containing gene (SHOX) deficiency. NICE TA188 recommends the use of somatropin, within the marketing authorisations for each preparation, for all indications listed in the final scope issued by NICE.

The relevant population for the current appraisal is pGHD. In TA188, despite the limitations of the evidence (only one study identified for GHD, of short duration and reported no data on HRQoL), the Committee concluded that there was sufficient evidence to demonstrate the efficacy of somatropin in promoting growth in children with the conditions considered, including pGHD. The Committee concluded that somatropin treatment can, in addition to promoting growth, improve QoL and may also reduce long term risk of cardiovascular disease, diabetes and fracture.

The clinical outcomes of interest considered in TA188 included: final height gained; height standard deviation score; growth velocity; growth velocity standard deviation score; body composition; biochemical/metabolic markers; adverse effects of treatment; 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. Given lack of available evidence the key outcome used in the economic model as a measure of clinical effectiveness of somatropin was height gain SDS. The Assessment group model was most sensitive to, age at start of treatment, length of treatment, adherence, and utility gain. Based on clinical opinion discontinuation was not factored into the base case

analysis. It is unclear from the TA188 Assessment Group Report the impact of each variable on the Incremental Cost Effectiveness Ratio (ICER), and the committees preferred assumptions of each.

There was uncertainty considering the utility values used in the model because of limited data available. Because there were no data on HRQoL in studies included in the systematic reviews, the Assessment Group used utility values from Christensen et al. 2007,[37] which were based on EuroQoL (EQ-5D) for different height SDS from the Health Survey for England for an adult general population. The study identified a positive correlation between an increase in height and a participant's EQ-5D score, and that adjusted for potential confounders, increasing values of height were associated with greater gains in QoL in shorter people compared with taller people. However, the Committee considered there were a number of limitations associated with using these values from only one study and that they were likely to underestimate both the true disutility associated with growth failure and the utility gain from somatropin treatment.

Taking all factors into consideration, including the issues around utility values and the variation in price of the somatropin products into consideration, the Committee agreed that the ICER for somatropin for GHD in children was likely to below the NICE cost-effectiveness threshold.

With reference to the intervention (somatrogon) several of these variables will remain consistent with those of the daily somatropin preparations, perhaps the largest exception to these would be the potential utility gained from reduced frequency of injections, i.e., moving from once daily to once weekly. Several studies have highlighted varying levels of increased utility experience when moving to less frequent injections.[38-40] This would have a positive impact on the cost-effectiveness of somatrogon vs. daily somatropin leading to a more conservative approach taken by the company when considering a cost-comparison approach as the proposed price point for somatrogon falls already within the existing range of the daily growth hormones. This potentially under-estimated the cost-effectiveness of somatrogon and thus represents additional uncaptured value to the National Health Service (NHS).

This submission proposed no significant shift in the measurement of clinical outcomes, therefore there is no expected shift from the previous conclusions drawn by the committee as part of TA188, in terms of either benefit or uncertainties.

B.2.2 Resource use assumptions

The evidence on resource use in Assessment Group report in TA188[13] was informed by Joshi and colleagues[41] and the Canadian Agency for Drugs and Technologies (CADTH) studies[42], which examined the resource use and patient costs during the duration of treatment after diagnosis. The resources and associated costs included were divided into treatment costs, monitoring costs, and adverse event (AE) costs. Similar to the clinical effectiveness and safety profiles, resource use was the same across all technologies and the only differentiating factor was the cost of each technology.

This submission proposes no changes to the treatment pathway for patients treated with somatrogon over the existing comparators, daily growth hormones (dGHs), as such the only cost items considered relevant for the cost comparison are medicine acquisition costs.

B.3 Clinical effectiveness

B.3.1 Identification and selection of relevant studies

Somatrogon is a long-acting recombinant growth hormone (LAGH) that has been studied as a once-weekly subcutaneous injection at doses ranging from 0.25, 0.48, and 0.66 mg/kg/week via traditional injection (vial and needle) and using a pre-filled pen device (available as 24 mg/1.2 mL and 60 mg/1.2 mL) in children with GHD.[2, 43-49] The recommended somatrogon dose as per the label is 0.66 mg/kg/week, which is the dose used in the Phase 3 studies. The selection of somatrogon dose for the Phase 3 studies was determined by safety parameters and in particular by the clinical effect, i.e. annual height velocity. Based on the 12-month auxology data from the Phase 2 dose-finding study in 52 patients, somatrogon 0.66 mg/kg/week was chosen as the dose equivalent to daily growth hormone (Genotropin®; non-proprietary name: somatropin) at a dose of 0.034 mg/kg/day (equivalent to 0.24 mg/kg/week). The choice of the Genotropin® (somatropin) dose in the trials was made based on the most commonly used dose (0.24mg/kg/week) worldwide in real world setting for paediatric growth hormone deficiency (GHD)[50] and is in line with the posology licensed for its use.[51]

Somatrogon's clinical program included five major studies. One pivotal Phase III study with its open-label extension, one Phase II study with its open-label extension and one Phase III study assessing treatment burden (Table 4).

Table 4: ***Clinical program of somatrogon***

Study	Study Title	Dosage, route of administration, and duration	Number of patients
CP-4-006 Phase 3 pivotal study	Phase III, Open-Label, Randomised, Multicenter, 12 Months, Efficacy and Safety Study of Weekly somatragon Compared to Daily Genotropin® Therapy in Pre-Pubertal Children with Growth Hormone Deficiency	Somatrogon 0.66 mg/kg weekly Genotropin® (somatropin) 0.034 mg/kg daily Subcutaneous Injections 12 months	N=224
CP-4-006 LT-OLE period	Phase III, Open-Label, Randomised, Multicenter, 12 Months, Efficacy and Safety Study of Weekly somatragon Compared to Daily	Somatrogon 0.66 mg/kg weekly Subcutaneous Injections	N=212

	Genotropin® Therapy in Pre-Pubertal Children with Growth Hormone Deficiency – Open Label Extension	Ongoing through registration	
C0311002 Phase 3 treatment burden study	A Phase III, Randomized, Multicenter, Open-Label, Crossover Study Assessing Subject Perception of Treatment of Burden with use of Weekly Growth Hormone (somatrogon) Versus Daily Growth Hormone (Genotropin®) Injections in Children with Growth Hormone Deficiency	Randomised 1:1 2-period crossover daily Genotropin® (somatropin) for 12 weeks followed by weekly somatrogon for 12 weeks Somatrogon 0.66 mg/kg weekly for 12 weeks followed by Genotropin® (somatropin) 0.034 mg/kg daily for 12 weeks Subcutaneous Injections 6 months	N=90
CP-4-004 Phase 2 dose finding study	Phase II, Safety and Dose Finding Study of Different somatrogon Dose Levels Compared to Daily r-hGH Therapy in Pre-pubertal Growth Hormone Deficient Children	Somatrogon 0.25 mg/kg weekly Somatrogon 0.48 mg/kg weekly Somatrogon 0.66 mg/kg weekly Genotropin® (somatropin) 0.034 mg/kg daily Subcutaneous Injections 12 Months	N=53
CP-4-004 Phase 2 OLE study	Phase II, Safety and Dose Finding Study of Different somatrogon Dose Levels Compared to Daily r-hGH Therapy in Pre-pubertal Growth Hormone Deficient Children – Open Label Extension	Somatrogon 0.25 mg/kg weekly Somatrogon 0.48 mg/kg weekly Somatrogon 0.66 mg/kg weekly Subcutaneous Injections 5 years	N=48

B.3.2 List of relevant clinical effectiveness evidence

Evidence for the clinical effectiveness of somatrogon is available from the clinical trial program (Table 5, Table 6,Table 7,Table 8).

Table 5: ***CP-4-006 Phase 3 pivotal study design***

Study	**A Phase 3, open-label, 12-month efficacy and safety study of weekly somatrogon compared to daily Genotropin® therapy in pre-pubertal children with GHD**
Clinicaltrials.gov identifier:	NCT02968004
Study design	Phase 3, open label, randomised, active controlled, multi-centre, parallel group, non-inferiority trial, followed by a single arm, long-term open-label extension (LT-OTE) study*
Population	Pre-pubertal child aged ≥ 3 and not above 11 years for girls or 12 years for boys with either isolated GHD, or GH insufficiency as part of multiple pituitary hormone deficiency After completion of 12 months treatment in the main study and continuing to meet the LT-OLE inclusion/exclusion criteria, patients were eligible to rollover into the LT-OLE treatment period with somatrogon.
Intervention(s)	Somatrogon 0.66 mg/kg/week once weekly for 12 months (n=109) Open Label Extension (OLE): Patients in the somatrogon group continued their original treatment.
Comparator(s)	Genotropin® (somatropin) 0.034 mg/kg/day once daily (n=115) OLE: All patients receiving Genotropin® (somatropin) were switched to receive somatrogon 0.66 mg/kg/week once weekly
Indicate if study supports application for marketing authorisation (yes/no)	Yes (registration study)
Reported outcomes specified in the decision problem	• Annual height velocity • Height standard deviation score-height relative to the distribution of height in children of the same chronological age • Body composition, and biochemical and metabolic markers • Change in bone maturation • Adverse effects of treatment • Health-related quality of life
All other reported outcomes	• Not Applicable

*LT-OLE ongoing

Table 6: ***C0311002 Phase 3 treatment burden study design***

Study	**A Phase 3, open-Label, crossover study assessing subject perception of treatment burden with use of weekly somatrogon versus daily growth hormone (Genotropin®) injections in children with GHD**
Clinicaltrials.gov identifier:	NCT03831880
Study design	Phase 3, open label, randomised, crossover trial
Population	Children aged 3 years old and <18 years with either isolated GHD, or GH insufficiency.
Intervention(s)	Children were randomised 1:1 to receive treatment in one of the two sequences: • Sequence #1 (n=43): Genotropin® (somatropin) (equivalent dose to pre-study dose) once daily for 12 weeks followed by somatrogon 0.66 mg/kg/week once weekly for 12 weeks • Sequence #2 (n=44): Somatrogon 0.66 mg/kg/week once weekly for 12 weeks followed by Genotropin® (somatropin) (equivalent dose to pre-study dose) once daily
Comparator(s)	See above
Indicate if study supports application for marketing authorisation (yes/no)	Yes (supportive study)
Reported outcomes specified in the decision problem	• Adverse effects of treatment

All other reported outcomes	**Primary endpoint**:
	Treatment burden assessed as difference between mean overall Life Interference total scores after each 12-week treatment period
	
	Secondary endpoints:
	• Assessment of treatment experience of children and caregivers for each treatment separately in the following categories:
	  ○ Pen ease of use
	  ○ Ease of injection schedule
	  ○ Convenience of injection schedule
	  ○ Satisfaction with treatment experience
	  ○ Willingness to continue injection schedule
	  ○ Injection signs and symptoms in children ≥8 years (children only)
	  ○ Caregiver assessment of signs in children <8 years (caregivers only)
	  ○ Caregiver Life Interference including Family Life Interference (caregivers only)
	  ○ Missed injections
	• Preferred treatment as selected by children and caregivers according to the following categories:
	  ○ Choice of injection pen
	  ○ Preferred injection schedule
	  ○ Convenience of injection schedule
	  ○ Ease of injection schedule
	  ○ Patient Life Interference
	  ○ Caregiver Life Interference (caregivers only)
	  ○ Family Life Interference (caregivers only)
	  ○ Benefit relating to injection schedule
	  ○ Intention to comply
	  ○ PGIS-IDA change from baseline

Table 7: ***CP-4-004 Phase 2 dose-finding study design (main study)***

Study	**Safety and dose finding study of different somatrogon dose levels compared to daily r-hGH therapy in pre-pubertal GHD children**
Clinicaltrials.gov identifier:	NCT01592500
Study design	Phase 2 randomised, open-label, dose-finding study
Population	Pre-pubertal child aged ≥ 3 and not above 10 years for girls or 11 years for boys with either isolated GHD, or GH insufficiency as part of multiple pituitary hormone deficiency
Intervention(s)	Somatrogon 0.25 mg/kg/week once weekly (n=13) Somatrogon 0.48 mg/kg/week once weekly (n=15) Somatrogon 0.66 mg/kg/week once weekly (n=14)
Comparator(s)	Genotropin® (somatropin) 0.034 mg/kg/day once daily (n=11)
Indicate if study supports application for marketing authorisation (yes/no)	Yes (supportive study)
Reported outcomes specified in the decision problem	• Annual height velocity • Height standard deviation score-height relative to the distribution of height in children of the same chronological age • Body composition, and biochemical and metabolic markers • Change in bone maturation • Adverse effects of treatment
All other reported outcomes	**NA**

Table 8: ***CP-4-004 Phase 2 open label extension (OLE) study design***

Study	**Safety and dose finding study of different somatrogon dose levels compared to daily r-hGH therapy in pre-pubertal growth hormone deficient children – open label extension (OLE)**
Clinicaltrials.gov identifier:	NCT02500316
Study design	There were 3 defined OLE study periods: • OLE period (Year 1 OLE): This period lasted for 12 months post-completion of the main study. Subjects continued dosing with the originally assigned dose levels of somatrogon (0.25, 0.48, and 0.66 mg/kg/week). Subjects originally assigned to daily Genotropin® (somatropin) in the main study were randomly re-assigned to 1 of the 3 somatrogon dose levels. • LT-OLE period (Years 2-4 OLE): This LT-OLE period was planned to follow the 12 months in Period III (ie, to start from second year of OLE and third year of the

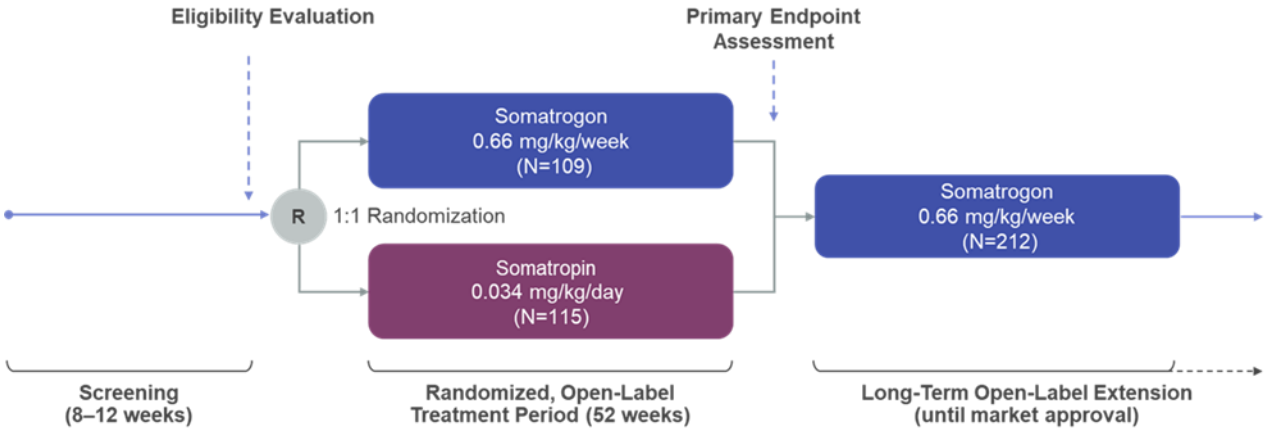
	overall study). All eligible subjects were transitioned to receive somatrogon at a dose of 0.66 mg/kg/week. • LT-OLE-PEN period (PEN): Subjects were transitioned to somatrogon 0.66 mg/kg/week SC administration using a single subject, multi-dose, disposable pre-filled pen device and formulation. This period continued until marketing approval.
Population	Subjects who completed 12 months of active treatment in the main study period (CP-4-004), remained eligible for inclusion in the study, and consented to participate in the OLE.
Intervention(s)	See above 'study design'
Comparator(s)	Subjects originally assigned to daily Genotropin® (somatropin) in the main CP-4-004 study were randomly assigned to 1of the 3 somatrogon dose levels. See above 'study design' for further details.
Indicate if study supports application for marketing authorisation (yes/no)	Yes (supportive study)
Reported outcomes specified in the decision problem	• Annual height velocity • Height standard deviation score-height relative to the distribution of height in children of the same chronological age • Body composition, and biochemical and metabolic markers • Change in bone maturation • Adverse effects of treatment
All other reported outcomes	NA

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

B.3.3.1 CP-4-006 Phase 3 pivotal study and LT-OLE study

CP-4-006 was a multicenter, randomised, open-label, active-controlled, parallel group non-inferiority study. Eligible patients were pre-pubertal children with confirmed diagnosis of GHD, aged ≥3 years and <11 (girls) or <12 years (boys), and without prior exposure to any hGH therapy. The primary endpoint was the annual height velocity (HV) after 12 months. Study participants were randomized 1:1 to receive either somatrogon (0.66 mg/kg/week; N=109) as a once weekly injection or Genotropin® (0.24 mg/kg/week; N=115) as a once-daily injection for 12 months. This is followed by an additional ongoing long-term OLE period for eligible patients.[45, 48, 52]

Figure 1: ***CP-4-006 pivotal phase 3 study trial design***



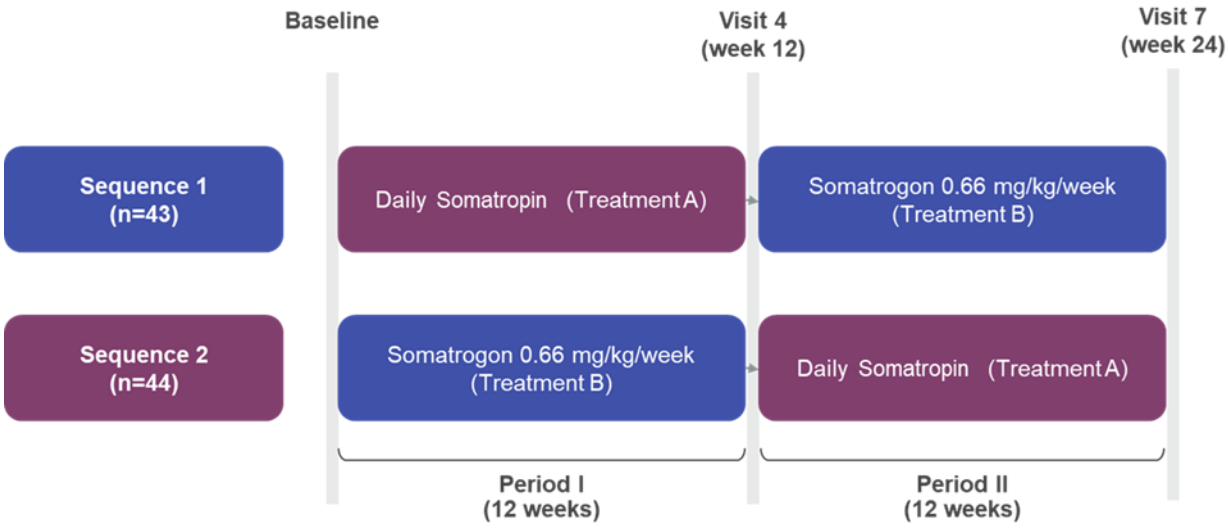
In the CP-4-006 pivotal study baseline demographic and other characteristics were balanced across both treatment groups. The mean age in years across the two groups was 7.83 (somatrogon) and 7.61 (somatropin) with a majority of male patients in both groups, 75.2% (somatrogon) and 68.7% (somatropin). The mean height in cm was 110.0 (somatrogon) and 109.9 (somatropin) across the two groups, with mean height SDS's of -2.94 (somatrogon) and -2.78 (somatropin). The mean bone maturation was 0.67 (somatrogon) and 0.66 (somatropin), with patients having a mean BMI in kg/m2 of 15.76 (somatrogon) and 15.56 (somatropin)[53]; 212 of the 222 subjects who completed the main study entered the CP4006 OLE period. As of the data cut-off date (01 November 2019), 205 subjects were continuing somatrogon treatment.

B.3.3.2 C0311002 Phase 3 treatment burden study

C0311002 was a 24-week, Phase 3, randomised, multicenter, open-label, crossover study assessing patient and caregiver perception of the treatment burden with use of somatrogon administered once weekly compared to Genotropin® administered once daily. The primary endpoint was the treatment burden assessed as the difference in mean Life Interference total scores after 12 weeks of treatment with either somatrogon or Genotropin®. Patients (aged ≥3 to <18 years) were randomised 1:1 to one of the two treatment sequences: Sequence 1 (N=43): Genotropin® once daily for 12 weeks followed by somatrogon once weekly for 12 weeks; or Sequence 2 (N=44): somatrogon once weekly for 12 weeks followed by Genotropin® once daily for 12 weeks. Regardless of the sequence, all patients received a somatrogon dose

of 0.66 mg/kg/week and a Genotropin® dose equivalent to their daily GH dose before the study.[54]

Figure 2: ***C0311002 phase 3 treatment burden study trial design***



Demographic and baseline characteristics were generally balanced across both treatment sequences. The mean age in years across the two sequences was 10.8 (somatropin /somatrogon) and 10.7 (somatropin /somatrogon) with a majority of male patients in both sequences, 79.1% (somatropin /somatrogon) and 86.4% (somatropin /somatrogon). The mean height in cm was 138.6 (somatropin /somatrogon) and 138.2 (somatropin /somatrogon) across the two sequences.[55]

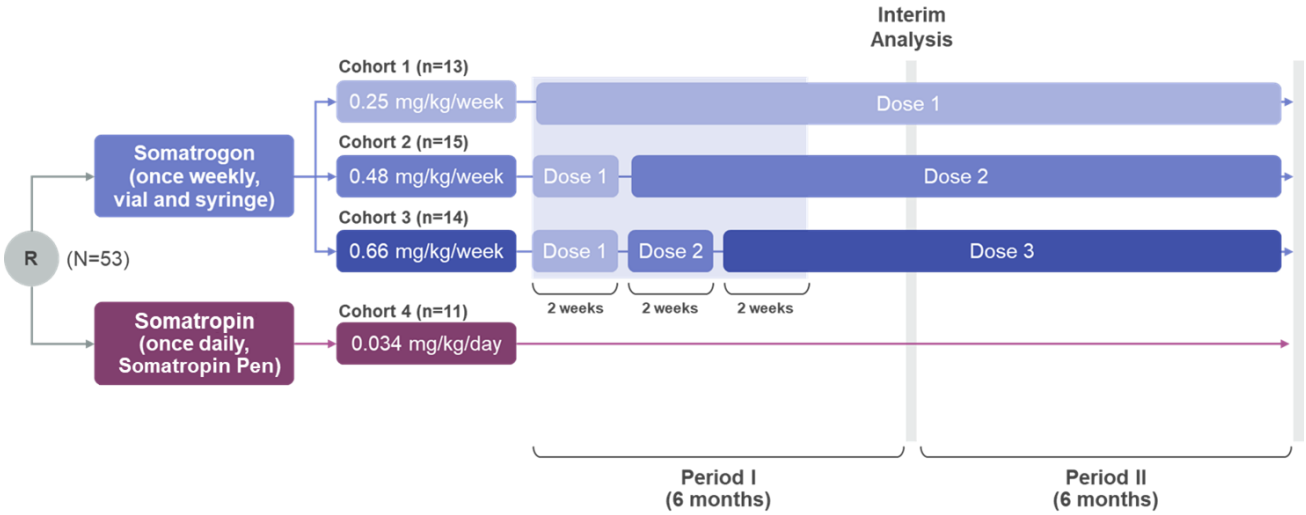
B.3.3.3 CP-4-004 Phase 2 dose finding study and OLE study

The Phase 2 trial was a 12-month, open-label, randomised, dose-finding, pharmacokinetic, pharmacodynamic, efficacy, safety and tolerability study. Inclusion criteria were the same as in global Phase 3 trial described above, except for age criteria (≥3 and <10 years for girls and <11 years for boys). The primary endpoint was the annual height velocity (HV) after 12 months. All patients randomised to somatrogon began the treatment of 2 weeks with the lowest dose (0.25 mg/kg/week). Subsequently, the dose was escalated to the next dose level every 2 weeks until the final allocated dose was reached (0.25 mg/kg/week, N=13; 0.48 mg/kg/week, N=15; and 0.66 mg/kg/week, N=14). Patients continued on the allocated dose for the rest of the 12 month main study. Genotropin®-treated patients (N=11) received the dose of 0.034 mg/kg once daily throughout the study.[46]

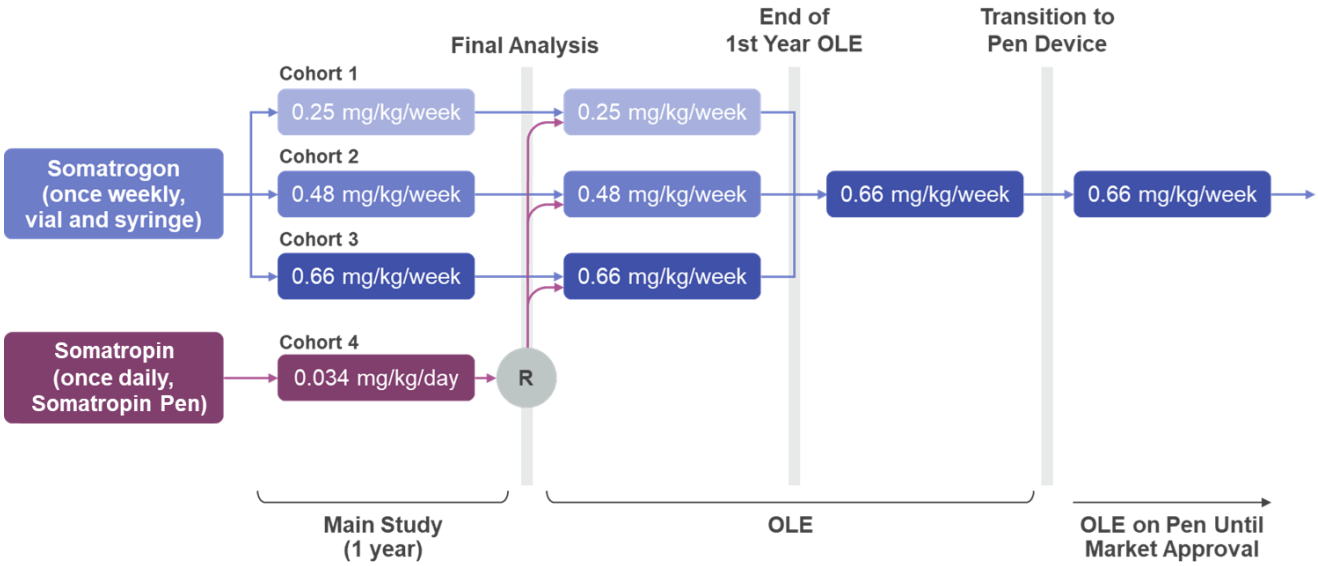
Subjects who completed the main study and provided their consent were eligible to be enrolled in the single-arm OLE study. Subjects who received somatrogon in the main study continued to receive somatrogon once weekly at the same dose (0.66 mg/kg/week) while subjects who received Genotropin® in the main study were switched to somatrogon (0.66 mg/kg/week).[49, 56]

Figure 3: ***CP-4-004 phase 2 and OLE study trial design***

Main study:



OLE:



A total of 56 patients from 14 centres in seven countries were randomised in the Phase 2 main study. Three patients were randomised and withdrew consent prior to receiving any study medication. Fifty-three patients (17 female and 36 male) were

enrolled and received somatrogon or somatropin. No patients were removed or withdrew from participation prematurely post dosing.

Baseline characteristics were balanced across the four treatment groups.[2] The distributions of patients' demographic and baseline characteristics included 14 females and 28 males treated across all three Somatrogon cohorts. There were eight males and three female patients treated in the somatropin cohort. Patients across all cohorts were predominantly white (96.1%). Mean age was comparable across all dose groups. Mean age for male participants in Somatrogon Cohorts 1-3 was 6.8, 6.2, and 6.7, respectively. The mean age for female participants in Somatrogon Cohorts 1-3 was 6.2, 6.4, and 6.5 respectively. Male patients in the somatropin cohort had a mean age of 6.7 while the female mean age was 4.7. Weight, height, height SDS, body mass index (BMI) and BMI SDS were well balanced across all cohorts.[57] A total of 48 subjects from 13 centres in 7 countries were randomized in the study and entered OLE. Two subjects discontinued from the study during Year 1 OLE, and 46 subjects (95.8%) completed Year 1 OLE, which was 2 years from the original study start (Figure 3). No subjects discontinued due to an AE during Year 1 OLE.

During Years 2-4, one subject was lost to follow-up during Year 2, 2 subjects withdrew during Year 3, and 1 subject discontinued due to an AE during Year 4. During the OLE on PEN, 8 subjects withdrew from the study and 1 subject withdrew due to an AE. The overall subject completion rate at the end of Year 1 OLE, Years 2-4 OLE and the PEN period ranged from 87.5% to 97.7%.

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Summaries of the statistical analysis plans for the pivotal Phase 3 study, Phase 3 treatment burden study and the Phase 2 dose-finding study are presented in Table 9, Table 10 and Table 11.

Table 9: ***Summary of the statistical methodology for CP-4-006 Phase 3 pivotal study***

Trial name (NCT)	**CP-4-006 Phase 3 pivotal study (NCT02968004)**
Hypothesis objective	To demonstrate that in terms of annual HV at 12 months (primary efficacy endpoint), weekly somatrogon is non-inferior to daily Genotropin® (somatropin) administration by a non-inferiority margin of 1.8 cm/year. Non-inferiority was concluded for the primary efficacy endpoint if the lower bound of the 2-sided 95% confidence interval (CI) for the mean treatment difference (somatrogon – somatropin) is ≥ 1.8 cm/year.
Sample size, power calculation	The following assumptions were made in the sample size calculation: • 2-sided alpha of 0.05, • 80% power, • between-patient standard deviation of annual growth rate of 2.5 cm/year in all treatment groups, • non-inferiority margin of –1.8 cm/year, • true mean treatment difference (somatrogon – somatropin) in the primary efficacy endpoint of –0.8 cm/year. With these assumptions, 100 treated patients per group would provide 80% power for the non-inferiority test. To allow for an approximate 10% dropout rate, 110 patients would be randomized to each treatment group, for a total of 220 patients.
Statistical analysis of primary endpoints	The CI for the difference of means between the 2 treatments was derived from an analysis using Analysis of Covariance (ANCOVA). The ANCOVA model included the stratification classes for treatment, age group, peak hGH value during stimulation test, region and gender, and Baseline Ht SDS as a covariate. The determination of non-inferiority was based on least squares means for the 2 treatments from the ANCOVA and the 95% CI of the differences between the treatments. The ANCOVA-based primary efficacy analysis was repeated using the modified intent-to-treat (mITT) set and the per protocol (PP) set. The ANCOVA-based primary efficacy analysis was repeated on the full analysis set using last observation carried forward (LOCF) in place of multiple imputation for the handling of missing data.
Statistical analysis of secondary and other endpoints	Annualised HV after 6 months of treatment, and change (from Baseline) in Ht SDS at 6 and 12 months were summarised with descriptive statistics. These 3 endpoints were each be analysed using a similar ANCOVA model as used for the primary endpoint, with terms for treatment and the randomisation strata (age, peak hGH value during stimulation test, region), gender

	and baseline value for each endpoint of interest. The model-derived least square means and standard error (SE) was used to construct 95% CI for the difference between treatment groups. These analyses are considered as supportive efficacy analyses. Change in bone maturation (BM), calculated as bone age (BA)/chronological age (CA) at the end of 12 months, compared to Baseline was characterised with descriptive statistics (mean, SD, and 95% CI) for each treatment group.

Table 10: ***Summary of the statistical methodology for C0311002 Phase 3 treatment burden study***

Trial name (NCT)	**C0311002 Phase 3 treatment burden study (**NCT03831880)
Hypothesis objective	To test the hypothesis that the difference in Life Interference Total Score between weekly and daily regimens is statistically significant.
Sample size, power calculation	In order to estimate the sample size, based on solicited internal expert opinion, the following assumptions were considered using a two-sided type-I error of 0.05: • The expected difference between the two treatment schedules in the Life Interference • Total Score is assumed to be from a distribution with mean = 0.45. This is considered to be a moderate effect size. • The standard deviation of the individual Total Score is assumed to be 1. • The within-subject correlation of scores measured on a same subject at two different times is assumed to be at least 0.3. Under these assumptions, a total of 75 subjects are needed at 90% power from a two-sided paired t-test for mean difference for the proposed study using Life Interference as the primary endpoint. As the Life Interference instrument has not been tested in prior clinical trials, the sample size was increased by approximately 20% to account for the uncertainty in variability of the life interference endpoint and to account for the potential dropouts, increasing the sample size for the study to approximately 90 subjects.
Statistical analysis of primary endpoints	The primary endpoint was analysed using a linear mixed effects model including sequence, period, and treatment as fixed effects and subject within sequence and within-subject error as random effects. This model was used to test the hypothesis that the difference in Life Interference Total Score between weekly and daily regimens is statistically significant.
Statistical analysis of secondary	The continuous secondary endpoints were analysed using a linear mixed effects model including sequence, period, and

and other endpoints	treatment as fixed effects, and subject within sequence and within-subject error as random effects.

Table 11: ***Summary of the statistical methodology for CP-4-004 Phase 2 dose-finding study***

Trial name (NCT)	**CP-4-004 Phase 2 dose-finding study (NCT01592500)**
Hypothesis objective	There was no formal hypothesis testing in the CP-4-004 study
Sample size, power calculation	A sample size of up to 14 patients per cohort was chosen for this pilot investigation, to obtain up to 10 patients per cohort having peak plasma growth hormone (ppGH) stimulation test levels ≤ 7 ng/ml and up to four patients per cohort with ppGH levels > 7 and ≤ 10 ng/ml. The justifications for this sample size are based on feasibility, precision about the mean and variance, and regulatory considerations
Statistical analysis of primary endpoints	Summary statistics (arithmetic mean, SD, minimum value, lower quartile, median, upper quartile, maximum value, number of non-missing values) were to be calculated for both full analysis subset (FAS) and per protocol (PP) populations by cohort. The primary efficacy endpoint, annual HV (cm/year) was calculated as: $\text{Height Velocity (cm/year)} = \frac{\textit{Height in Visit } 12 - \textit{Height in Visit } 1}{(\textit{Date of Visit } 12 - \textit{Date of Visit } 1)/365.25}$ The last observation carried forward (LOCF) method was to be used for handling missing data at the 12 month analysis.
Statistical analysis of secondary and other endpoints	The secondary efficacy endpoints analysed include: (1) Annualized HV (cm/year) at six month visit $\text{Height Velocity (cm/year)} = \frac{\textit{Height in Visit } 10 - \textit{Height in Visit } 1}{(\textit{Date of Visit } 10 - \textit{Date of Visit } 1)/365.25}$ (2) Change from Screening to six month visit in height (HT) SDS [HTSDS] (Delta HTSDS) (3) Change from Screening to Month 12 visit in HTSDS (Delta HTSDS) For the three auxology/clinical endpoints, the results were to be summarized using descriptive statistics. The 95% CI is to be provided for mean annual HV and used to subjectively compare each dose level of somatrogon and somtatropin, as well as the individual somatrogon groups. The last observation carried forward (LOCF) method was to be used for handling missing data at the 12 month analysis.

B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

The clinical effectiveness of somatrogon is demonstrated from the clinical trial program, where direct head-to-head comparison with the relevant comparator, somatropin (Genotropin®) is available. As per the scope, and TA188, the different somatropin daily preparations are considered to offer equivalent clinical benefits and all recommended for the treatment of pGHD. Therefore, network meta-analyses/indirect treatment comparisons were not deemed necessary. Despite this, a systematic literature review (SLR) was conducted to identify all relevant clinical evidence on the efficacy and safety of somatrogon and relevant comparators for the treatment of patients with pGHD. In total, the SLR identified 20 records reporting on 18 unique studies. Full details of the SLR search strategy, study selection process and results can be found in Appendix D.

B.3.6 Clinical effectiveness results of the relevant studies

B.3.6.1 CP-4-006 Phase 3 pivotal study

- The Phase 3 pivotal study met the primary efficacy objective. Somatrogon administered once weekly was non-inferior to Genotropin® (somatropin) administered once daily as measured by mean annual HV after 12 months of treatment in prepubertal children with GHD.
- Other growth-related secondary endpoints, including annualised HV at 6 months, mean changes in height SDS as well as changes in bone maturation were comparable for both treatment groups.

Primary endpoint

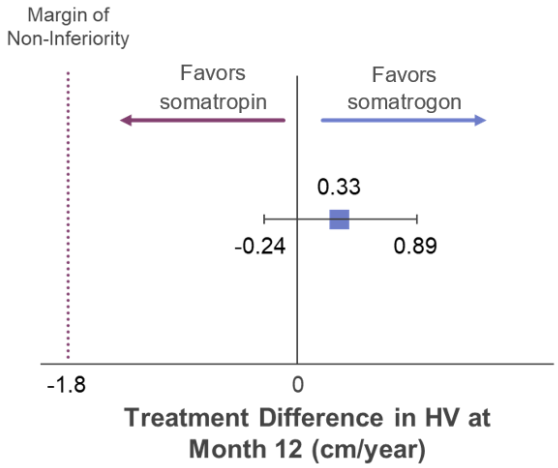
This Phase 3 pivotal study[52, 58] met its primary objective and demonstrated noninferiority of somatrogon administered once weekly to Genotropin® (somatropin) administered once daily with respect to annual HV at 12 months in prepubertal children with GHD (see Table 12; Figure 4). The lower bound of the two-sided 95% confidence interval (CI) for mean HV was greater than the prespecified noninferiority margin of -1.8 cm/year. Although mean HV was numerically higher in the

somatrogon group, superiority of weekly somatrogon over daily somatropin was not achieved.

Table 12: ***Phase 3 pivotal study primary endpoint: Annual HV (cm/year); FAS***

Primary endpoint	Somatropin (N=115)	Somatrogon (N=109)
Annualised HV after 12 months, cm/year	9.78	10.10
Treatment difference, somatrogon−somatropin (95% CI)	0.33 (-0.24 to 0.89)	

Figure 4: ***Phase 3 pivotal study showing non-inferiority of once weekly somatrogon vs once daily somatropin***



Secondary endpoints

The mean annualised HV at 6 months for the somatrogon group was comparable to the somatropin group (Least Square [LS] means 10.59 and 10.04 cm/year, respectively) with a LS mean treatment difference and 95% CI of 0.55 [-0.13, 1.23] (Table 13).

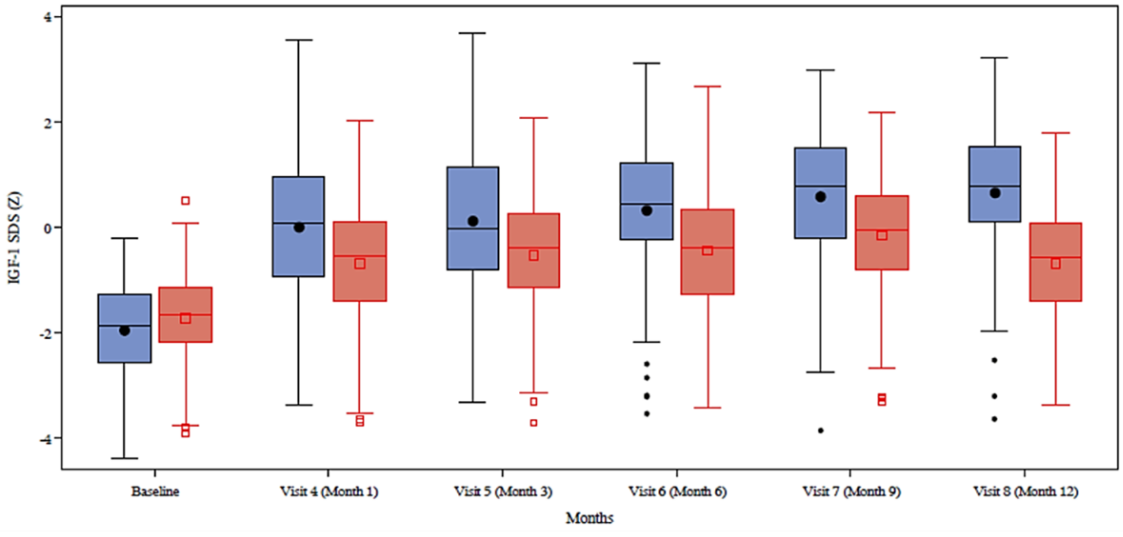
Similar improvements for the mean change in height SDS from baseline to 6 months were observed for the somatrogon and somatropin groups (LS mean treatment difference and 95% CI: 0.06 [-0.01, 0.13]). Similar improvements for the mean change in height SDS from baseline to 12 months were also noted for both treatment groups. Both treatment groups showed similar changes in bone maturation values at 12 months, indicating the bone age did not advance discordantly relative to chronological age (Table 13).

Table 13: **Phase 3 pivotal study key secondary endpoints**

Growth-related secondary endpoints	Somatropin (N=115)	Somatrogon (N=109)
Annualised HV after 6 months, cm/year (LS mean)	10.04	10.59
Treatment difference, somatrogon−somatropin (95% CI)	0.55 (-0.13, 1.23)	
Change from baseline in height SDS at 6 months, LS mean	0.48	0.54
Treatment difference, somatrogon−somatropin (95% CI)	0.06 (-0.01, 0.13)	
Change from baseline in height SDS at 12 months, LS mean	0.87	0.92
Treatment difference, somatrogon−somatropin (95% CI)	0.05 (-0.06, 0.16)	
Change from baseline in bone maturation at 12 months, mean (SD)	0.06 (0.10)	0.05 (0.09)

IGF-1 SDS values (Figure 5) approached 0 at one month post-baseline in the somatrogon group and remained in the target range up to 12 months, whereas in the somatropin group, IGF-1 SDS values remained near 0 at all post-baseline visits, ranging from -0.69 SDS to -0.16 SDS.

Figure 5: ***Box plot of IGF-1 SDS over time during the Phase 3 pivotal study, FAS***



	Baseline	Visit 4 (Month 1)	Visit 5 (Month 3)	Visit 6 (Month 6)	Visit 7 (Month 9)	Visit 8 (Month 12)
Treatment	N	N	N	N	N	N
Somatrogon	109	107	109	107	108	107
Somatropin	115	115	113	113	113	110

Note: The filled circles and empty squares inside the boxes are the means, lines inside boxes are medians. The ends of each box represent lower and upper quartiles, and bars at the ends of the whiskers represent lower and upper extremes. The individual data points outside the boxes are outliers.

QoL was assessed in a number of countries during the Phase 3 pivotal study, using the Quality of Life in Short Stature Youth (QoLISSY) questionnaire which captured 3 dimensions (physical, social and emotional) and was measured at baseline and Month 12. The raw scores were transformed to a scale of 0 to 100. Higher scores represent a higher QoL. Two versions of the QoLISSY were used in a dyadic approach to assess the parent and child's assessment of QoL: QoLISSY-PARENT, to be completed by the parent or caregiver for subjects <7 years; QoLISSY-CHILD, to be completed by subjects aged 7 years or older. Overall, somatrogon treatment improved QoL, as measured by validated QoLISSY for the core total score and for physical, social and emotional subscales, similar to that seen following somatropin treatment. Both QoLISSY-CHILD and QoLISSY-PARENT demonstrated that both treatment groups had similar increases in core total scores and subscale scores from baseline and 12 months (Table 14), indicating similar improvements in QoL following treatment with somatrogon administered once weekly or somatropin administered once daily.

Table 14: ***Summary of QoLISSY score change from baseline in the Phase 3 pivotal study, FAS***

Summary of QoLISSY score		**Somatropin (N=115)**	**Somatrogon (N=109)**
Caregivers score for Children <7 years	n	XX	XX
	Physical Month 12 change from baseline, Mean (SD)	XX.XX (XX.XX)	X.X (XX.XX)
	Social Month 12 change from baseline, Mean (SD)	X.XX (XX.XX)	X.X (XX.XX)
	Emotional Month 12 change from baseline, Mean (SD)	X.XX (XX.XX)	X.XX (XX.XX)
	Total* Month 12 change from baseline, Mean (SD)	X.XX (XX.XX)	X.XX (XX.XX)
Caregivers score for Children ≥7 years	n	XX	XX
	Physical Month 12 change from baseline, Mean (SD)	X.XX (XX.XX)	XX.XX (XX.XX)
	Social Month 12 change from baseline, Mean (SD)	X.XX (XX.XX)	XX.XX (XX.XX)
	Emotional Month 12 change from baseline, Mean (SD)	XX.XX (XX.XX)	XX.XX (XX.XX)
	Total* Month 12 change from baseline, Mean (SD)	X.XX (XX.XX)	XX.XX (XX.XX)

*The QoLISSY core total score is calculated by the sum of the means of these 3 dimensions (physical, social, and emotional) and divided by 3

B.3.6.2 CP-4-006 LT-OLE period

Of the 222 subjects who completed the CP-4-004 main study, 212 subjects entered the LT-OLE[59]. As of the cut-off date of 01 November 2019, efficacy data was available for 94 subjects at Month 18 (6 months of OLE), and 9 subjects at Month 24 in the OLE period (12 months of OLE).

Annualised HV with once weekly somatrogon treatment remained above baseline through the OLE period. The annualised HV for subjects who switched from somatropin to somatrogon at the beginning of the OLE period was consistent with subjects who received somatrogon during the main study and throughout the OLE period (Table 15). Of note, no subject in the CP-006 OLE had achieved final height as of the data cut-off of 01 November 2019.

Change in height SDS from baseline demonstrated sustained improvement with weekly somatrogon in the main study period, and this improvement continued over the OLE period (Table 15). Height SDS values also improved with weekly somatrogon treatment in the main study period, and this trend was maintained over time in the OLE period. Improvements in change in height SDS from baseline and HT SDS for subjects who switched from somatropin to somatrogon at the beginning of the OLE period were consistent with subjects who received somatrogon during the main study and throughout the OLE period (Table 15).

IGF-1 SDS values with weekly somatrogon treatment approached 0 early in the main study period and remained in the target therapeutic range through the OLE period. The trend in IGF-1 SDS values in subjects who switched from somatropin to somatrogon at the beginning of the OLE period was consistent with subjects who received somatrogon during the main study and throughout the OLE period (Table 15).

Table 15: ***Annualised HV, change in height SDS and IGF-1 SDS over time from main Phase 3 pivotal study through OLE periods (ongoing)***

Growth outcomes	Time	Originally randomised to somatropin (N=115)	Originally randomised to somatrogon (N=109)
Annualised HV (cm/year)	(Main study) Month 6		
	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	(Main study) Month 12		
	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	(OLE) Month 18		
	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	(OLE) Month 24		
	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Change in height SDS	(Main study) Month 6		
	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	(Main study) Month 12		
	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	(OLE) Month 18		
	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	(OLE) Month 24		
	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
IGF-1 SDS	(Main study) Month 6		
	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	(Main study) Month 12		
	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	(OLE) Month 18		
	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	(OLE) Month 24		
	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]

B.3.6.3 C0311002 phase 3 treatment burden study

- The primary analysis of the Phase 3 treatment burden study demonstrated, with statistical significant difference, an improved (i.e. lower) mean overall Life Interference total score after 12 weeks of treatment with somatrogon administered once weekly compared to daily Genotropin® (somatropin).
- Consistent with the primary endpoint, the results from secondary endpoints showed an overall benefit in treatment experience with somatrogon once weekly dosing regimen compared to somatropin once daily dosing regimen.
- Once weekly somatrogon has been demonstrated to increase intention to comply with the injection schedule compared to daily somatropin among patients and caregivers.

Primary endpoint

In the Phase 3 treatment burden study,[55, 60] the least square mean of the overall Life Interference total scores was lower for somatrogon administered once weekly (9.63) compared to somatropin administered once daily (24.13). The mean difference (somatrogon – somatropin) based on the linear mixed effects model was -15.49 with a two-sided 95% CI of (-19.71, -11.27) (Table 16). Since the 95% CI excludes zero, it can be concluded that the treatment burden of a somatrogon once weekly injection schedule is lower than that of a once daily somatropin injection, and the difference is statistically significant (p<0.0001) at the nominal 0.05 level.

Table 16: ***Phase 3 treatment burden study primary endpoint: Overall life interference total scores***

Primary endpoint	Somatropin (N=85*)	Somatrogon (N=82*)
Overall life interference total scores, mean (95% CI)	24.13 (20.61, 27.65)	8.63 (5.05, 12.22)
Treatment difference, somatrogon−somatropin (95% CI)	-15.49 (-19.71, -11.27) P<0.0001	

*Number of participants with non-missing values.se

Secondary endpoints

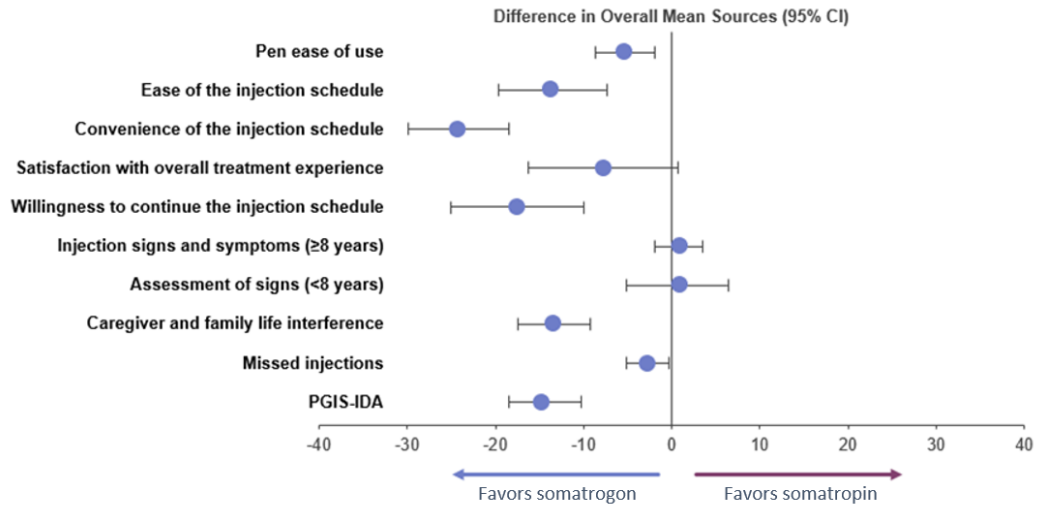
The estimated mean score differences for most variables within the Dyad Clinical Outcome Assessment (DCOA) 1 questionnaire showed an improvement (i.e., negative estimated mean difference) during the once weekly somatrogon injection schedule compared with the once daily somatropin injection schedule (

Figure 6), with statistically significant differences ($p<0.05$) demonstrated for the followings:

- Pen ease of use: -5.39 (-8.69, -2.09)
- Ease of the injection schedule: -13.60 (-19.74, -7.45)
- Convenience of the injection schedule: -24.34 (-30.10, -18.57)
- Willingness to continue injection schedule: -17.60 (-25.15, -10.06)
- Caregiver life interference (including Family life interference): -13.47 (-17.59, -9.35)
- Missed injections: -2.76 (-5.16, -0.36).

Overall mean scores were similar between both injection schedules for injection signs and symptoms (for participants 8 years and above: 13.6 for both injection schedules) and the assessment of signs (as reported by the caregiver for the children aged <8 years: 9.4 for the once daily somatropin injection schedule and 9.7 for the somatrogon injection schedule).

Figure 6: ***Phase 3 treatment burden study secondary endpoints: Patient and caregiver assessments of treatment experience (DCOA 1 and PGIS-IDA)***

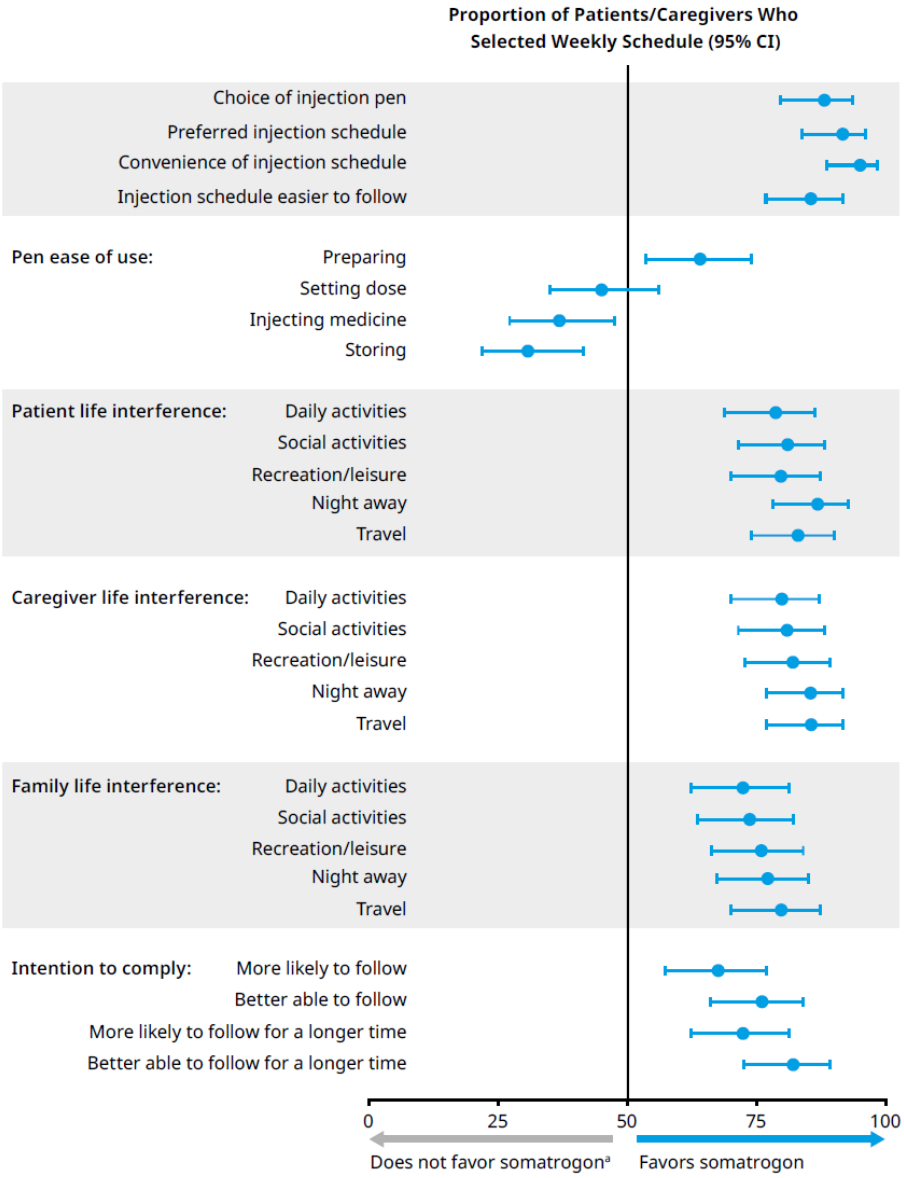


Note: Lower score represents improvement

Similarly, the majority of subjects/caregivers preferred the somatrogon once weekly dosing regimen/pen on every aspect of all but one (pen ease of use) of the DCOA 2 domains (

Figure 7). For the three items of pen ease of use domain (setting the dose, injecting the medicine, and storing the pen) for which the percentage of subjects that preferred somatrogon was less than 50%, there was a substantial proportion of subjects that had no preference (38.1%, 29.8%, 64.3%, respectively) between the two injection schedules. Nevertheless, there was a greater preference for weekly somatrogon over daily somatropin across all four “intention to comply” domains.

Figure 7: ***Phase 3 treatment burden study secondary endpoints: Patient and caregiver preference for the weekly injection schedule, after experiencing both treatment regimens (DCOA 2)***



Note: Higher score represents improvement

B.3.6.4 CP-4-004 Phase 2 dose finding study

- In the Phase 2 dose finding study, somatrogon dose of 0.66 mg/kg/week has demonstrated the best annualised HV, HV SDS and change in height SDS that is clinically better than 0.25 and 0.48 mg/kg/week, and closest to Genotropin® (somatropin) 0.034 mg/kg/day.

Primary endpoint

In the Phase 2 dose finding study,[2] at the 12 month visit, mean HV in the somatrogon cohorts were 10.4 (95% CI: 8.9, 12.0), 11.0 (95% CI: 9.7, 12.2), and 11.4 (95% CI: 9.2, 13.7) cm/year in Cohorts 1 (0.25 mg/kg/week), 2 (0.48 mg/kg/week), and 3 (0.66 mg/kg/week), respectively (FAS; Table 17). The mean HV for the somatropin group was 12.5 cm/year (95% CI: 11.0-13.9 cm/year). HV does not appear to differ substantially across the somatrogon dose levels. Growth did however appear to increase with the dose level. The 95% CI for each of the somatrogon cohorts overlap with the CI for somatropin, with the highest somatrogon dose group (Cohort 3, 0.66 mg/kg/week) having the closest mean value (Table 17).

Table 17: ***Phase 2 dose finding study primary endpoint: Annual HV (cm/year); FAS***

Primary endpoint	Somatropin	Somatrogon		
	0.34 mg/kg/day (N=11)	0.25 mg/kg/week (N=13)	0.48 mg/kg/week (N=15)	0.66 mg/kg/week (N=14*)
HV at 12 months, cm/year	12.5	10.4	11.0	11.4
95% CI of mean	11.0, 13.9	8.9, 12.0	9.7, 12.2	9.2, 13.7

*One patient in the 0.66 mg/kg/week somatrogon treatment group was wrongly included in the study. Patient diagnosed with psychosocial dwarfism (exclusionary condition) following study completion. Mean HV is higher with the exclusion of this patient (11.9 cm/year; 95% CI 9.8-14.1)

Secondary endpoints

The mean HV at six months for the daily somatropin cohort was 15.0 (95% CI: 13.1, 16.9). Results in the weekly somatrogon cohorts were 11.8 (95% CI: 13.1, 16.9), 12.5 (95% CI: 11.1, 13.8), and 13.0 (95% CI: 9.9, 16.0) for Cohorts 1 (0.25

mg/kg/week), 2 (0.48 mg/kg/week), and 3 (0.66 mg/kg/week), respectively (Table 18).

The change in height SDS (ΔHT SDS) from screening to six and 12 months are summarised in Table 18. Mean change in height SDS improved from six months to 12 months in all cohorts.

Overall, the 0.66 mg/kg/week dose of somatrogon did not differ significantly from daily 0.34 mg/kg/day somatropin at six or 12 months with regard to annualised HV, HV SDS and ΔHT SDS data (Table 18).

Table 18: ***Phase 2 dose finding study secondary endpoints: Annual HV (cm/year); FAS***

Secondary endpoints	Somatropin	Somatrogon		
	0.34 mg/kg/day (N=11)	**0.25 mg/kg/week (N=13)**	**0.48 mg/kg/week (N=15)**	**0.66 mg/kg/week (N=14)**
HV at 6 months, cm/year	15.0	11.8	12.5	13.0
95% CI of mean	(13.1, 16.9)	(9.6, 13.9)	(11.1, 13.8)	(9.9, 16.0)
ΔHT SDS from screening to six months, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
ΔHT SDS from screening to 12 months, mean (SD)	1.51 (0.47)	1.09 (0.53)	1.19 (0.49)	1.35 (0.69)

B.3.6.5 CP-4-004 Phase 2 OLE study

- Subjects treated for up to five years in CP-4-004 Phase 2 OLE study on either presentation of somatrogon (vial or pen) demonstrated sustained improvement in clinical parameters of growth including annual HV, change in height SDS and height SDS, with continual normalisation of height progressively. Continued bone maturation over time was also reported.

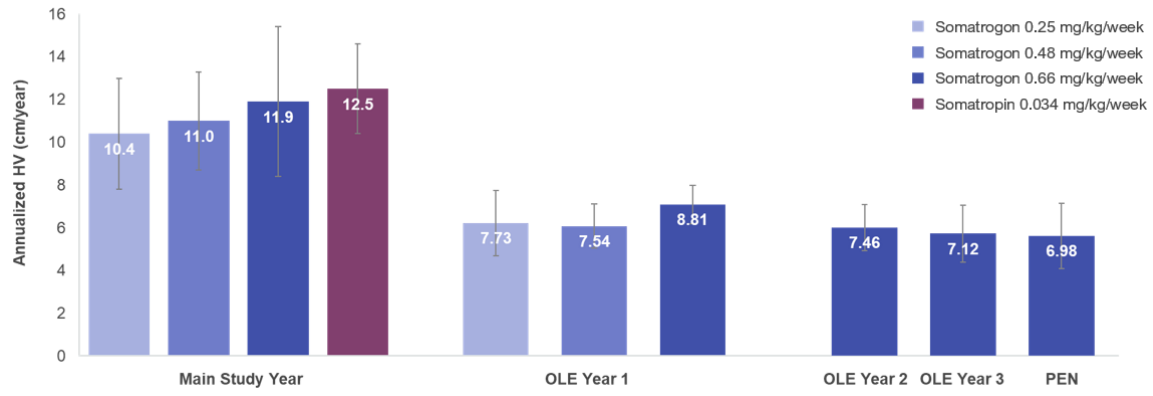
Overall analysis of efficacy

A summary of the annual HV at the end of years 1, 2, and 3 of the OLE study[61] and after switching from the vial formulation to the pen device is shown in Figure 8. The

mean annual HV was the greatest during Year 1 OLE and decreased with every subsequent year thereafter. The mean annual HV for subjects who received somatropin during the main study and were switched to somatrogon during Year 1 OLE was consistent with subjects who received somatrogon during the main study. As shown in *Note: The growth response to growth hormone treatment is typically maximal in the first year of treatment and then gradually decreases over the subsequent years of treatment.*[16]

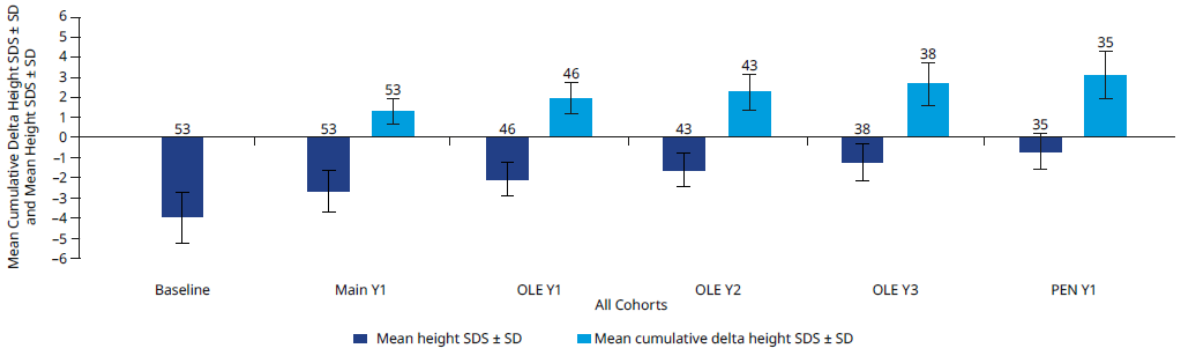
Figure 9, height SDS and change in height SDS also continued to increase throughout the OLE, and by the end of Year 5 of the OLE period (PEN), height SDS was within the normal range (-0.69 ± 0.87).

Figure 8: ***Annual HV at end of years 1, 2 and 3 of the OLE study and after switching to PEN during the Phase 2 OLE study***



Note: The growth response to growth hormone treatment is typically maximal in the first year of treatment and then gradually decreases over the subsequent years of treatment.[16]

Figure 9: ***Summary of height SDS for all cohorts combined at each year in the Phase 2 OLE study, FAS***



The observed increase in bone maturation at the end of Year 1 OLE was similar across treatment groups, which was consistent with results reported from the main Phase 2 study. The observed mean changes in bone maturation were consistent across years 2-3 and after transition to the pen formulation and demonstrated continued bone maturation over time (Table 19).

Table 19: ***Bone maturation change at each year with somatrogon treatment in the Phase 2 OLE study, FAS***

Bone maturation change at end of year (years)	Yr 1 OLE study			Yr 2 (N=44)	Yr 3 (N=43)	Yr 4 (N=38)	12M before Pen (N=15)	12M after Pen (N=25)
	0.25mg/kg/wk (N=16)	0.48 mg/kg/wk (N=17)	0.66 mg/kg/wk (N=15)					
n	[redacted]							
Mean (SD)	[redacted]							

N = subjects that entered the study period; n = subjects with bone maturation data for the study period.
Note: Bone maturation = Bone age/Chronological age

B.3.7 Subgroup analysis

A forest plot for subgroups (age group, gender, peak GH levels at baseline and geographical region) that were pre-specified in the Phase 3 pivotal study is presented in Appendix D. Results across the subgroups were mostly consistent with the overall results for the full trial populations.[58]

For the Phase 3 treatment burden study, results of the subgroup analyses as assessed by Overall Life Interference within the prespecified subpopulations (age, caregivers vs self-injection, and burdened vs not burdened) were consistent with the overall results of the primary analysis[55] (Appendix D).

B.3.8 Meta-analysis

Due to the nature of the evidence, non-inferiority randomised controlled trial (RCT), head-to-head evidence was provided in the summary of clinical evidence (see Section B.3.6). As part of TA188 the NICE committee concluded that all dGHs were of similar clinical equivalence. Therefore, no meta-analysis of all available relevant therapies has been conducted as part of this submission.

B.3.9 Indirect and mixed treatment comparisons

As a robust head-to-head clinical trial was conducted, and all relevant therapies captured within this submission as identified in the final NICE Scope were previously deemed to have similar clinical equivalence as part of TA188.[11] As such, no additional indirect and mixed treatment comparisons have been undertaken. See section B.3.5 for more details.

B.3.10 Adverse reactions

- Somatrogon was well tolerated, and the safety profile was similar to Genotropin® (somatropin), with no unexpected adverse events (AE). The majority of AE were mild to moderate in severity.
- In the global Phase 3 study, most common treatment-emergent AE in both treatment groups included injection site pain, nasopharyngitis, headache, and pyrexia.
- Across all somatrogon program trials, the incidence of injection site reactions was higher among somatrogon than among somatropin-treated patients. Most events were mild to moderate in severity and with few exceptions did not result in discontinuation.
- A higher number of patients were positive for anti-drug antibodies (ADA) in the somatrogon group compared to somatropin. A post-hoc analysis showed no differences between ADA-positive and ADA-negative patients in terms of efficacy and safety.
- No clinically meaningful differences between somatrogon and somatropin were observed for glucose metabolism, haematology, chemistry, thyroid function, lipid profiles, and urinalysis parameters.

B.3.10.1 CP-4-006 Phase 3 pivotal study

A summary of the adverse events (AE) in the Phase 3 pivotal study[58] is presented in Table 20. Somatrogon was generally well tolerated in paediatric subjects with GHD. The incidence of subjects with AE was comparable between the somatrogon (87.2%) and somatropin (84.3%) groups. The rates of the most common AE (occurring in ≥10% of patients) in either the somatrogon or somatropin group are presented in Table 21. The majority of AE were mild to moderate in severity: somatrogon, 78.9%;

Genotropin®, 79.1%. The incidence of severe AE was numerically higher in the somatrogon treatment group (8.3%) compared with the somatropin group (5.2%), due to the higher incidence of severe injection site pain (4.6% and 2.6% for somatrogon and somatropin, respectively), which was the most frequently reported severe AE in both treatment groups. The onset of the pain tended to be during

the first 6 months of treatment and the incidence decreased over time. Per protocol, injection site pain was to be reported as an AE if the subject recorded a pain severity score of ≥4 in the patient diary. Injection site pain was a solicited data point; the difference between the somatrogon and somatropin groups may be attributed to the way injection site pain was recorded in the trial. In the somatrogon group, the severity of injection site pain after each weekly injection was recorded, whereas, in the somatropin group, the most severe pain for the week was recorded (ie, once a week) rather than after each daily injection. Furthermore, if a somatropin-treated subject experienced multiple instances of pain with severity ≥4 during a week, only one occurrence would be recorded in the diary out of a potential maximum of 7 episodes with daily injections for the week.

There were no deaths during the study. The incidence of serious adverse events (SAE) was low for both somatrogon (2.8%) and somatropin (1.7%) groups and none were considered related to study treatment. Only one subject in the somatrogon group permanently discontinued the study due to an AE (injection site erythema and injection site induration [hardening]).

Overall, 29 subjects experienced IGF-1 levels > 2 SDS sometime during the study (somatrogon: n = 26; somatropin; n = 3). There was a total of 26 subjects in the somatrogon group with initially high IGF-1, but 14 of them were not high on the mandatory retest. Closer scrutiny of these 26 samples showed that 23 of them were obtained on day 2 or 3 after administration, which represents peak IGF-1 levels, not the mean, explaining the high IGF-1 levels. A total of 12 patients did require a dose reduction, as per protocol (due to 2 consecutive measurements with SDS > 2). Using the data collected, a pharmacokinetics (PK)/pharmacodynamics (PD) analysis was performed to simulate IGF-1 profiles for each of the study subjects and to estimate the mean IGF-1 SDS over the dosing interval, regardless of when the sample had been collected. Among somatrogon-treated subjects, 10 of 535 (1.9%) samples that

corresponded to mean IGF-1 SDS over the dosing interval were > 2. These 10 instances of mean IGF-1 SDS >2 occurred in 3 subjects and no subject had a mean IGF-1 SDS ≥ 3.[52]

Table 20: ***Summary of AE in the Phase 3 pivotal study***

Number (%) of subjects, n (%)	Somatropin (N=115)	Somatrogon (N=109)
Subjects evaluable for AE	115	109
Number of AE	570	868
Subjects with AE	97 (84.3)	95 (87.2)
Subjects with SAE	2 (1.7)	3 (2.8)
Subjects with severe AE	6 (5.2)	9 (8.3)
Subjects discontinued from study due to AE	0	1 (0.9)
Subjects with dose reduced or temporary discontinuation due to AE	2 (1.7)	3 (2.8)

Table 21: ***Most common (≥10% in either group) all-cause AE in the Phase 3 pivotal study***

All-Causes AE, n (%)	Somatropin (N=115)	Somatrogon (N=109)
Injection site pain	29 (25.2)	43 (39.4)
Nasopharyngitis	29 (25.2)	25 (22.9)
Headache	25 (21.7)	18 (16.5)
Pyrexia	16 (13.9)	18 (16.5)

No clinically meaningful differences in adverse event of special interest (AESI) between treatment groups, except injection site reactions (somatrogon: 43.1% and somatropin: 25.2%) and immunogenicity (somatrogon: 18.3% and somatropin: 7.8%), which were higher in the somatrogon group compared to the somatropin group.

Among the 109 somatrogon-treated subjects, 84 subjects (77.1%) tested anti-drug antibodies (ADA)+ for somatrogon at any time during the main study. Analyses comparing clinical endpoint results for ADA+ and ADA- subjects showed that somatrogon ADAs did not have an effect on safety during the 12-month main study period.

There were no glucose metabolism abnormalities in the somatrogon treatment group. There was no new onset of diabetes or hyperglycemia in any subject treated with somatrogon. No clinically meaningful differences between treatment groups were observed for thyroid function, lipids, vital assessments or for physical examinations. There were no confirmed Hy's Law cases identified in the study. Neither treatment group had any clinically meaningful changes in electrocardiogram (ECG).

B.3.10.2 CP-4-006 LT-OLE period

Upon completion of the main study, 212 subjects continued into the OLE[59]. As of the data cut-off date of 01 November 2019, there were 207 active subjects receiving treatment with somatrogon. This period covers up to 18 months of exposure in the OLE.

Somatrogon continued to be well-tolerated in the ongoing OLE. The summary of AE from the Phase 3 LT-OLE period is reported in Table 22. The incidence of subjects reporting AE in the group originally randomised to receive somatrogon in the main study was 47.1% versus 68.5% in the group originally randomised to receive somatropin in the main study period who then switched to somatrogon in the OLE. Most subjects, overall and in each initial randomisation group, had AE that were mild ([redacted]% overall) to moderate ([redacted]% overall); [redacted]% subjects overall had severe AE. The most frequently reported AE was injection site pain (22.6%); the incidence was higher in the group originally randomised to somatropin (33.3%) compared to the group originally randomised to somatropin (11.5%). There were five reports (2.4%) of severe injection site pain and one severe report of injection site deformation.

No deaths have been reported. Seven subjects (3.3%) reported SAE, but none were considered treatment related. Five subjects discontinued due to an AE, including injection site pruritus, injection site erythema, injection site pain and anxiety (that is not related to study treatment).

During the OLE phase, no clinically meaningful differences in AESI between subjects based on their original randomised treatment groups (either somatropin or somatrogon arms in the main Phase 3 study) were observed, except injection site

reactions, and immunogenicity, which were higher in the group originally randomised to somatropin compared to the group originally randomised to somatrogon. The overall incidence of injection site reactions and immunogenicity in the OLE was 26.9% and 5.2%, respectively.

Immunogenicity results were available for 79 subjects in the OLE period. Among 38 subjects who received somatrogon in the main study period, 26 subjects (68.4%) tested ADA+ at Month 6 in the OLE. These subjects had their first ADA+ result during the main study and continued to be ADA+ into OLE. There were no subjects originally randomised to somatrogon who had tested ADA- in the main study who then tested ADA+ upon entering OLE. Among 41 subjects who received somatropin in the main study period, 8 subjects (19.5%) tested ADA+ at Month 6 in the OLE after switching to somatrogon.

The clinical laboratory profile in the CP-4-006 OLE is consistent with that observed during the main study period. There were no clinically significant laboratory abnormalities reported during the OLE period. No confirmed Hy's Law cases have been identified in the study. Overall, there have been no trends in vital sign abnormalities, physical examinations, or clinically meaningful changes in ECG.

Table 22: ***Summary of AE in the Phase 3 LT-OLE period (cut-off date of 01 November 2019)***

Number (%) of subjects, n (%)	Somatropin	Somatrogon
Subjects evaluable for AE	108	104
Number of AE	431	250
Subjects with AE	79 (68.5)	49 (47.1)
Subjects with SAE	2 (1.9)	5 (4.8)
Subjects with severe AE	6 (5.6)	5 (4.8)
Subjects discontinued from study due to AE	5 (4.6)	0
Subjects with dose reduced or temporary discontinuation due to AE	1 (0.9)	2 (1.9)

B.3.10.3 C0311002 phase 3 treatment burden study

The safety profile reported from the Phase 3 treatment burden study[55] was similar for both study drugs, with AE reported in 44.2% of somatropin-treated and 54.0% of somatrogon-treated patients. The most common AE was injection site pain which was reported in 11 (12.8%) and 13 (14.9%) patients when treated with daily

somatropin and weekly somatrogon, respectively. No SAE were reported during either of the treatment periods. One participant discontinued somatrogon following an AE of moderate injection pain. During the somatropin period, 3 patients had temporary discontinuation due to a total of 4 AE (viral upper respiratory tract infection, nasopharyngitis, otitis media and viral infection).

B.3.10.4 CP-4-004 Phase 2 dose finding study

Somatrogon was generally well-tolerated throughout the 12 months of the main study[57]. The incidence of subjects with AE was [redacted]% and comparable across the somatrogon cohorts (doses of 0.25 mg/kg/week [[redacted]%], 0.48 mg/kg/week [[redacted]%], and 0.66 mg/kg/week [[redacted]%]), and the somatropin group (0.034 mg/kg/day [[redacted]%]. Most subjects across the somatrogon and somatropin groups had AE that were mild to moderate (somatrogon: [redacted]%; somatropin: [redacted]%). There were [redacted] severe AE reported during the study but only [redacted] (injection site pain) considered related to study treatment (0.66 mg/kg/week somatrogon). The most common AE (≥10% in either treatment group) reported for either treatment group throughout the 12 months are summarised in Table 23. There were no treatment-related SAEs, or AE-related discontinuations in any of the groups.

With regard to AESI, no significant findings attributed to somatrogon were observed in glucose metabolism. One case of mild adrenal insufficiency (somatrogon 0.25 mg/kg/week) and one case of moderate secondary adrenocortical insufficiency (0.48 mg/kg/week) were assessed as being possibly related to study drug. Hypothyroidism was indicated as an AE for 4 subjects: 1 subject in each of the 3 somatrogon dose groups and 1 subject in the somatropin group.

Ten out of 42 somatrogon-treated subjects (23.8%) tested ADA+ for somatrogon at 6 months (Week 26) and 5 subjects (11.9%) tested ADA+ at 12 months (Week 52), all of which were specific for hGH. No somatrogon-treated subjects were reported as having neutralising antibodies (Nabs) to either somatrogon or hGH. Overall, there was no impact of testing ADA+ on efficacy or safety parameters.

Laboratory assessments supported the tolerability of somatrogon treatment. One subject experienced IGF-1 SDS levels that fell outside the desired range (>2 SDS) requiring a dose modification per protocol from 0.66 mg/kg/week to 0.48 mg/kg/week

prior to Visit 6 (Week 14). There were no AE associated with the increased IGF-1. The majority of mean blood chemistry and hematology values were within normal limits, with the exception of relative eosinophil and relative lymphocyte levels. These levels were also high at screening. No significant overall changes were observed in mean vital signs.

Table 23: ***Most common (≥10% in either treatment group) all-cause AE in the Phase 2 study***

	Somatropin	Somatrogon		
All-Cause AE, n (%)	**0.34 mg/kg/day (N=11)**	**0.25 mg/kg/wk (N=13)**	**0.48 mg/kg/wk (N=15)**	**0.66 mg/kg/wk (N=14)**
Any TEAE	8 (72.7)	10 (76.9)	10 (66.7)	10 (71.4)
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory Tract Infection	[redacted]	[redacted]	[redacted]	[redacted]
Anemia	[redacted]	[redacted]	[redacted]	[redacted]
Varicella	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory Tract Infection (Viral)	[redacted]	[redacted]	[redacted]	[redacted]

B.3.10.5 CP-4-004 Phase 2 OLE study

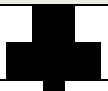
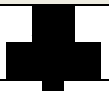
The overall incidence of subjects with AE from the Phase 2 OLE study[57] (up to 5 years) is presented in Table 24. A total of 39 subjects (81.3%) reported any AE during the OLE period. Most AE were mild or moderate in severity, and most were considered unrelated to study treatment. There were 3 subjects (6.3%) who reported at least one SAE during the OLE period, all of which were considered unlikely to be related to study treatment with the exception of 1 instance of scoliosis. Two subjects reported AE leading to study discontinuation.

In terms of AESI, 2 subjects reported scoliosis, both considered possibly and probably related to study treatment. During the PEN period, 1 subject reported mild hypercholesterolemia and 1 reported mild injection site bruising, both considered possibly related to study treatment.

Among 48 subjects who entered the OLE, 18 (37.5%) tested ADA+ for somatrogon at any time during the OLE. This included 10 subjects who had previously tested ADA+ in the main study. Of these 18 subjects, 16 demonstrated specificity for hGH and 3 demonstrated specificity of CTP. No subjected tested positive for NAbs.

Clinical laboratory evaluation results were similar to results reported for the main study. Measurements of glucose metabolism, thyroid status, cortisol levels, lipid parameters, and haematology/chemistry remained within normal limits. No physical examination, vital sign, or ECG abnormalities of note were observed.

Table 24: ***Summary of AE in the Phase 2 OLE study***

Number (%) of subjects, n (%)	Overall (N=48)	Yr 1 (N=48)	Yr 2 (N=44)	Yr 3 (N-43)	Yr 4 (N=38)	PEN (N=40)
AE						
SAE						
Study drug related AE						
AE leading to study drug reduction or interruption						
AE leading to study discontinuation						

B.3.11 Conclusions about comparable health benefits and safety

Growth hormone deficiency (GHD) is the most common pituitary hormone deficiency, affecting between 1 in 3500 and 1 in 4000 children in the UK. Paediatric GHD has significant physical, psychological, and emotional consequences that are carried throughout adulthood and can result in a very high opportunity cost to patients, caregivers, and society.

GHD is currently treated with daily injections of recombinant human GH. GH replacement therapy has been used for over 30 years in tens of thousands of patients (primarily children) and has proved to be safe and effective. Treatment typically begins once a diagnosis is made and is continued for a mean duration of 4-11 years with the goal of reaching a relatively normal rate of growth and development.[62]

Somatropin is the GH currently marketed in the UK. Several GH products, which are all given once-daily by subcutaneous injection, were recommended as a treatment option for children with GHD based on NICE MTA, TA188 and were deemed clinically equivalent by the committee. Currently the standard of care requires daily injections which has been shown to be problematic in terms of treatment burden and adherence that could lead to suboptimal outcomes.

Somatrogon is a long-acting growth hormone (LAGH) for once weekly treatment of children with GHD. It has been demonstrated in a robust clinical trial program that somatrogon dosed once-weekly in prepubertal children with GHD to have similar benefit-risk and tolerability profiles, an overall benefit in treatment experience, and was non-inferior to somatropin dosed once daily with respect to the primary endpoint of HV at 12 months of treatment. Long term treatment with somatrogon also demonstrated continual improvements in annual HV, height SDS, and change in height SDS in patients treated for up to five years.

Somatrogon's once a week injection therapy reduces injection frequency and burden and has been demonstrated to increase intention to comply with the weekly injection schedule compared to dGH. Patient preference studies have also shown that both patients and caregivers prefer a weekly injection over the current daily injection.[25] Finally, an important aspect of the once a week versus daily injections is that it has the potential to positively impact paediatric patients' QoL through reduced life interference and treatment burden.

Somatrogon therefore importantly provides an additional treatment option for children with GHD, significantly reducing the number annual injections required over the patient's treatment period.

B.3.12 Ongoing studies

Pfizer is launching a new, voluntary, multi-country (including UK) registry (EU post-authorisation study register number: EUPAS4371517) that will collect long-term data on patients who are prescribed once weekly somatrogon and other daily growth hormone by physicians, in a routine clinical setting.[63] The primary objective of this non-interventional, prospective cohort study will be to assess the safety and effectiveness of somatrogon under real world conditions. It is intended to collect real

world experience of routine clinical practice as defined by the treating physicians, including data related to safety, treatment adherence and patient-reported outcomes.

[redacted]

Outside of the UK, Pfizer is conducting several other studies including but not limited to: assessing adherence; caregiver & patient burden; and experience of switching to less frequent injections.

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Somatrogon is the first once weekly injection available for the treatment of GHD for children. All currently available treatment options licenced for the same indication require once daily injections. All products are administered as subcutaneous injections.

Service provisions for the dGH have previously been outlined in TA188 (see Section B.2.2). Despite the movement from a once daily injection to once weekly for those patients being treated with somatrogon there is no expectation for there to be a change in service provision or management between the products.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

Cost inputs considered in the base-case analysis comprised of drug acquisition costs only, where treatment costs per year per patient were estimated. The acquisition costs have been sourced from British National Formulary (BNF).[64]

Costs were calculated for the average age and weight of a patient for children with growth hormone deficiency. The average weight (40kg) of a patient was based on the mean start age (9 years) and estimated finishing age (16 years), taking the relevant weight from the KIGS data base as part of the assumption used in TA188, the rounded midpoint age (13 years).[13]

The per milligram treatment dose was taken based on the phase 3 clinical trial (see section B.3.1) for both somatrogon and somatropin. For somatrogon this was 0.66 mg/kg/week and an equivalent dose of 0.034 mg/kg/day (equivalent to 0.24 mg/kg/week) for somatropin. The same dose (0.24 mg/kg/week) was applied for all dGH comparators, as per the economic model for TA188 where the dose for all dGH therapies was assumed to be the same. and applied also in the economic model for TA188.

Due to the nature of a cost-comparison model and that there is no difference in efficacy or treatment duration across the relevant comparators, discontinuation has

not been factored into the analysis. This was also not considered as part of the base case analysis for the Assessment group model in TA188.

Furthermore, compliance (adherence) has not been factored into the analysis. There is extensive evidence in the literature that missing more than 1 injection per week leads to reduced HV compared to fully adherent patients.[17, 65] However, somatrogon has the potential to improve treatment outcomes by reducing treatment frequency and burden and increasing compliance and adherence. Furthermore, the once a week versus daily injections has the potential to positively impact paediatric patients' QoL through reduced life interference and treatment burden and utility gain, utility being a key driver of cost-effectiveness.[38-40, 66] These would be additional benefits not captured in the cost comparison analysis and could be considered as an underestimation of the value of somatrogon to the National Health Service England (NHSE).

B.4.2.2 Intervention and comparators' acquisition costs

Unit costs for each comparator and somatrogon are summarised in Table 25. The daily growth hormone dose of 0.034 mg/kg/day (equivalent to 0.24 mg/kg/week) was chosen based on the most commonly used dose worldwide in real world setting for pGHD and is in line with the posology licensed for its use. This was also the dose investigated in the pivotal study for somatrogon where non-inferiority to somatropin was demonstrated.

Due to the procurement of these medicines the company does not expect patient access schemes (PAS) to be in place, and therefore the list prices most accurately reflect the real-world prices. The per mg/kg costs vary across the daily somatropin therapies, which were all previously deemed cost effective as part of TA188.[11]

The dosage of all treatment options is based on the patient's body weight. The base-case analysis assumed that patients weigh 40kg. This weight is estimated based on average mean weight of patient assuming linear growth in weight year on year. A change in weight is expected to have a proportionate change across all technologies and therefore not have an impact on the comparative costs.

Table 25: ***Acquisition costs of the intervention and comparator technologies***

	Somatrogon	**Humatrope®**	**Zomacton®**	**NutropinAq®**	**Norditropin®**	**Genotropin®**	**Omnitrope®**	**Saizen®**
Pharmaceutical formulation	Solution for injection	Powder and solvent for solution for injection	Powder and solvent for solution for injection.	Solution for injection	Two pharmaceutical forms are available: 1. Solution for injection in cartridge 2. Solution for injection in pre-filled pen	Powder and solvent for solution for injection	Solution for injection in a cartridge	Two pharmaceutical forms are available: 1. Solution for injection in cartridge 2. Powder and solvent for solution for injection
(Anticipated) care setting	Primarily Hospital setting	Primarily Hospital setting	Primarily Hospital setting	Primarily Hospital setting	Primarily Hospital setting	Primarily Hospital setting	Primarily Hospital setting	Primarily Hospital setting
Acquisition cost (excluding VAT) *	24mg/1.2ml, 1=£189.60 60mg/1.2ml, 1=£474.00	6mg, 1=£108.00. 12mg, 1=£216.00. 24mg, 1=£432.00	1=£68.28	1=£203.00; 3=£609.00.	5mg/1.5ml, 1=£115.90. 10mg/1.5ml, 1=£231.80. 15mg/1.5ml, 1=£347.70	5.3mg, 1=£92.15. 12mg, 1=£208.65	5mg/1.5ml 5=£368.74. 10mg/1.5ml 5=£737.49. 15mg/1.5ml 5=£1106.22	5.83mg/ml, 1 x 1.03ml (6mg)=£139.08. 8mg/ml: 1 x 1.5ml (12mg)=£278.16; 1 x 2.5ml (20mg)=£463.60.
Method of administration	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection
Doses	0.66mg/kg/week	0.025-0.035mg/kg/day	0.025-0.035mg/kg/day	0.025-0.035mg/kg/day	0.025-0.035mg/kg/day	0.025-0.035mg/kg/day	0.025-0.035mg/kg/day	0.025-0.035mg/kg/day
Dosing frequency	Once weekly	Once daily	Once daily	Once daily	Once daily	Once daily	Once daily	Once daily
Dose adjustments	In patients whose serum IGF-1 concentrations exceed the mean reference	N/A	Generally a daily injection of 0.02 – 0.03 mg/kg bodyweight or 0.7 - 1.0 mg/m^2 body surface area. The total	N/A	The dosage is individual and must always be adjusted in accordance with the individual's clinical and biochemical	Generally a dose of 0.025 - 0.035 mg/kg body weight per day or 0.7 - 1.0 mg/m² body surface area per day is	Generally a dose of 0.025 - 0.035 mg/kg body weight per day or 0.7 - 1.0 mg/m2 body surface area per day is	N/A

	value for their age and sex by more than 2 SDS, the dose of somatrogon should be reduced by 15%. More than one dose reduction may be required in some patients.		weekly dose of 0.27 mg/kg or 8 mg/m^2 body surface area should not be exceeded (corresponding to daily injections of up to about 0.04 mg/kg)		response to therapy.	recommended. Even higher doses have been used.	recommended. Even higher doses have been used.	
Average length of a course of treatment	Long-term; mean treatment length is 7 years (please refer to the economic model for treatment).[13] Cost comparison looks at the estimated annual treatment cost of an average patient, given all patient variable parameters will be consistent across all treatment options.							
Average cost of a course of treatment (acquisition costs only)	£7.90 per mg / £10,845 est. annual cost*	£18.00 per mg / £8,911 est. annual cost*	£17.07 per mg / £8,450 est. annual cost*	£20.30 per mg / £10,049 est. annual cost*	£21.27-£23.18 per mg / £11,475 est. annual cost*	£17.39 per mg / £8,609 est. annual cost*	£14.75 per mg / £7,302 est. annual cost*	£23.18 per mg / £11,475 est. annual cost*
(Anticipated) average interval between courses of treatment	N/A							
(Anticipated) number of repeat courses of treatment	Treatment should be discontinued when there is evidence of closure of the epiphyseal growth plates (see section 4.3). Treatment should also be discontinued in patients having achieved final height or near final height.	Treatment should be continued until the end of the growth has been reached.	The duration of treatment, usually a period of several years, will depend on maximum achievable therapeutic benefit.	Treatment should be continued in children and adolescents until their epiphysis are closed.	Patients should be re-evaluated for GH secretory capacity after growth completion. When GHD persists after growth completion, growth hormone treatment should be continued to achieve full somatic adult	Where childhood onset GHD persists into adolescence, treatment should be continued to achieve full somatic development (e.g. body composition, bone mass).	Where childhood onset GHD persists into adolescence, treatment should be continued to achieve full somatic development (e.g. body composition, bone mass).	Treatment should be discontinued when the patient has reached a satisfactory adult height or the epiphyses are fused.

					development including lean body mass and bone mineral accrual.			

*per mg cost taken from BNF; estimated annual cost based on daily dose of 0.034mg/kg (converted to weekly) and weekly dose of 0.66mg/kg/week (somatrogon) and average child weight of 40kg. Additional information:

1) The daily growth hormone dose of 0.034 mg/kg/day (equivalent to 0.24 mg/kg/wk) was chosen based on the most commonly used dose (0.24mg/kg/wk) worldwide in real world setting for pGHD, and is in line with the posology licensed for its use. This was also the dose investigated in the pivotal study for somatrogon.

2) Weight is estimated based on average mean weight of patient assuming linear growth in weight year on year. A change in weight is expected to have a proportionate change across all technologies.

B.4.2.3 Intervention and comparators' healthcare resource use and associated costs

TA188 Assessment report identifies several healthcare resource utilisation and other associated costs for treatment of daily growth hormone.[13] The costs used in this model were also based off the previous Health Technology Assessment (HTA) report.[67] No difference in costs were identified within the dGHs, i.e., all dGH incurred identical treatment costs with the only variable factor in overall costs being the acquisition cost of the medicine.

An SLR was conducted to identify cost and resource use data relevant to the decision problem from the published literature as summarised in Appendix G. In total two studies were identified that met the pre-defined inclusion criteria. It was clearly concluded that since Somatrogon is expected to incur identical costs to that of the dGHs the only costs deemed relevant for inclusion into this submission for consideration are the medicine acquisition costs.

Although not required, an SLR was also conducted to identify health-related quality of life (HRQoL) studies relevant to the decision problem from the published literature. None of the studies met the NICE reference case in terms of requirements for health state utility value (HSUV) evidence, i.e., health states should be described by patients and valued using UK societal values. The studies reported disease specific or general quality of life outcomes only. A complete description of the search strategy is presented in Appendix I.

B.4.2.4 Adverse reaction unit costs and resource use

There was no significant difference in the AEs reported between somatrogon and somatropin in the PH3 clinical trial. As such AE costs were not included in the cost comparison (see Section B.3.10).

B.4.2.5. Miscellaneous unit costs and resource use

None that are relevant.

B.4.2.6 Clinical expert validation

None that are relevant.

B.4.2.7 Uncertainties in the inputs and assumptions

None that are relevant.

B.4.3 Base-case results

Annual treatment costs for somatropin, estimated per patient based on a simple cost acquisition model, range from £7,302 - £11,475 and somatrogon has an estimated annual cost of £10,845, see Table 26 for breakdown. Crucially this price point sits within the existing price range of available treatment options, and [redacted]%.

Daily somatropin preparations have different device options which appeal to different patient segments, and each provide variable levels of patient support offerings. Somatrogon will be provided with a comprehensive patient support program including starter kits, ancillary provision, homecare delivery and nursing, a patient helpline, and a patient website.

This additional value offering, as well as the significant reduction in treatment burden, and potential increased utility experienced from reduced frequency of injections[38-40, 66], have not been quantified or included within the analysis. Therefore, given the positive impact these benefits have on both patients, the use of a cost-comparison can be considered an underestimation of the true value of somatrogon to the NHS. This should be taken into consideration when considering the optimum price point of somatrogon within the growth hormone market.

*Table 26: **Base-case results***

Technologies	Estimated Annual Acquisition costs (£)	Resource / Adverse event / Other costs (£)	TOTAL COSTS (£)	Market Share (%)[1]
Somatrogon	**£10,845**	**N/A**	**£10,845**	[redacted] %
Norditropin®	£11,475	N/A	£11,475	[redacted] %
Saizen®	£11,475	N/A	£11,475	[redacted] %
Nutropin AQ®	£10,049	N/A	£10,049	[redacted] %
Humatrope®	£8,911	N/A	£8,911	[redacted] %
Genotropin®	£8,609	N/A	£8,609	[redacted] %
Zomacton®	£8,450	N/A	£8,450	[redacted] %
Omnitrope®	£7,302	N/A	£7,302	[redacted] %

Annual treatment costs (12 months) based per patient

B.4.4 Sensitivity and scenario analyses

A sensitivity analysis was conducted as part of the Assessment Group report in TA188, considering a number of key variables and the impact on the ICER, based on lower and upper bounds. These included:

- Dosage, mg/kg
- Utility gain
- Compliance
- Treatment age, years
- Utility benefit spread
- Cost of rGH treatment (per mg)
- Standard mortality rate

The deterministic sensitivity analysis concluded that the results were most sensitive to dose. As per TA188, the dose varied from 0.025mg/kg/day to 0.039mg/kg/day with impact on the ICER of £23,482 to £39,484. An addendum was submitted by the Assessment Group with a revised cost per mg/kg, impacting the upper bound of the ICER to £35,917 for a dose of 0.039mg/kg/day.[11, 13] In the company analysis a somatropin dose of 0.034 mg/kg/day (equivalent to 0.24 mg/kg/week) was used. This

was the dose investigated in the pivotal study for somatrogon where non-inferiority to 0.66 mg/kg/week somatrogon was demonstrated (see section B.3.3.3). Given that the somatropin dose of 0.034 mg/kg/day was deemed cost-effective as part of TA188, and that there is not any evidence available comparing the clinical effectiveness of other somatropin doses to somatrogon, neither a sensitivity nor scenario analysis was determined necessary.

The variables which impact on the annual treatment costs, as outlined above, will generally be consistent across all available daily treatment options and will result in proportional changes for all available treatment options, therefore having little, or no, impact on the comparative treatment costs. The exception to these are:

1) acquisition costs
2) dose, and
3) utility gain

Given that 1) somatrogon has demonstrated to sit within the current price range of the seven available somatropin preparations, 2) the dose used to estimate annual treatment costs for somatropin has previously been deemed cost-effective, and 3) that a reduced number of injections could lead to higher utility (see section B.4.2.1) favorably impacting the cost-effectiveness, coupled with the relative consistency of all other variables across each product, a sensitivity analysis, nor scenario analysis, was deemed required.

B.4.5 Subgroup analysis

None that are relevant.

B.4.6 Interpretation and conclusions of economic evidence

Somatrogon is the first once-weekly, LAGH commercially available in the UK, with MHRA marketing authorisation received in March 2022. This represents the first new treatment option, with proven reduced life interference and treatment burden, for children suffering from growth hormone deficiency since the 1980’s demonstrating the

need to ensure children can access this treatment option as soon as possible through the NHS services.

In summary, somatrogon clearly demonstrates adherence to three crucial criteria that should allow for a rapid / pragmatic review with a simple cost acquisition model:

1) Somatrogon has similar efficacy and safety to daily somatropin, demonstrated through direct head-to-head evidence in the phase 3 clinical study.

2) Somatrogon will displace daily somatropin and is expected to have no difference in terms of costs (resource, administration, or adverse event costs). It is not expected to have any budget impact, please see the Budget Impact Analysis (BIA) submission.

3) There are no sub-group populations relevant for somatrogon.

In addition, somatrogon has demonstrated improved treatment convenience and potential increase in quality of life (QoL) for patients and carers through increased utility. Demonstrating that there is additional value available to the NHSE not captured as part of this analysis, with the results depicting that somatrogon has a lower annual treatment cost to several comparators routinely available on the NHS, [redacted].[1]

The choice of product should remain being made on an individual basis, after informed consent discussion between the treating physician and the patient and/or their carer about the advantages and disadvantages of the products available.

Based on the evidence laid out in this submission, there is a very low decision risk given the simplicity and limited uncertainty, and Pfizer would like to request that priority 2 is applied, to implement a shorter, less resource intensive technology appraisal process.

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B.6 Appendices

Appendices C-I including the references (full list below) can be found with the file name:

ID5086 Somatrogon_Appendices_[AiC]

Appendix C: Summary of product characteristics (SmPC)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Cost and healthcare resource identification, measurement and valuation

Appendix H: Checklist of confidential information

Appendix I: Identification, selection, and synthesis of health-related quality-of-life studies

References for Appendices

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Somatrogon for treating growth disturbance in children and young people aged 3 and over [ID5086]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Child Growth Foundation
3. Job title or position	Membership & Parent Support Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	We support parents, families and children who are affected by a growth problem. We are a charity, so totally self-funding and rely on donations. Approx 1500 members
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	**Talking to patients and carers**

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Frustration receiving the correct support from healthcare professionals. Often difficulties with diagnosis. Often being told that everything is fine and he/she will catch up. Some patients struggle with daily injections, so adherence can be affected. Often it can be a lifelong treatment.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**Many patients/carers are happy with the current treatment, although some do struggle with daily injections. This can result is psychological problems for the child as well as the carer.**
8. Is there an unmet need for patients with this condition?	Psychological support. Patient choice. If the patient is given their choice of treatment they are more likely to adhere.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	**One injection per week instead of daily injections can benefit children who struggle with daily injections.**

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Worry that is will not work and not as effective as daily injections. Concerns that the injection will be much more painful than the daily injection. Concerns that there may be more side effects.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who are needle phobic will find a weekly injection easier than a daily one Parents who struggle with a young child who does not want daily injections and does not understand why. Some children really do not like the daily injection, and it is really difficult for the carer to inject their child every day.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Not that I am aware of.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Once weekly treatment is more convenient than daily treatment. • There is currently no treatment other than daily injections. • For a needle phobic child, once a week, would likely be a much better option for treatment. • Psychologically, the child/carer will find treatment much easier. • If the child struggles with daily treatment, adherence may improve because it is just one injection per week, as opposed to seven injections.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - **YES**

For more information about how we process your personal data please see our privacy notice.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Somatrogon for treating growth disturbance in children and young people aged 3 and over [ID5086]

NICE medicines optimisation team briefing

November 2022

Advice

A full single technology appraisal of somatrogon for growth disturbance from growth hormone deficiency (GHD) in children and young people is unlikely to add value. A fast-track appraisal with a cost comparison comparing somatrogon to somatropin is appropriate.

Rationale

Once weekly somatrogon shows similar clinical efficacy and safety to once daily somatropin for growth disturbance from GHD in children and young people. This is based on evidence from 1 phase 2 and 3 phase 3 open label, head to head randomised controlled trials (RCTs). Somatrogon has the same mechanism of action as somatropin, is used in the same patient population, and at the same point in the treatment pathway. Somatropin has already been recommended for treating growth failure in children in TA188 (May 2010).

However, differences between somatrogon and somatropin in acquisition cost, funding route, service delivery and factors that affect patient choice and adherence to treatment need to be considered. It is unclear from the available evidence if weekly somatrogon is associated with a clinically meaningfully reduction in treatment burden compared with daily somatropin. Tolerability related to mild to moderate injection site reactions was worse with somatrogon.

Technology overview

Somatrogon (Ngenla) is a solution for injection containing 24 mg or 60 mg of somatrogon in a single-patient, multiple-use disposable prefilled pen for subcutaneous (SC) injection (summary of product characteristics [SPC] for somatrogon).

Context

Short stature associated with GHD is an uncommon condition of childhood. Current standard care is daily SC injections of somatropin (recombinant human growth hormone [rhGH]). Adherence to daily SC rhGH is positively correlated with growth response and final height. Non-adherence (in part due to the treatment burden of daily injections) has been identified as a reason for less favourable treatment outcomes (European public assessment report [EPAR] on somatrogon [Ngenla]). NICE assessed somatropin for treating growth failure in children in a technology appraisal in 2010 (TA188).

Table 1: Characteristics of somatrogon compared with somatropin

	Somatrogon	Somatropin
Indication	Treatment of children and adolescents from 3 years with growth disturbance due to insufficient secretion of growth hormone.	7 preparations of somatropin are available in the UK. All have a very similar indication to somatrogon for growth disturbance or growth failure due to inadequate or insufficient secretion of growth hormone (GHD) in children and young people. Somatropin preparations also have additional indications to somatrogon.
Dosage and route of administration	0.66 mg/kg given once weekly by SC injection. Adjusted as needed based on growth velocity, adverse reactions, body weight and serum insulin-like growth factor 1 (IGF-1) concentrations.	For GHD: Child: 23 to 39 micrograms/kg daily or 0.7 to 1 mg/m^2 daily by SC or intramuscular injection (BNFC, October 2022)

Mechanism of action	Modified version of recombinant human growth hormone with a half-life of 28 hours allowing once weekly dosing. Has receptor binding properties and a mechanism of action analogous to human growth hormone (EPAR on somatrogon [Ngenla]).	Recombinant human growth hormone with a half-life of 2 to 3 hours; given once daily. Stimulates the release of IGF-1, which promotes changes in growth and metabolism in children with inadequate endogenous growth hormone.
Resource impact	Subcutaneous treatment: less frequent administration High-cost drug	Subcutaneous treatment: more frequent administration

Current practice

There is no NHS England commissioning pathway for growth disturbance from GHD in children and young people. Somatropin is commissioned by integrated care boards for this indication, following NICE guidance. After initiation by specialists in secondary care, it is generally supplied via homecare or prescribed under shared-care arrangements in primary care.

A clinical pathway for diagnosing and managing growth disturbance from GHD in children and young people is set out by the British Society for Paediatric Endocrinology and Diabetes (BSPED 2012). Current treatment is with somatropin, and somatrogon will likely fit into this pathway; with diagnosis, treatment initiation and monitoring taking place in the same way. However, acquisition cost, funding route, care setting, support services and patient preference for a particular device based on individual factors (including burden of daily dosing) will likely determine place in therapy.

From April 2022, somatropin is included in the national tariff payment system as baseline activity, and costs for this medicine are no longer recharged to commissioners via a high-cost drugs route, which was the previous arrangement. Somatrogon, however, is on the high-cost drugs list. Differences in funding routes for these 2 medicines that fit within the

same clinical pathway could have unintended consequences and lead to cost pressures.

Patient preference plays a large part in growth hormone treatment, and patients and their families or carers are offered a choice of devices in line with TA188. This states, 'The choice of product should be made on an individual basis after informed discussion between the responsible clinician and the patient and/or their carer about the advantages and disadvantages of the products available, taking into consideration therapeutic need and the likelihood of adherence to treatment. If, after that discussion, more than one product is suitable, the least costly product should be chosen.'

Factors for decision making

Effectiveness

One phase 2 (n=54) and 2 phase 3 (n=228 and n=44) open-label RCTs have reported on the effectiveness and safety of weekly somatrogon compared to daily somatropin for GHD. The population was similar in each study: prepubertal treatment naïve children aged 3 years or older (but not over 10 years for girls or 11 years for boys).

The phase 2 dose comparison study (Zelinska et al 2017) found that only the highest dose (0.66 mg/kg/week) had comparable efficacy to daily somatropin (0.24 mg/kg/week) at 12 months follow-up. This dose was used in both the main (Deal et al 2022), and subsequent (Horikawa et al 2022), phase 3 trials compared with daily somatropin.

In both phase 3 RCTs, somatrogon was non-inferior (noninferiority margin ≥-1.8 cm/year) to somatropin for the primary endpoint of annualised height velocity at 12 months (n=222: 10.1 cm/year versus 9.78 cm/year respectively, mean difference 0.33 cm [95% CI -0.24 to 0.89]; n=44: 9.65 cm/year versus 7.87 cm/year respectively, mean difference 1.79 cm [95% CI 0.97 to 2.61]). For the secondary outcomes

of these studies (height velocity at 6 months, bone maturity, and IGF-1 findings), weekly somatrogon was not inferior to daily somatropin. In pre-planned subgroup analyses (for example age group, gender, peak GH levels and study region), findings were generally consistent with the main results.

Safety

Contraindications for somatrogon and somatropin are similar. Both are contraindicated if there is evidence of tumour activity, and they should not be used for growth promotion in children with closed epiphyses.

Very common adverse effects with somatrogon (≥1:10) are injection site reactions (25.1%), headache (10.7%) and pyrexia (10.2%) (SPC for somatrogon).

In the main phase 3 RCT (Deal et al 2022), the overall proportion of participants with adverse events was similar between somatrogon (87.2%) and somatropin (84.3%). Both treatment groups had a similarly low proportion of serious adverse events (somatrogon 2.8% and somatropin 1.7%), and none were considered treatment related. The comparative rates of adverse events were similar between somatrogon and somatropin, except for injection site reactions which were higher for somatrogon (injection site pain [39.4% vs 25.2%], injection site erythema [8.3% vs 0%] and injection site pruritus [5.5% vs 0%]). Switching from somatropin to somatrogon in the phase 3 open-label extension was also associated with an increased report of painful injection site reactions (EPAR on somatrogon [Ngenla]).

Antidrug antibodies were more common in those taking somatrogon (77.1%) than somatropin (15.6%) in the main phase 3 RCT. However, post hoc analysis comparing antibody status to clinical outcome found no evidence of an effect on efficacy or adverse events.

Participants reporting an IGF-1 level >2 standard deviations [SDs] at any time were higher in the somatrogon group, and this increased over time. Many of the high IGF-1 samples were taken at 2 to 3 days after the prior dose (rather than at 4 days as recommended) and so were measuring peak rather than mean IGF-1 levels. However, 12 participants in the somatrogon group required a dose reduction (Deal et al 2022).

Patient centred factors

Optimal outcomes for GHD are likely related to treatment adherence, and an intervention that reduces the treatment burden of daily to weekly injections could improve clinical outcomes and increase quality of life. However, in the main phase 3 RCT, adherence rates for weekly somatrogon and daily somatropin were high and similar in both groups (99.4% adherence for somatrogon and 99.7% for somatropin; although this partially reflects being in a clinical trial).

Treatment burden was also assessed in an unpublished, open-label, phase 3, multicentre cross-over RCT (NCT03831880, Pfizer Inc. 2020; see EPAR on somatrogon [Ngenla]). This included 87 children aged 3 years to less than 18 years with GHD who were currently receiving dose-stable daily somatropin for at least 3 months. Participants received either 12 weeks of daily somatropin followed by 12 weeks of weekly somatrogon, or weekly somatrogon followed by daily somatropin for the same period. The primary endpoint of treatment burden (assessed as the difference in mean overall life interference total scores and completed by the participant/caregiver) was lower with somatrogon than somatropin (mean difference -15.49 (95% CI: -19.71 to -11.27 on a 0 to 100 scale; $p<0.0001$). Subgroup analyses of these scores for age group (younger and older), caregiver administration, and self-administration were consistent with the main results.

In addition to treatment burden, other factors affect patient choice and adherence to treatment. Somatrogon is only available as a pre-filled pen,

which may not be suitable or preferable for all children. There are numerous somatropin preparations available as pre-filled pens, injection cartridges and vials; additionally with shorter, thinner, and shielded needle technologies to help with fear of needles. The use of any device requires adequate training of patients and families to ensure it can be used easily and correctly, including the ability to titrate the dose where needed.

Other manufacturers have developed technologies to monitor adherence with products such as the easypod® system, and many offer support services in collaboration with homecare teams.

The marketing authorisation for somatrogon is limited to children and young people from 3 years with GHD. Somatropin has broader indications, including other conditions in children and use in adults. Somatrogon is not an option in these circumstances, which may be an issue when transitioning from children and young people's services to adult services.

Health inequalities

GHD is more common in males (Shepherd et al 2019), as seen in the main phase 3 RCT (Deal et al 2022) where 72% of participants were male. Suboptimal adherence has been linked to Black family background in a US study of children with GHD (Loftus et al 2022). Treatment adherence in children with GHD has also been linked to issues such as poverty, low educational attainment, and inadequate social support (Haverkamp and Gasteyger 2011).

Limitations of the evidence

All the studies (except NCT03831880) were limited to treatment naïve, prepubertal children (not over 10 years for girls or 11 years for boys) at baseline. Evidence of the effectiveness of somatrogon in older children, who may be diagnosed due to delayed puberty, is not reported.

There is a lack of longer-term safety data for somatrogon. Both the phase 2 and main phase 3 (to 24 months from enrolment) study had open label extension periods to assess longer term efficacy and safety, and published results are awaited. For the secondary outcome of IGF-1 concentration, it is not currently known what represents a safe and optimal level; or the implications of IGF-1 level >2 SDs on acromegaly and glucose intolerance.

The Horikawa et al (2022) study was conducted in an ethnic Japanese population and used a lower locally approved dose of daily somatropin compared with the other studies. Additionally, no method of allocation concealment, randomisation or sample size calculation is reported. There were reported differences in some baseline characteristics (mean age, age groups) between the intervention and control groups, and missing efficacy data was not accounted for.

Overall Life Interference in the unpublished study (NCT03831880) was assessed using the Dyad Clinical Outcomes Assessment Questionnaire, which had questions about life interference (daily activities, social activities, leisure, night away from home and travel), changes to life routine and bother of GH injections. Raw scores from this were converted to a 0 to 100 scale, with a lower score meaning less life interference (better outcome). However, the pre-test construction and validity of the questionnaire, and clinical significance of the statistically significant mean difference reported are unclear.

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External Assessment Group Report

Cost comparison evaluation process

Somatrogon for treating growth disturbance in children and young people aged 3 and over

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
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Declared competing interests of the authors

The EAG have no competing interests.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Mark Rodgers wrote Section 4 (evaluation of clinical evidence) of the report.

Peter Murphy wrote Sections 5 and 6 (evaluation of cost-effectiveness) of the report.

Lucy Beresford wrote Sections 2 and 3 (background and decision problem) of the report.

Melissa Harden reviewed the systematic review searches and wrote sections of the report pertaining to the searches.

Mark Simmonds oversaw the review of clinical evidence, and the report as a whole.

Claire Rothery oversaw the review of cost-effectiveness evidence, and the report as a whole.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

Copyright statement

Table of Contents

Table of Tables

Table of Figures

List of abbreviations

AE	Adverse Event	MHRA	Medicines and Healthcare products Regulatory Agency
AESI	Adverse Event of Special Interest	MTA	Multiple Technology Appraisal
BNF	British National Formulary	NHS	National Health Service
CI	Confidence Interval	NICE	The National Institute for Health and Care Excellence
CMU	Commercial Medicines Unit	OLE	Open-label Extension
CS	Company Submission	PAS	Patient Access Schemes
DCOA	Dyad Clinical Outcome Assessment	pGHD	Paediatric Growth Hormone Deficiency
EAG	External Assessment Group	PD	Pharmacodynamics
FAS	Full Analysis Subset	PK	Pharmacokinetics
GH	Growth Hormone	QoL	Quality of Life
GH-1	Growth Hormone-1 Gene	QoLISSY	Quality of Life in Short Stature Youth
GHD	Growth Hormone Deficiency	RCT	Randomised Controlled Trial
hGH	Human Growth Hormone	rhGH	Recombinant Human Growth Hormone
HRQoL	Health-related Quality of Life	RR	Relative Risk
HTA	Health Technology Assessment	SAE	Serious Adverse Event
HV	Height Velocity	SD	Standard Deviation
ICER	Incremental Cost Effectiveness Ratio	SDS	Standard Deviation Score
IGF	Insulin-like Growth Factor	SHOX	Short Stature Homeobox-containing Gene
ITT	Intention to Treat	SLR	Systematic Literature Review
KIGS	Pfizer International Growth Database	SmPC	Summary of Product Characteristics
LAGH	Long-acting Growth Hormone	TA	Technology Assessment
LS	Least Square	UK	United Kingdom
LT-OLE	Long Term Open Label Extension		

EXTERNAL ASSESSMENT REPORT: COST COMPARISON EVALUATION PROCESS

1 EXECUTIVE SUMMARY

1.1 Summary of the clinical evidence

The clinical evidence in the CS was focussed on a non-inferiority trial (CP-4-006; 224 patients) comparing somatrogon to Genotropin®. The EAG also considered another similar trial (Horikawa et al 2022, 44 patients) that was identified in the company review, but not discussed in the CS. The trials were both at low risk of bias. The trials showed that somatrogon is not inferior to Genotropin for key outcomes related to growth, including height velocity and height standard deviation score. The evidence suggested that somatrogon may be slightly superior in effect, but it is reasonable to assume equivalence between the two treatments.

Adverse event data from the trials suggested a similar adverse event profile for somatrogon and Genotropin®, although numbers of specific adverse events were generally too small to draw firm conclusions. Injection pain and injection-related adverse events were more common with somatrogon than Genotropin®. Patients using somatrogon were more likely to develop anti-drug antibodies (immunogenicity). This did not appear to impact on efficacy or safety during the trial, but its long-term implications are unclear.

Other trial data showed that somatrogon and Genotropin® had similar quality of life outcomes. In long-term follow-up patients using somatrogon continued to show sustained growth. There was evidence that patients and parents preferred weekly somatrogon over daily somatropin, with somatrogon reducing interference in daily life.

1.2 Summary of cost-effectiveness evidence

The costs considered in the company's cost comparison analysis comprised of drug acquisition costs only, which were estimated per patient per year. The annual drug acquisition costs were based solely on the unit costs (list prices) and the average daily or weekly dose for a child with an average weight of 40kg. A dose of 0.034mg/kg/day was assumed to align with the Genotropin® dose used in the CP-4-006 trial. The resulting mean annual costs per patient for somatrogon (£10,845) were within the range of annual costs of the seven preparations of daily somatropin (Genotropin®; Humatrope®; Norditropin®; NutropinAq®; Omnitrope®; Saizen®; and Zomacton®) for rhGH, which ranged from £7,302 to £11,475.

1.3 EAG critique of cost-comparison approach to this technology assessment

The EAG considers that a cost-comparison approach is an appropriate method to assess this technology. The evidence presented suggests that somatrogon and Genotropin® are broadly equivalent in effect, with patients experiencing similar health benefits, with comparable rates of growth. NICE requires that the technologies assessed by the cost comparison approach show similar or greater health benefits; the EAG thinks that those conditions have been met by this technology.

The EAG notes that somatrogon has been compared only to Genotropin®, but seven preparations of somatropin (rhGH) are available in the UK. Although there appears to be no evidence directly comparing different somatropin preparations, the EAG considers it reasonable (based on existing NICE guidance) to assume that they are equivalent in efficacy, and so somatrogon is broadly equivalent in efficacy to them all.

The approval of somatrogon is not expected to change the clinical pathway for treating paediatric GHD, as the company consider that somatrogon will displace the currently available daily somatropin.

The EAG notes that the potential for more frequently reported pain from weekly somatrogon injections should be balanced against the disadvantages of daily injections for somatropin. There is currently no evidence that increased injection pain adversely effects quality of life.

Somatrogon appears to lead to greater immunogenicity in patients than somatropin. The consequences of this are unclear but may need to be considered when evaluating long-term use of somatrogon.

The EAG considers the company's cost-comparison analysis to be appropriate under the assumption of near equivalence in efficacy of somatrogon and somatropin, with no expected differences in (i) healthcare resource use and associated costs, other than the drug acquisition costs; (ii) adverse event profiles of the drugs; (iii) treatment duration (or long-term discontinuation rates); (iv) drug wastage; or (v) treatment adherence.

The EAG notes that the modelled dose used to cost the comparators in the company base case was 0.034 mg/kg/day. Although this dose aligns with the CP-4-006 trial, the BNF lists the recommended dose range for children with deficiency of growth hormone as 0.023 – 0.039 mg/kg/day for all licensed preparations of daily somatropin.[1] To demonstrate the impact of the assumption of the comparator dose on the results of the cost-comparison analysis, the EAG presents sensitivity analysis in which the dose is varied to align with the recommended dose range listed in the BNF, i.e., 0.023 – 0.039 mg/kg/day. The EAG considers an average dose of 0.025 mg/kg/day to be more appropriate for use in the cost-comparison analysis as this dose is more likely to represent an average dose over time after titration.

2 BACKGROUND

Growth hormone deficiency (GHD) in children occurs when there is a disruption to growth hormone secretion, owing to abnormal function of the hypothalamus and pituitary gland. For most children with GHD, their disease is idiopathic (where there is no known cause of disease), but it can also be acquired during childhood (due to events such as trauma, or brain tumour), or is congenital, and has been present from birth. GHD in children is estimated to affect between 1 in 3500-4000 children.[2]

While the management of GHD varies based on the age of the child and condition at diagnosis, daily subcutaneous growth hormone injections remain the main treatment option for children with the disease. However, non-compliance and poor adherence is a commonly reported problem and can impact long-term treatment response. The company consider that the introduction of somatrogon could improve adherence and quality of life of those affected by GHD.

The company provide a comprehensive summary of GHD, its epidemiology and impact on patients and carers. They also provide evidence of how somatrogon may improve compliance. With regards to the treatment pathway, the company did not detail alternative management strategies without growth hormone, which was included in the final scope.

2.1 Mechanism of Action

Somatropin and somatrogon are recombinant (or synthetic) forms of human growth hormone (GH). Somatropin (which includes seven prepartations: Humatrope®, Zomacton®, Nutropin Aq®, Norditropin®, Genotropin®, Omnitrope® and Saizen®). is administered once daily, usually at night, to mimic the natural fluctuation of GH secretion.[2] Somatrogon is a long-acting rhGH, with modified C-terminal peptides to increase the half-life of the drug, allowing for weekly dosing. rhGHs are also used for children with Turner syndrome, Prader-Willi syndrome, short stature homeobox-containing gene (*SHOX*) deficiency, chronic renal insufficiency, or for children born small for gestational age with subsequent growth failure at 4 years.

The EAG considers that somatrogon has a similar mechanism of action to Genotropin and to somatropin in general. We note that there appears to be no clinical trial evidence demonstrating equivalence of Genotropin and other commercial forms of somatropin; however NICE guidance and clinical opinion received suggests that the different preparations of somatropin can be considered equivalent.

The secretion of GH follows a circadian rhythm and follows the sleep pattern with the peak secretion of hGH occurring at night.[3] Somatropin is often administered nightly, to mimic the natural, diurnal cycle of hGH. Unlike somatropin, somatrogon is given weekly, which does not correlate to the natural

physiology of hGH. There are concerns that this may impact the clinical efficacy of long-acting growth hormones, and could lead to long-term metabolic abnormalities or desensitisation of the growth hormone receptors.[4] However, the EPAR for somatrogon does suggest that laboratory parameters related to glucose metabolism, thyroid function and cortisol levels were generally within their normal limits for the length of the trials.

3 CRITIQUE OF THE DECISION PROBLEM IN THE COMPANY'S SUBMISSION

3.1 Population

In the final scope for this appraisal, the population of interest includes children and adolescents from three years of age with growth disturbance due to insufficient secretion of growth hormone. This is in line with the marketing authorisation for somatrogon.

However, the eligibility criteria for two of the trials differs to the final scope which may impact the generalisability of the evidence. As Table 1 shows, the main trial (CP-4-006), and the Phase 2 dose escalation trail (CP-4-004) limit their population to pre-pubertal children, meaning the maximum age for enrolment is limited to 11 years for girls, and 12 years for boys. This does create issues of generalisability compared to the population who will be able to receive GH treatment based on the marketing authorisation. Clinical input from the NICE pharmacist team suggested that children often present in two peaks for diagnosis, once at around age 4-5 years (when children start school), and later at the onset of puberty. According to the EPAR for somatrogon,[5] children diagnosed younger are likely to have a complete deficiency of GHD, whereas those who present at a later age will have GHD deficiency to a lesser extent. As the trials only include pre-pubertal children with GHD, the efficacy of somatrogon compared to somatropin in population who present later (at puberty) is unknown.

Furthermore, adherence may decrease in teenage years which may be impacted by an increased need for autonomy.[6] As treatment compliance can impact effectiveness, the efficacy seen in pre-pubertal children may not translate to a similar level of efficacy in adolescents. While the company argue that somatrogon will improve adherence as patients are only required to administer the drug once a week; similar patterns in compliance are likely to remain.[7]

Table 1. Eligibility criteria and baseline age for each trial included in this appraisal

Trial	Eligibility Criteria	Age. Mean (SD)/[Range]	
		Somatrogon	**Somatropin**
CP-4-006	Pre-pubertal child aged ≥3 and not above 11 years for girls, or 12 years for boys with either isolated GHD or GH insufficiency as part of multiple pituitary hormone deficiency.	7.8 [3.01-11.96]	7.61 [3.05-11.85]
C0311002	Children aged 3 years old and <18 years with either isolated GHD, or GHD insufficiency	10.7 (3.7)	10.8 (3.4)
CP-4-004	Pre-pubertal child aged ≥3 and not above 10 years for girls or 11 years for boys with either isolated GHD, or GHD insufficiency as part of multiple pituitary hormone deficiency.	6.1 (2.2) (0.66 mg/kg cohort)	5.7 (1.9)
Horikawa et al (2022)	Pre-pubertal child aged ≥3 and not above 10 years for girls or 11 years for boys with either isolated GHD	5.28 (1.84)	6.78 (2.34)

Th evidence presented does not include patients with rarer causes of restricted growth, such as Turner syndrome, Prader-Willi syndrome or short stature homeobox-containing gene (*SHOX*) deficiency. The MHRA marketing authorisation for somatrogon[8] states that somatrogon has not been evaluated in such patients; the EAG therefore considers this to be a reasonable omission.

3.2 Comparator

According to the final scope set by NICE, the comparators of interest are daily rhGH (somatropin), and management without human growth hormone as the relevant comparators.

The market share for Genotropin®, which is the comparator used in the trials in the clinical effectiveness is [redacted] and is the [redacted]. Norditropin® is the [redacted] accounting for [redacted] of the market share.

The company consider that all seven preparations of somatropin are relevant comparators for this appraisal. While the comparators chosen are the same in biological formulation, they differ in their method of administration. Some are available in pre-filled pens, some are injection cartridges and vials. Some include shielded needle technologies to help with the fear of needles.

The EAG consider that overall, the comparators included in the company appraisal are similar to those included in the decision problem and final scope. This is in-line with the decision made by the committee in TA188; where, despite limited and poor-quality evidence, the committee considered that there appeared to be no differences in the clinical effectiveness of the various somatropin products.[9] The main comparator included in the analysis (Genotropin®) is commonly used for GHD in England. As this is the only comparator which provides head-to-head evidence on the clinical effectiveness of somatrogon, there is uncertainty as to whether the different methods of administration that are offered

with the alternative, active comparators may impact adherence and compliance, and therefore efficacy.

The NICE scope states that management strategies without the use of human growth hormone should be considered in this appraisal. The company do not provide direct clinical or narrative evidence for the effectiveness of somatrogon against non-active management of GHD. The EAG accepts that this is reasonable, given that somatrogon is intended as replacement for somatropin, and is not a distinct treatment, and that it is expected that only children with a contraindication to rhGH or who decline treatment will receive non-active management for GHD.

3.3 Outcomes

Some outcomes listed in the scope were not reported, on the grounds that they were not collected in the clinical trials and were not part of the original assessment of somatropin. The EAG considers that the set of outcomes reported in the submission is reasonable.

4 SUMMARY OF THE EAG'S CRITIQUE OF CLINICAL EFFECTIVENESS EVIDENCE SUBMITTED

4.1 EAG queries relating to the company submission

After receiving the CS, the EAG submitted several queries to the NICE pharmacists. Any outstanding queries or uncertainties that could not be resolved are mentioned in the relevant section of this EAG report.

4.2 Systematic literature review

Appendix D of the CS reported a systematic literature review (SLR).

4.2.1 Searches

The EAG noted the following weaknesses in the search strategies reported in Appendix D:

- Retrieval was restricted to English language studies only.
- Although somatrogon and the specific comparators were included in the search strategies, broader terms were missing from the textword searches in the title and abstract of records, in particular: long acting growth hormone (LAGH) and recombinant human growth hormone (RhGH).
- Missing synonyms for the age group: infancy, teen*, pubert* and for GHD: short stature.
- Studies prior to 2009 would not have been identified by the search.
- Limited searching for previous systematic reviews.

The EAG considers that the searches will have identified all trials of somatrogon, but may not have identified all potentially relevant studies of other RhGH preparations.

4.2.2 Study selection

Appendix D.1.3 of the CS reports study eligibility criteria. Briefly, inclusion was restricted to RCTs (Phase II and above) evaluating recombinant human growth hormone, long-acting human growth hormone, or management strategies not involving human growth hormone in children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone (GHD).

Appendix D describes appropriate procedures to minimise the risk of errors and bias in the selection, data extraction and risk of bias assessment of included studies.

4.2.3 Included studies

The SLR identified 20 records relating to 19 studies, though only two of these were included in the full CS (CP-4-004 Phase 2 dose finding study, and CP-4-006 Phase 3 pivotal study[10, 11]). Most of the other identified studies did not evaluate somatrogon. However, the EAG believes that one of the identified RCTs, Horikawa *et al* (2022)[12] meets the decision problem and therefore should have been included in the full CS. See Section 4.3.2.1 for details.

4.3 Clinical effectiveness evidence for somatrogon

Section B.3.1 of the CS describes five studies from the clinical trial program for somatrogon:

- One Phase II dose-finding study (CP-4-004) and its open-label extension study (CP-4-004 OLE)
- One pivotal Phase III randomised controlled trial (RCT; CP-4-006) and its open-label extension study (CP-4-006 LT-OLE)
- One Phase III RCT (C0311002) assessing treatment burden

Sections B.3.2 to B.3.4 of the CS summarise the design and methodology of these five studies.

4.3.1 Dose finding

The CS summarises one small-scale four-armed Phase II dose-finding study (CP-4-004) that compared three doses of somatrogon (0.25, 0.48, and 0.66 mg/kg/week) versus Genotropin® (0.034 mg/kg/week).

The results of this study are reported in tables 17 and 18 of the CS (p.49-50). In terms of annual height velocity (HV) the 95% CIs for somatropin and each somatrogon cohort overlapped, with the highest somatrogon dose group (0.66 mg/kg/week) having the closest mean value to daily Genotropin® (11.4 vs. 12.5 cm/year).

4.3.2 Efficacy of somatrogon relative to somatropin (Genotropin®)

The CS summarises one RCT (CP-4-006) that directly compared somatrogon (0.66 mg/kg/week as a once weekly injection; n=109) to somatropin (Genotropin® 0.24 mg/kg/week as a once-daily injection n=115) for 12 months.[10, 11] From here on for simplicity, this will be described as the "pivotal RCT". Results of the pivotal RCT are presented in section B.3.6.1 of the CS.

4.3.2.1 Additional Phase 3 RCT evidence

A second RCT comparing somatrogon to Genotropin® (Horikawa et al, 2022[12]) was identified in the company's SLR but not presented in their main submission. The reasons for excluding this trial were

not reported. However, the EAG believes the trial is relevant to the decision problem, so this report will summarise the characteristics and results of Horikawa et al alongside the pivotal RCT.

Table 2 summarises the characteristics of the pivotal RCT and Horikawa et al and Table 3 summarises the participant characteristics that are available for both studies.

Other than sample size, the key difference between Horikawa and the pivotal RCT relates to the dose of the two study agents. The dose of Genotropin® was 0.034 mg/kg body weight per day in the pivotal RCT and 0.025 mg/kg body weight per day in Horikawa. Both doses fall within the range recommended in the Summary of Product Characteristics (0.025 - 0.035 mg/kg) for Genotropin®. See Section 5.2.2 for a detailed discussion of somatropin dosing in the NHS.

The dose of somatrogon in the pivotal trial was 0.66 mg/kg/week once weekly for 12 months. In Horikawa et al, participants received somatrogon in three escalating doses (0.25, 0.48, and 0.66 mg/kg/week; 2 weeks at each dose) for 6 weeks. After this period, subjects continued to receive somatrogon once weekly at a dose of 0.66 mg/kg/week for 46 weeks. Children therefore received 0.66 mg/kg/week for 52 weeks in the pivotal RCT and 48 weeks in Horikawa et al.

There were differences between the studies in terms of mean age (7.72 vs 6.03 years), sex (71.9% vs 47.7% male), race (100% Asian in Horikawa), and peak GH level (32% >7ng/mL in pivotal RCT).

Both trials used a -1.8cm/year non-inferiority margin for the primary outcome of annual height velocity (HV).

4.3.2.2 Risk of bias in somatrogon vs Genotropin® RCTs

Table 4 shows the company's risk of bias assessment for the pivotal and Horikawa RCTs (taken from Appendix D of the CS) alongside the EAG's assessment of the same studies. It appears that the company's assessment of Horikawa et al is based solely on the peer-reviewed journal article[12] whereas the EAG's assessment also incorporated information from the study protocol and statistical analysis plan.[13, 14]

The primary source of potential bias in both trials is the absence of blinding. However, it is unclear whether this would systematically bias outcomes in favour of either treatment arm, and the overall risk of bias in both trials appears to be low.

Table 2: Pivotal (CP-4-006) and Horikawa et al RCT

Study	**A Phase 3, open-label, 12-month efficacy and safety study of weekly somatrogon compared to daily Genotropin® therapy in pre-pubertal children with GHD[10, 11]**	**Horikawa et al. Efficacy and Safety of Once-Weekly Somatrogon Compared with Once-Daily Somatropin (Genotropin®) in Japanese Children with Pediatric Growth Hormone Deficiency: Results from a Randomized Phase 3 Study[12]**
Clinicaltrials.gov identifier:	NCT02968004	NCT03874013
Study design	Phase 3, open label, randomised, active controlled, multi-centre, parallel group, non-inferiority trial, followed by a single arm, long-term open-label extension (LT-OTE) study*	Phase 3, open-label, randomized, active-controlled, parallel-group study
Population	Pre-pubertal child aged ≥ 3 and not above 11 years for girls or 12 years for boys with either isolated GHD, or GH insufficiency as part of multiple pituitary hormone deficiency After completion of 12 months treatment in the main study and continuing to meet the LT-OLE inclusion/exclusion criteria, patients were eligible to rollover into the LT-OLE treatment period with somatrogon.	Japanese prepubertal children (boys: 3 to <11 years; girls: 3 to <10 years) with a confirmed diagnosis of GHD. Subjects who completed the 12-month main study were eligible to participate in a single-arm, long-term, open-label extension involving once-weekly administration of somatrogon.
Intervention(s)	Somatrogon 0.66 mg/kg/week once weekly for 12 months (n=109) Open Label Extension (OLE): Patients in the somatrogon group continued their original treatment.	Subjects in the somatrogon group received once-weekly SC injections of somatrogon in 3 escalating doses (0.25, 0.48, and 0.66 mg/kg/week; 2 weeks at each dose) for 6 weeks. After this period, subjects continued to receive somatrogon once weekly at a dose of 0.66 mg/kg/week for 46 weeks (n=22)
Comparator(s)	Genotropin® (somatropin) 0.034 mg/kg/day once daily (n=115) OLE: All patients receiving Genotropin® (somatropin) were switched to receive somatrogon 0.66 mg/kg/week once weekly	Once-daily SC injections of Genotropin at 0.025 mg/kg/day or 0.175 mg/kg/week, which is the approved Genotropin dose in Japan
Reported outcomes specified in the decision problem	Annual height velocity Height standard deviation score-height relative to the distribution of height in children of the same chronological age Body composition, and biochemical and metabolic markers Change in bone maturation Adverse effects of treatment Health-related quality of life	Annual height velocity Change in height standard deviation score compared to baseline after 12 months Biochemical markers (biochemical markers (IGF-1 and insulin-like growth factor-binding protein 3 [IGFBP-3]) Change in bone age/maturation Adverse effects of treatment
All other reported outcomes	Not Applicable	Pharmacokinetic (PK) and pharmacodynamic (PD) profiles of 3 different doses of once-weekly somatrogon.

Table 3: Baseline characteristics of pivotal (CP-4-006) and Horikawa et al RCTs

	Pivotal RCT			**Horikawa et al 2022**		
	Somatrogon (n = 109)	**Genotropin (n = 115)**	**Total (N = 224)**	**Somatrogon (n = 22)**	**Genotropin (n = 22)**	**Total (N = 44)**
Mean age, years	7.83 (range 3.01-11.96)	7.61 (range 3.05-11.85)	7.72 (range 3.01-11.96)	5.28 (SD 1.84)	6.78 (SD 2.34)	6.03 (SD 2.21)
Sex, *n* (%)						
Male	82 (75.2)	79 (68.7)	161 (71.9)	9 (40.9)	12 (54.5)	21 (47.7)
Female	27 (24.8)	36 (31.3)	63 (28.1)	13 (59.1)	10 (45.5)	23 (52.3)
Race, *n* (%)						
White	81 (74.3)	86 (74.8)	167 (74.6)	0	0	0
Black or African American	0	2 (1.7)	2 (0.9)	0	0	0
Asian	24 (22.0)	21 (18.3)	45 (20.1)	22 (100)	22 (100)	44 (100)
American Indian or Alaska Native	1 (0.9)	0	1 (0.4)	0	0	0
Native Hawaiian or Other Pacific Islander	0	1 (0.9)	1 (0.4)	0	0	0
Other	3 (2.8)	5 (4.3)	8 (3.6)	0	0	0
Peak GH level group, *n* (%)						
Low[a]	22 (20.18)	21 (18.26)	43 (19.20)	1 (4.5)	1 (4.5)	2 (4.5)
High[b]	53 (48.62)	56 (48.70)	109 (48.66)	21 (95.5)	21 (95.5)	42 (95.5)
Highest[c]	34 (31.19)	38 (33.04)	72 (32.14)			

[a] ≤3 ng/mL
[b] >3 ng/mL to ≤7 ng/mL (pivotal RCT) or >3 ng/mL to ≤6 ng/mL (Horikawa et al)
[c] >7 ng/mL (pivotal trial)

Table 4 Company and EAG risk of bias assessment of pivotal (CP-4-006) and Horikawa et al 2022 RCTs

Study Name	ROB assessor	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the onset of the study in terms of prognostic factors, for example, severity of the disease?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
CP-4-006 (NCT02968004)	Company	Yes, Interactive Web Response Technology system	Yes, Interactive Web Response Technology system	Yes	No, open-label	No	No	Yes - full analysis set included all randomised subjects who received at least 1 dose of the study drug, and this constituted the primary efficacy analysis set
	EAG	Yes, Interactive Web Response Technology system	Yes, Interactive Web Response Technology system	Yes	Unclear, open-label "…certain identified roles within the Sponsor and Pfizer's organization remained blinded to the treatment assignments". Further details were inaccessible.	No	No	Yes - full analysis set included all randomised subjects who received at least 1 dose of the study drug, and this constituted the primary efficacy analysis set
Horikawa 2022 (NCT0387401)	Company	Unclear	Unclear	Yes	Partly, single-blind (outcomes assessor)	No	No	Partly, safety data reported for all randomised participants. Efficacy data only analysed for participants completing treatment.
	EAG	Yes, Interactive Web Response Technology system	Yes, Interactive Web Response Technology system	Unclear, Baseline difference in mean age may not be prognostic	No for height measures. Outcome assessor blinded for bone age	No	Unclear – some biochemical endpoints in the study protocol are redacted as commercially confident information	Partly, safety data reported for all randomised participants. Efficacy data only analysed for participants completing treatment (1/22 discontinuation from Genotropin arm).

4.3.2.3 Efficacy results of somatrogon vs Genotropin® RCTs

Table 5 summarises the key efficacy outcomes from the two RCTs and Figure 1 provides forest plots for meta-analyses of the height-related outcomes measures (height velocity [HV] and mean difference in height standard deviation score [SDS] from baseline at 6 and 12 months).

The pivotal RCT showed no statistically significant differences between weekly somatrogon and daily Genotropin®, with similar improvements in HV and change in SDS for both arms. The smaller Horikawa et al study[12] showed statistically significantly larger gains in HV and SDS for weekly somatrogon than daily Genotropin®.

Random effects meta-analyses of these outcomes favoured somatrogon, due to the larger treatment effect observed in the Horikawa trial, but results were not statistically significant, so assuming equivalence remains reasonable.

In all HV analyses (from individual trials and fixed and random effects meta-analyses), the lower bound of the 95% confidence interval (CI) was greater than the company's stated *a priori* noninferiority margin of -1.8 cm/year. Based on the available data, somatrogon is very unlikely to be inferior to Genotropin® in terms of growth outcomes.

Table 5: Efficacy outcomes for pivotal (CP-4-006) and Horikawa et al RCTs

Outcome	**Pivotal RCT**	**Horikawa et al 2022**
Height velocity (HV) at month 12 LS mean cm/year (95% CI)	Somatrogon: 10.10 (9.58, 10.63) Genotropin: 9.78 (9.29, 10.26)	Somatrogon: 9.65 Genotropin: 7.87
Difference in HV at month 12 Mean cm/year (95% CI)	0.33 (-0.24, 0.89)	1.79 (0.97, 2.61)
HV at month 6 LS mean cm/year (95% CI)	Somatrogon: 10.59 (9.96, 11.22) Genotropin: 10.04 (9.47 to 10.62)	Somatrogon: 10.35 Genotropin: 8.47
Difference in HV at month 6 Mean cm/year (95% CI)	0.55 (−0.13, 1.23)	1.88 (0.74, 3.03)
Mean difference in height SDS from baseline to 12 months	0.05 (−0.06, 0.16)	0.42 (0.23, 0.61)
Mean difference in height SDS from baseline to 6 months	0.06 (−0.01, 0.13)	0.26 (0.12, 0.41)
Mean (SD) change bone maturation at 12 months	Somatrogon: 0.05 (0.09) Genotropin: 0.06 (0.10)	Somatrogon: 0.052 (0.065) Genotropin: 0.035 (0.062)

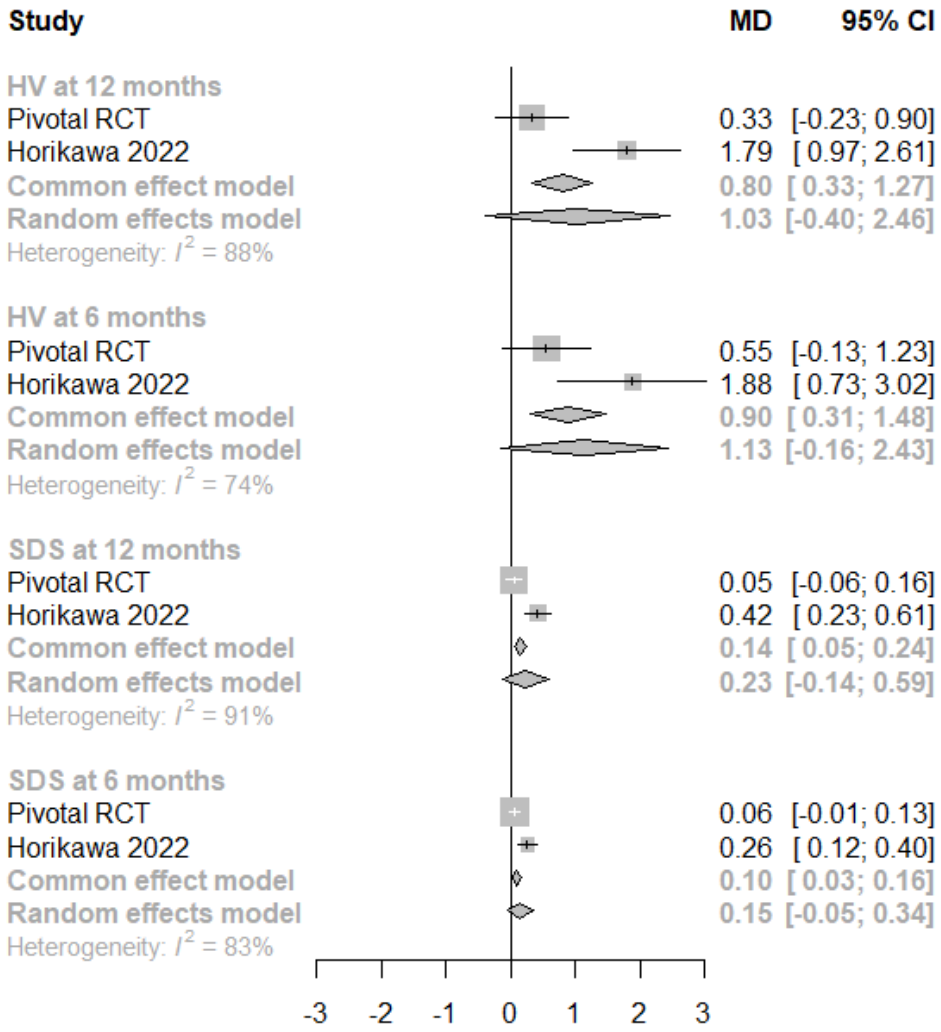


Figure 1 Meta-analysis of growth outcomes for pivotal and Horikawa et al RCTs

4.3.2.4 Subgroup analyses

Appendix E of the CS presents a forest plot of subgroups from the pivotal trial (age group, gender, peak GH levels at baseline and geographical region) for HV at 12 months. Results were generally consistent with the overall HV results, with overlapping confidence intervals across most subgroups.

Horikawa et al did not report the results of any subgroup analyses.[12]

4.3.2.5 Biochemical endpoint - IGF-1 SDS

Figure 5 of the CS illustrates serum insulin-like growth factor 1 standard deviation scores (IGF-1 SDS) for the pivotal RCT. The SmPC for somatrogon recommends monitoring of IGF-1, with necessary dose adjustments targeted to achieve average IGF-1 standard deviation score (SDS) levels

in the normal range, i.e. between -2 and +2 (preferably close to 0 SDS).[8, 15] Negative baseline mean serum IGF-1 values for both somatrogon and Genotropin® transitioned to being within the normal range for all follow-up visits during the 12-month treatment period.

Figure 3 of Horikawa et al[12] showed a similar improvement from negative baseline scores in both treatment arms, though mean IGF-1 SDS values in the Genotropin® group remained below zero (range −0.59 to −0.25) at all post-baseline visits and mean SDS values in the somatrogon group exceeded 1.[12]

These data suggest that IGF-1 SDS levels remain relatively stable and within the targeted range over 12 months of treatment for both somatrogon and Genotropin®.

4.3.2.6 Quality of life

Table 14 (p.42) of the CS summarises quality of life data collected in the pivotal trial using the validated Quality of Life in Short Stature Youth (QoLISSY) questionnaire. Both somatrogon and Genotropin® groups achieved similar increases in core total scores and subscale scores from baseline and 12 months, indicating similar improvements in QoL following treatment.

QoL data were available for only a subset of participants ([redacted]) due to the (non-)availability of translated tools in different countries, and the CS does not provide information on the clinical or statistical significance of the observed QoL benefits. Nevertheless, it appears that somatrogon and Genotropin® have broadly similar effects on quality of life.

4.4 Longer term effects of somatropin

The results of open-label extension periods of the pivotal RCT (CP-4-006) and dose finding (CP-4-004) studies are reported in sections B.3.6.2 and B.3.6.4 of the CS respectively.

4.4.1 Pivotal trial extension

All participants completing the pivotal RCT were eligible to enter the open-label extension, in which all participants received 0.66mg/kg/week somatrogon. The CS reports sustained improvements in annualised HV, change in height SDS, and IGF-1 SDS at 6 and 12 months following the main 12-month trial. Mean values for participants crossing over from the Genotropin® arm became more similar to those who received somatrogon during the main study.

It should be noted that 24-month follow-up data (i.e. 12 months after completion of the main trial) were available for just nine participants, so the reported mean values are unlikely to be meaningful. As the cut-off date for efficacy data was November 2019, the EAG believes that a more recent data

cut could be available. However, this was not clear from the submission documents and the EAG did not have an opportunity to ask the company for clarification.

4.4.2 Dose finding trial extension

The open-label extension of the dose finding study (CP-4-004) reported sustained improvement in annual HV, change in height SDS, height SDS and bone maturation up to five years from baseline. However, the CS did not report data for participants crossing over from Genotropin® to somatrogon separately.

4.5 Evidence on treatment burden

Section B.3.6.3 of the CS reported the findings of C0311002, a 24-week, Phase 3, randomised, multicentre, open-label, crossover study assessing patient and caregiver perception of the treatment burden with weekly somatrogon compared to daily Genotropin®. Statistically significant treatment difference on 'Life Interference' total score (15.49, 95% CI -19.71, -11.27, $p<0.0001$) in favour of weekly somatrogon. However, the clinical meaningfulness of a difference of this magnitude is unclear.

The study also reported a range of secondary outcomes captured by the Dyad Clinical Outcome Assessment (DCOA) 1 and DCOA 2 questionnaires, the majority of which had statistically significantly better scores in patients receiving weekly somatrogon than daily Genotropin® (see CS figures 6 and 7, p.46-7).

The DCOA 1 questionnaire included a 'missed injections' measure, on which estimated mean difference scores favoured once weekly somatrogon injection schedule over once daily Genotropin® (-2.76, 95% CI: -5.16, -0.36).

Though unblinded with several unclear study procedures, this crossover trial appears to be at relatively low risk of bias (see Table 6), and any potential carryover effects would likely reduce rather than increase the observed difference in outcomes between treatment arms.

As treatment duration for each treatment in study C0311002 was only 12 weeks, it cannot capture the longer-term treatment burden for somatrogon or Genotropin®.

Table 6 EAG risk of bias assessment of treatment burden study (CO311002)

Study Name	ROB assessor	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the onset of the study in terms of prognostic factors, for example, severity of the disease?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
C0311002	EAG	Unclear, subjects were randomised, but method is unclear. (n.b. Subjects crossed over between treatment arms at 12 weeks)	Unclear, no details of whetherallocation was concealed.	Yes (n.b. Subjects crossed over between treatment arms at 12 weeks)	No, open-label	No	No	Yes, full analysis set included all randomised subjects who received at least one dose of study intervention. The analyses of primary and secondary endpoints were performed using the FAS population.

4.6 Safety/adverse events

Adverse events were reported in the CS for all five included trials. For full data see Tables 20 to 25 of the CS.

4.6.1 Pivotal trial CP-4-006

In the Phase III trial (CP-4-006) the numbers of patients with adverse events were similar between the somatrogon (87.2%) and somatropin (84.3%) groups, but there were more events in the somatrogon arm (868) than the somatropin arm (570), giving a rate ratio of 1.61 (95% CI 1.46 to 1.79).

Higher rates of adverse events were mainly because of higher rates of injection site pain on somatrogon (39.4% vs 25.2%), and higher rates of injection site reactions (43.1% vs 25.2%) There was also a higher rate of serious injection site pain with somatrogon (4.6% vs 2.6%). Serious adverse events were rare, and too few to identify any possible differences between arms. One person withdrew from the somatrogon arm due to adverse events; none did from the somatropin arm. Further details of adverse events were reported in Deal et al 2022 (Table 3)[16]. There was no evidence of any difference in event rates between arms, but numbers for each AE type were small in both arms.

Immunogenicity was more common with somatrogon (18.3% vs 7.8%), and 77.1 % of somatrogon patients tested positive for anti-drug antibodies.

4.6.2 Other trials

Results for the extension of the phase III trial were reported, but as all patients received somatrogon, we do not consider them in detail here. Injection site pain remained the most common AE, but at a lower rate than in the main trial phase (11.5% in patients originally randomised to somatrogon).

Results for the treatment burden study (C0311002) were briefly described, and similar to the main phase III trial.

In the Phase II trial (CP-4-004) adverse event rates were similar in somatrogon ([redacted]) and somatropin ([redacted]) arms. Anaemia appeared to be [redacted] with somatrogon, [redacted], but small numbers mean it is not possible to ascertain whether there were any meaningful differences between arms.

4.6.3 Horikawa et al

The trial of Horikawa et al[12] reported similar adverse event data, but included too few participants to draw clear conclusions on safety. Adverse events were more common with somatrogon (100%) than

with genotropin (77.3%); a relative risk of 1.29 (95% CI: 1.01 to 1.63). The difference was mostly due to a higher rate of injection site pain (RR 5.33, 95% CI 1.81 to 15.74). Most events of injection-site pain were reported during the first 6 months of the study. 82% (18/22) of somatrogon patients developed anti-drug antibodies, compared with 18% (4/22) of somatropin patients

4.6.4 Summary

A summary of adverse events is given in Table 7. The EAG notes that the main adverse event concern with somatrogon is that appears to be a painful injection, with substantially more patients experiencing injection pain or injection-related AEs than with daily somatropin. The EAG notes that the consequences of a painful injection, but only once a week, must be balanced against less painful injections every day. The high incidence of patients with anti-drug antibodies when using somatrogon may be of concern. There is no evidence that it impacts efficacy or adverse events during the trial period but the long-term impact is unclear.

Table 7 Treatment emergent adverse events for pivotal (CP-4-006) and Horikawa et al RCTs

	Pivotal RCT		**Horikawa et al 2022**	
Number (%) of subjects	***Somatrogon (n = 109)***	***Genotropin (n = 115)***	***Somatrogon (n = 22)***	***Genotropin (n = 22)***
Number of AEs	868	570	359	106
Subjects with AEs	95 (87.2%)	97 (84.3%)	22 (100.0%)	19 (86.4%)
Subjects with serious AEs	3 (2.8%)	2 (1.7%)	2 (9.1%)	2 (9.1%)
Subjects with severe AEs	9 (8.3%)	6 (5.2%)	2 (9.1%)	2 (9.1%)
Subjects discontinued from study due to AEs	1 (0.9%)	0	0	1 (4.5%)
Subjects discontinued study drug due to AE and continued study	0	0	0	0
Subjects with dose reduced or temporary discontinuation due to AEs	3 (2.8%)	2 (1.7%)	0	0

5 SUMMARY OF THE EAG'S CRITIQUE OF COST EVIDENCE SUBMITTED

Whether it is appropriate for the assessment to proceed as a cost-comparison analysis rests primarily on the clinical effectiveness and the appropriateness of assuming equal (or very similar) efficacy and safety of somatrogon to at least one relevant comparator. The EAG critique of the cost comparison evidence assumes that it is appropriate for the assessment to proceed as a cost comparison analysis, and seeks to answer under what circumstances somatrogon is likely to be cost saving or equivalent in cost to the comparators.

5.1 Summary of costs and assumptions

The company presents a formal cost comparison of weekly somatrogon against seven preparations of daily rhGH treatment of somatropin: Genotropin®; Humatrope®; Norditropin®; NutropinAq®; Omnitrope®; Saizen®; and Zomacton®. All seven preparations are considered relevant comparators. It is assumed here that somatrogon and all comparators have equivalent efficacy as this appears to be the accepted position of NICE (TA188). However, the EAG notes that there is no direct evidence comparing different somatropin preparations. Somatropin was previously appraised by NICE for the treatment of growth failure in children in NICE Technology Appraisal TA188.[9]

The costs considered in the company's cost comparison analysis comprised of drug acquisition costs only, which were estimated per patient per year. The annual drug acquisition costs were based solely on the unit costs and the average daily or weekly dose, these are presented in Table 8. Comparator costs were calculated assuming a dose of 0.034mg/kg/day to align with the Genotropin® dose used in CP-4-006. All annual drug acquisition costs were based on a child with an average weight of 40kg, with a mean start age of 9 years and estimated finishing age of 16 years (i.e., the average weight corresponds to the rounded midpoint age of 13 years from the KIGS data base).[17]

Table 8 Unit costs and the average daily dose

Preparation	Unit cost (per mg)	Daily dose (per mg/kg)	Weekly dose (per mg/kg)
Genotropin®	£17.39	0.034	0.238
Omnitrope®	£14.75	0.034	0.238
Norditropin®	£23.18	0.034	0.238
Saizen®	£23.18	0.034	0.238
Humatrope®	£18.00	0.034	0.238
Nutropin AQ®	£20.30	0.034	0.238
Zomacton®	£17.07	0.034	0.238
Somatrogon	£7.90	n/a	0.660

The unit costs included in the analysis are based on the list price provided by the company and those listed in the British National Formulary (BNF).[1] There is no patient access scheme (PAS) proposed for somatrogon and the company states that it does not expect a PAS to be in place for the comparators. The Commercial Medicines Unit (CMU) manages procurement for somatropin; the corresponding prices are detailed in a separate confidential appendix.

Key assumptions in the company analysis include:

- There are no differences in the healthcare resource use and associated costs for somatrogon and comparators other than the drug acquisition costs. This means all healthcare resource use and associated costs are assumed to cancel each other out when comparing somatrogon to comparators. Despite the movement from a once daily injection of somatropin to a once weekly injection of somatrogon, the company does not expect there to be a change in service provision or management between the products. The assumption of equivalent service provision and management costs for somatropin products is supported by TA188 and the results of the company's systematic literature review (SLR) on healthcare resource utilisation in Appendix G of the CS.
- There are no expected differences in the adverse event profiles of somatrogon and comparators meaning that the resource use and costs associating with managing such adverse events are expected to be equivalent. This was based on the CP-4-006 clinical trial which the company asserts showed no significant difference in the AEs reported between somatrogon and somatropin.
- There are no expected differences in treatment duration (or discontinuation rates) between somatrogon and comparators, either due to a loss of efficacy or AEs. This also reflects the base case analysis for somatropin products used in TA188.

- All comparators are dosed at a daily dose of 0.034 mg/kg. The assumption of equivalent dosages across the somatropin products is based on TA188.
- There is no drug wastage of somatrogon and comparators.
- The average length of a course of treatment is assumed to be 7 years (from 9 – 16 years of age) for somatrogon and comparators.
- Treatment adherence is assumed to be equivalent across somatrogon and comparators.
- In addition to the cost comparison analysis, the company provided market share information for the somatropin products based on company data. (Pfizer data on file) This can be seen in Table 9

Table 9 Market Share

Technologies	Market Share (%)
Somatrogon	**[redacted]%**
Norditropin®	[redacted]%
Saizen®	[redacted]%
Nutropin AQ®	[redacted]%
Humatrope®	[redacted]%
Genotropin®	[redacted]%
Zomacton®	[redacted]%
Omnitrope®	[redacted]%

5.2 EAG critique of cost-comparison analysis

The EAG conducted a technical validation of the executable model by cross-checking values against the submission and auditing formulae. The EAG detected no errors in the executable model.

The main EAG critique centres on the following aspects of the analysis:

- Service provision and management costs
- Dose
- Unit costs
- Adverse events
- Market share
- Wastage

5.2.1 Service provision and management costs

As has been detailed in Section 5.1, the company's cost comparison analysis assumed no difference in resource use between somatrogon and comparators other than the drug acquisition costs. The SLR

conducted by the company identified two studies: TA188[9] and Phelan et al.[18] Both studies indicated no difference in resource across growth hormone preparations albeit the EAG considers the Phelan et al. study to be of limited relevance as the study enrolled premenopausal adult women only. Ultimately, the EAG is satisfied the service provision and management costs would be the same across somatrogon and comparators.

5.2.2 Dose

The modelled dose used to cost the comparators in the company base case was 0.034 mg/kg/day. Although this aligns with the dose used in the CP-4-006 trial, this dose does not align with the assumption used in TA188 in which the dose was assumed to be 0.025 mg/kg/day for all somatropin products. The BNF lists the recommended dose range for children with deficiency of growth hormone as 0.023 – 0.039 mg/kg/day for all licensed preparations of daily somatropin[1] meaning that the company's assumption regarding the dose is towards the top end of the recommended range in the NHS.

Evidence from the KIGS study[17] appears to indicate 0.034 mg/kg/day may indeed be higher than the average dose used in the NHS. In the company submission, it was stated 0.034 mg/kg/day was chosen based on the most commonly used dose worldwide in real world setting for pGHD and is in line with the posology licensed for its use.[17] The KIGS data, however, shows higher average doses in the US compared to Europe indicating the worldwide average may be higher than those used in the NHS. The weekly doses in Europe from KIGS are closer to 0.21 mg/kg/week (equivalent to 0.030 mg/kg/day) for idiopathic GHD and congenital GHD; and 0.18 mg/kg/week (equivalent to 0.026 mg/kg/day) for acquired GHD. The generalizability of the results are uncertain as it is unclear what proportion of the study population are based in the UK and the data does include participants starting treatment up to 35 years ago. A dose of 0.025 mg/kg/day was used in Horikawa et al (see Section 4.3.2.1). Advice provided to the EAG also indicated that the dose reported in the pivotal trial represented the starting dose used for somatrogon and somatropin, but these were adjusted (titrated) every 3 months based on the subject's body weight. The KIGS study appears to be representing an average dose over time, while the trial is a starting dose at diagnosis, not the average dose after titration.

Further, the EAG considers there to be uncertainty regarding the company's assertion that a dose of 0.034 mg/kg/day for the comparators was shown to be cost-effective in TA188. This is not made explicit in TA188 and the updated results presented in an addendum to TA188 appear to indicate an ICER above £30,000 per QALY at a dose of 0.034 mg/kg/day. The results of the cost-effectiveness analysis in TA188 does show the results are most sensitive to the dose indicating the importance of identifying the correct dose.

To demonstrate the impact of the assumption of the comparator dose on the results of the cost comparison analysis, the EAG presents sensitivity analysis in which the dose is varied to align with the recommended dose range listed in the BNF, i.e., 0.023 – 0.039 mg/kg/day.[1] The results of this sensitivity analysis can be seen in Section 6.2.1.

5.2.3 Unit costs

The unit costs of the comparators provided in the company analysis were based on costs listed in the BNF.[1] Although the EAG largely agrees with the unit costs included in the analysis, the company used a unit cost of £23.18 per mg for Norditropin®. In the BNF, there are two NHS indicative prices for Norditropin®, listed as £106.35 and £115.90 for 5 mg per 1.5 ml, which equate to £21.27 and £23.18, respectively. This indicates the company have opted for the most expensive of the two prices when costing Norditropin®. It is uncertain which of the two represents the costs the NHS is likely to pay for Norditropin®; therefore, the EAG considers the impact of including the lower of the listed costs on the results of the cost comparison analysis. The results are presented in Section 6.2.1.

The EAG is satisfied will all other unit costs included in the analysis.

5.2.4 Adverse events

The costs of managing adverse events were excluded from the cost comparison analysis as there is no significant difference in the adverse events reported between somatrogon and somatropin in CP-4-006. Yet, the EAG highlights a number of adverse events concerns, notably that there is a higher incidence of injection pain for somatrogon than for daily somatropin; and the presence of a higher incidence of patients with anti-drug antibodies when using somatrogon (see Section 4.6).While these may not be considered to have an impact on differences between treatment duration, any differences in AE profiles may lead to different associated costs between comparators. The EAG is satisfied that the exclusion of AE costs in the analyses does not bias the results and that differences in safety profile between comparators, which may be important when considering patient experience, are unlikely to represent a driver of the cost analysis.

5.2.5 Market share

The company presented data on the UK market share of the seven daily somatropin preparations during the period December 2020 - 2021. The results indicate the market leaders are [redacted] However, the EAG does not have access to this data and is unable to comment on the validity and relevance of these figures. The EAG welcomes comments from committee regarding the market share in the UK as this may have implications for the comparator costs with which to compare somatrogon. Given the range of comparator costs estimated in the company base case (Section 6.1) and the EAG base case (Section 6.2.2), the choice of the

relevant comparator is fundamental when answering the question of whether the Somatrogon has costs similar to or less than the relevant comparator.

5.2.6 Additional comments

5.2.6.1 Wastage

The company's approach assumed no wastage for somatrogon or any of the comparator preparations. This aligns with the assumptions used in the MTA informing TA188.[19] The EAG considers that there may be a difference in wastage across the comparators given there are a number of different preparations (e.g. solution and powder) however the EAG expects any wastage to have a very minor impact on cost differences between the products.

5.2.6.2 Duration and discontinuation

The company assumed a mean treatment duration of 7 years for somatrogon and comparators based on TA188. The EAG is unaware of any evidence to suggest differential treatment durations or discontinuation rates between somatrogon and comparators. Without long-term data, the EAG is satisfied with the assumption of near equivalence in duration and discontinuation as applied in the company's base case.

5.2.6.3 Dose adjustment

The company have assumed equivalence in the dose adjustment across somatrogon and comparators. Dose adjustment appears to be tailored to the needs of the individual child

The EAG does note that the annual costs are sensitive to the dose (see Section 6.2.1) and as such any differential dose adjustments may have an impact on the differential annual costs. The EAG is satisfied with the equivalence assumption in the company base case but does note this is an area of outstanding uncertainty and an area that may have an impact on the differential costs should there be evidence of differential dose adjustment.

5.2.6.4 Adherence

The cost comparison presented by the company does not factor adherence to treatment into the analysis. The company states somatrogon has the potential to improve treatment outcomes by increasing compliance and adherence, based on evidence from the treatment burden trial (see Section 4.5).

Patient choice is expected to be an important factor in maximising adherence to treatment and that may be determined by the patient support package on offer for the different products. The company states that somatrogon will be provided with a comprehensive patient support program including starter kits, ancillary provision, homecare delivery and nursing, a patient helpline, and a patient

website, which is expected to match that offered for somatropin preparations. As such, the EAG considers the assumption of equivalence in adherence to be appropriate.

5.2.6.5 Uncaptured QALY benefit

The nature of a cost-comparison analysis assumes equivalence in health outcomes across comparators and as such QALYs are not captured in the analysis. The company do, however, state there may be increased utility associated with a reduced number of injections albeit evidence of this is not provided or included in the analysis. An SLR conducted by the company shows there are no studies capturing health-related quality of life (HRQoL) relevant to the decision problem and as such any associated QALY gains are uncertain. Health-related quality of life improvements associated with the comparators was a major uncertainty in TA188[9] and as such this remains a major area of uncertainty in the appraisal of treatments for GHD.

5.3 Summary

Despite the presence of some areas of uncertainty highlighted in Section 5.2, the EAG is largely satisfied with the company's approach of basing the cost comparison analysis on the drug acquisition costs alone. In the company base case, somatrogon has similar costs to comparators, with lower costs than Norditropin® and Saizen® but higher costs than Nutropin AQ®, Humatrope®, Genotropin®, Zomacton® and Omnitrope®. However, implicit in this assessment is the assumption that the comparators are dosed at 0.034 mg/kg/day which has been highlighted as a concern by the EAG. Whether the somatrogon costs remain comparable to comparators when the dosing assumption is altered to align with the dosing assumption in TA188 is shown in Section 6.2.

6 COMPANY AND EAG COST COMPARISON RESULTS

The following section details the results of the company's base case, the results of additional analyses conducted by the EAG, followed by the EAG-preferred base case. All results are based on the list prices because there is no PAS proposed for Somatrogon and no PAS in place for any of the comparators. All results inclusive of the CMU prices are provided in a separate confidential appendix.

6.1 Company cost comparison results

The company presented mean annual costs per patient for Somatrogon and comparators. The results of the company's base case can be seen in Table 10.

Under the company's assumptions and using the lists prices, somatrogon has an annual drug acquisition cost of £10,845, which is lower than Norditropin and Saizen but higher than Nutropin AQ, Humatrope, Genotropin, Zomacton and Omnitrope. This means that the drug acquisition cost of Somatrogon is within the range of comparators.

The company did not present any sensitivity or scenario analyses.

Table 10 Company base-case results adapted from Table 26, pg. 70, CS

Technologies	Estimated Annual Acquisition costs (£)	Resource / Adverse event / Other costs (£)	TOTAL COSTS (£)	Market share
Somatrogon	**£10,845**	**N/A**	**£10,845**	**[redacted]%**
Norditropin®	£11,475	N/A	£11,475	[redacted]%
Saizen®	£11,475	N/A	£11,475	[redacted]%
Nutropin AQ®	£10,049	N/A	£10,049	[redacted]%
Humatrope®	£8,911	N/A	£8,911	[redacted]%
Genotropin®	£8,609	N/A	£8,609	[redacted]%
Zomacton®	£8,450	N/A	£8,450	[redacted]%
Omnitrope®	£7,302	N/A	£7,302	[redacted]%

6.2 EAG cost comparison results

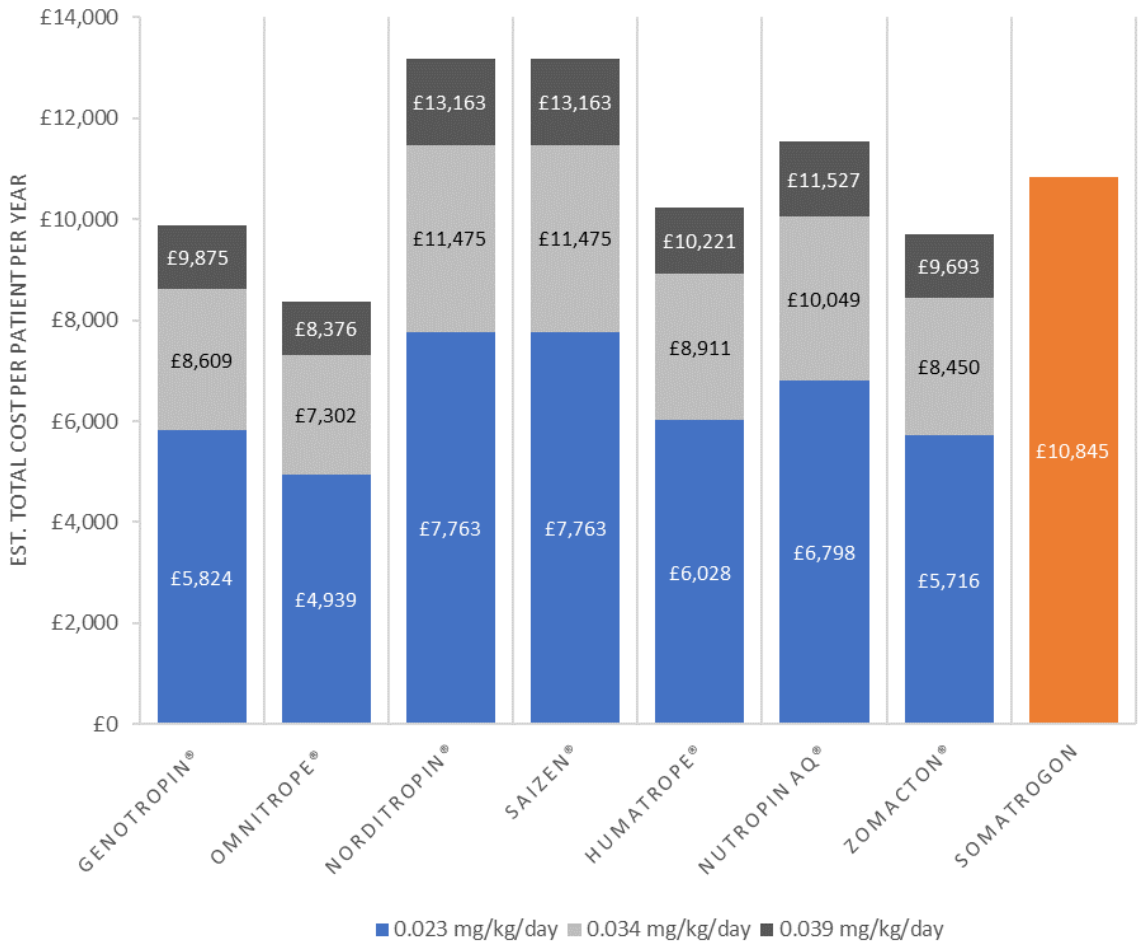
6.2.1 EAG exploratory analyses

6.2.1.1 Comparator dose

As described in Section 5.2, the EAG considers there to be uncertainty regarding the comparator dose used in the company analysis. To explore this, the EAG presents the results of a sensitivity analysis in which the company's base case results are presented, that is assuming a dose of 0.034 mg/kg/day, alongside the results based on 0.023 mg/kg/day and 0.039 mg/kg/day to align with the lower and upper end of the recommended range listed in the BNF.

The results shown in Figure 2 demonstrate the sensitivity of the annual cost per patient to the dose. At a dose of 0.023mg/kg/day, the comparators with the highest annual costs are Norditrope® and Saizen® at £7,763, considerably lower than the annual cost of somatrogon at £10,845. At a dose of 0.039 mg/kg/day the annual cost of somatrogon is lower than Norditropin®, Saizen® and Nutropin AQ® but still remains higher than Genotropin®, Omnitrope®, Humatrope® and Zomacton®.

Figure 2 Sensitivity analysis of varying the daily dose on the annual cost



To align with the assumptions in TA188, Table 11 shows the results of the cost comparison in which the comparators are dosed at 0.025 mg/kg/day.

Table 11 EAG Scenario analysis 1: comparator dose assumption

	Base case	Scenario 1 (dose 0.025 mg/kg/day)	Change from baseline
Genotropin®	£8,609	£6,330	-£2,279
Omnitrope®	£7,302	£5,369	-£1,933
Norditropin®	£11,475	£8,438	-£3,038
Saizen®	£11,475	£8,438	-£3,038
Humatrope®	£8,911	£6,552	-£2,359
Nutropin AQ®	£10,049	£7,389	-£2,660
Zomacton®	£8,450	£6,213	-£2,237
Somatrogon	**£10,845**	**£10,845**	**£0**

6.2.1.2 Unit cost of Norditropin

As described in Section 5.2, the BNF lists two prices for Norditropin®: £23.18 and £21.27. The company costed Norditropin® assuming a unit cost of £23.18. The following scenario presents the results of using the alternative Norditropin® unit cost of £21.27.

Table 12 EAG Scenario analysis 2: Alternative Norditropin® cost

	Base case	Scenario 2 (Alternative price of Norditropin®)	Change from baseline
Genotropin®	£8,609	£8,609	n/a
Omnitrope®	£7,302	£7,302	n/a
Norditropin®	£11,475	£10,530	-£946
Saizen®	£11,475	£11,475	n/a
Humatrope®	£8,911	£8,911	n/a
Nutropin AQ®	£10,049	£10,049	n/a
Zomacton®	£8,450	£8,450	n/a
Somatrogon	**£10,845**	**£10,845**	**n/a**

6.2.2 EAG-preferred base case

The EAG-preferred base case reflects most assumptions included in the company base case with the exception of the company's assumption regarding the dose of the comparators. The EAG considers the dose of 0.025 mg/kg/day to be more appropriate (see Section 5.2). The results of the EAG base case be seen in Table 11.

The results indicate the annual costs of somatrogon are considerably higher than comparators. The annual cost of somatrogon under the EAG's assumptions is £10,845. Norditropin® and Saizen® are the comparators with the highest annual cost, estimated to be £8,438 under the EAG's-preferred assumptions, meaning somatrogon costs £2,407 more per annum. Compared to Omnitrope®, the comparator with the lowest annual costs, somatrogon is estimated to cost £5,476 more per annum.

Based on data provided to the company, [redacted] is estimated to be the market leader with [redacted]% of the market share. However, as detailed in Section 5.2, the EAG welcomes comments on the market leader and therefore the most appropriate comparator for somatrogon.

7 EQUALITIES AND INNOVATION

The EAG notes that the availability of weekly injections of somatrogon, rather than daily somatropin is an important innovation in the delivery of therapy that could potentially improve acceptance of, and compliance with, treatment.

From the company submission, it appears that other pharmaceutical companies have developed alternative weekly-injection alternatives to somatropin. It is currently unclear to the EAG where in the development pathway these alternatives are, and when, or if, they might become available in the UK.

The EAG is not aware of any equality issues for this assessment, but we have not received any clinical advice in this area.

8 EAG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE BY THE COMPANY

8.1 General conclusions

The EAG considers that the evidence presented in the CS is generally robust, of good quality, and supports the case for using a cost-comparison in this assessment. The clinical trial evidence presented suggests that somatrogon and Genotropin® are broadly equivalent in effect, with patients experiencing similar health benefits, with comparable rates of growth. We note that one clinical trial (Horikawa et al 2022) was identified by the company but not discussed in detail in the CS. The reasons for this are unclear; however, its results are consistent with other trial evidence

The EAG notes that somatrogon has been compared only to Genotropin®, but seven preparations of somatropin (rhGH) are available in the UK. Although there appears to be no evidence directly comparing different somatropin preparations, the EAG considers it reasonable (based on existing NICE guidance in TA188) to assume that they are equivalent in efficacy, and so somatrogon is broadly equivalent in efficacy to them all.

The EAG notes that the potential for greater pain from weekly somatrogon injections should be balanced against the disadvantages of daily injections for somatropin. There is currently no evidence that increased injection pain adversely effects quality of life.

Somatrogon appears to lead to greater immunogenicity in patients than somatropin. The consequences of this are unclear, but may need to be considered when evaluating long-term use of somatrogon.

NICE requires that the technologies assessed by the cost comparison approach show similar or greater health benefits; the EAG thinks that those conditions have been met by this technology.

8.2 Conclusions on cost-effectiveness

The EAG is largely satisfied with the company's approach to the cost-comparison analysis based on drug acquisition costs alone. In the company's base case, somatrogon has similar costs to the comparators when the comparators are dosed at 0.034 mg/kg/day. The EAG has highlighted that although this dose aligns with the starting dose used in the CP-4-006 trial, the BNF lists the recommended dose range for children with deficiency of growth hormone as 0.023 – 0.039 mg/kg/day for all licensed preparations of daily somatropin.[1]. At the lower end of this dose range (0.023mg/kg/day), the comparators with the highest annual costs are Norditrope® and Saizen® at £7,763, which are considerably lower than the annual cost of somatrogon at £10,845. At the higher end of the dose range (0.039 mg/kg/day), the annual cost of somatrogon is lower than Norditropin®, Saizen® and Nutropin AQ® but still remains higher than Genotropin®, Omnitrope®, Humatrope® and Zomacton®. The EAG considers a dose of 0.025 mg/kg/day to be appropriate for the cost-comparison analysis because it is more likely to represent an average dose over time after titration. At this dose, the annual costs of somatrogon are higher than all the licensed preparations of daily somatropin.

8.3 Areas of uncertainty

The EAG notes that it received very limited clinical advice for this assessment. Consequently, there are areas of clinical and economic uncertainty which the EAG have been unable to resolve. We recommend that an expert in growth hormone deficiency and its treatment consider these outstanding issues. The issues are summarised in Table 13.

Table 13 Outstanding areas of uncertainty

Issue	Description	Report section
Impact of weekly injection on pharmacokinetics	A weekly injection may not reflect the diurnal nature of natural growth hormone secretion, with unclear long-term consequences	Section 2.1
Dosage of somatropin	Daily dose of somatropin can vary from 0.023 to 0.039 mg/kg/day (BNF guidance) and may vary between patients and over time. It is not clear whether 0.034 mg/kg/day (as used in the pivotal trial) is the most suitable comparator dose, with implication for cost-effectiveness.	Sections 4.3.2 and 5.2.2
Missed injections	The impact of missing a weekly somatrogon injection is likely to be larger than missing a daily somatropin injection. The consequences of a missed or delayed injection are unclear.	Section 4.5
Impact of injection site pain	The impact of the higher incidence of injection-site pain with somatrogon is unclear, particularly with regards to adherence and acceptance.	Section 4.6
Immunogenicity	Patients receiving somatrogon were more likely to develop anti-drug antibodies. The long-term consequences of this are unclear, and may require expert pharmacovigilance.	Section 4.6
Market share	The CS reported market share estimates for the different somatropin formulations. It is unclear whether these reflect NHS practice, or may vary by location.	Section 5.2.5

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